Re-imagining the Surveillance

of Invasive Mould Diseases

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Abstract

Invasive mould diseases (IMDs) have significant health and economic costs for immunocompromised patients. IMDs are now the predominant fungal pathogens in haematology-oncology patients who also carry the greatest burden of fungal infections overall. This thesis captures the high hospitalisation cost of invasive fungal diseases (IFDs) based on detailed patient level data. It explores the optimal methodology to cost these infections and postulates a novel resource metric in costly antifungal drug consumption as an alternative to currency estimates. It examines the comparative effectiveness of antifungal prophylaxis in haematology-oncology patients at high risk for IMDs documenting over a decade, the declining incidence of IMD following the adoption of mould active antifungal prophylaxis with reductions in other clinically relevant outcomes such as empiric antifungal therapy and non-specific pulmonary infiltrates also observed. Our analyses of azole and liposomal amphotericin prophylaxis go beyond demonstrating the evolving epidemiology of fungal infections in response to changing therapeutic practices but also illustrate that knowledge of local epidemiology informs clinical decision making. The latter, culminating in clinical practice recommendations regarding the optimisation of posaconazole for either prophylaxis or treatment of established IFDs and, in a broader context, recommendations strengthening antifungal drug stewardship programs in hospitals.

Despite the health and cost implications of IMDs and effort invested in preventing them, prospective continuous surveillance is not routinely

performed in many hospitals. Reasons for this omission include cost and the absence of an easily identifiable laboratory prompt. Traditional approaches to surveillance, which are reliant on bedside review, administrative or laboratory-based methods, are resource-intensive activities, error prone and subject to either under-reporting and/or variability in case ascertainment.

This thesis will argue the case for prospective surveillance of IMDs and provide a potential technological solution to facilitate its practice in hospitals. From a surveillance standpoint, the primary screening method is critically important in order to maximise case finding while minimising its cost and effort. For IMDs however, the optimal screening method is undefined. This thesis considers targeting computed tomography (CT) reports as an appropriate screening method for IMD surveillance. CT is a key diagnostic modality for IMDs stipulated in consensus guidelines; pulmonary involvement is present in the overwhelming majority of cases; it is widely available in hospitals and being a non-invasive test it is uniformly performed when IMDs are suspected with results available in a timely fashion. Non-culture based tests (NCBTs) such as galactomannan (GM) or polymerase chain reaction (PCR) are less suitable as screening tools due to their variable availability, delays in turn-around and a diminished sensitivity in the presence of concomitant mould-active antifungal agents.

This thesis describes the development of a text classifier that uses natural language processing (NLP) for the first time to flag CT reports supportive of IMDs. NLP is a computational method for analysing human language that has

been applied for the detection of a variety of medical conditions, but not IMDs. As a high-throughput technology, it has the potential to identify CT reports with suspected IMD in real-time. Thus, it may deliver to hospitals a feasible, sustainable and cost-effective solution to IMD surveillance with minimal interruption to routine clinical workflow.

Text analytical tools are a means of unlocking the wealth of patient-level data that is largely confined to unstructured (i.e., free-text) documents in health care. Modernisation of data management and an investment in data infrastructure could help the health industry keep pace with changing clinical practice while also supporting large scale comparative effectiveness studies of 'real-world' patients who are free from the protocol-driven biases of clinical trials. In future, the partnering of enormous volumes of routinely collected clinical data with genomic or molecular advances could help progress bioinformatics which predict disease and personalise treatments that are both effective and cost-beneficial.

Declaration

This is to certify that:

    i.   the thesis comprises only my original work towards the PhD except where indicated in the Preface,

   ii.   due acknowledgement has been made in the text to all other material used,

  iii.   the thesis is fewer than 100 000 words in length, exclusive of tables, maps, bibliographies and appendices as approved by the Research Higher Degrees Committee.

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Preface

The following comprise publications and selected abstracts authored during PhD candidature. Symbols indicate the following:

* * Included in thesis; peer review publication.

* ^ Selection in the 'Top 10 Mycology Papers' session at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) ASM, San Francisco, 2012.

* # Select abstracts presented during candidature.

* ## Manuscript submitted during candidature, unpublished.

* ∞ Published during candidature; not included in thesis; peer review publication.

* Ananda-Rajah, M.R., Grigg, A. & Slavin, M.A. (2012). Making sense of posaconazole therapeutic drug monitoring: A practical approach. *Curr Opin Infect Dis, 25*(6), 605–611. doi: 10.1097/QCO.0b013e328359a56e (see Appendix 1).

*^ Ananda-Rajah, M.R., Slavin, M.A. & Thursky, K.T. (2012). The case for antifungal stewardship. *Curr Opin Infect Dis, 25*(1), 107–115. doi: 10.1097/QCO.0b013e32834e0680 (see Appendix 2).

*^ Ananda-Rajah, M.R., Grigg, A., Downey, M.T., Bajel, A., Spelman, T., Cheng, A., Slavin, M.A. (2012). Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in

patients with acute myeloid leukaemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period. *Haematologica, 97*(3), 459–463. doi: haematol.2011.051995 (see Appendix 3).

*   Ananda-Rajah, M.R., Cheng, A., Morrissey, C.O., Spelman, T., Dooley, M., Neville, A.M. & Slavin, M. (2011). Attributable hospital cost and antifungal treatment of invasive fungal diseases in high-risk haematology patients: An economic modelling approach. *Antimicrob Agents Chemother, 55*(5), 1953–1960. doi: AAC.01423–10 (see Appendix 4).

\#   Ananda-Rajah, M.R., Martinez, D., Suominen, H., Thursky, K., Slavin, M. & Cavedon, L. (2012). Electronic surveillance of invasive fungal diseases in haematology-oncology patients using natural language processing of computed tomography reports: Towards real-time prospective surveillance. *52nd Interscience Conference on Antimicrobial Agents and Chemotherapy ASM, San Francisco* (see Appendix 5).

\#   Ananda-Rajah, M., Grigg, A.P., Thursky, K., Bajel, A. & Slavin, M. (2011). Prophylactic effectiveness and safety of intermittent liposomal amphotericin in high-risk haematological patients. *51st Interscience Conference on Antimicrobial Agents and Chemotherapy ASM, Chicago* (see Appendix 6).

\#   Ananda-Rajah, M.R., Grigg, A., Downey, M.T., Bajel, A., Thursky, K.T. & Slavin, M.A. (2009). A decade of azole antifungal prophylaxis in acute myeloid leukaemia patients from an Australian tertiary centre. *49th Interscience Conference on Antimicrobial Agents and Chemotherapy ASM, San Francisco.*

\#   Ananda-Rajah, M.R., Morrissey, C.O., Woodger, J., Neville, A.M., Frost, M. & Slavin, M.A. (2008). The cost of invasive fungal infections in patients undergoing allogeneic (allo) stem cell transplantation (SCT) or chemotherapy for acute leukaemia. Abstract #377548. *48th Interscience Conference on Antimicrobial Agents and Chemotherapy/ 46th Infectious Diseases Society of America ASM, Washington.*

\#\#   Martinez, D., Ananda-Rajah, M.R., Suominen, H., Slavin, M.A., Thursky, K.A., Cavedon, L. (2013). Automatic detection of patients with invasive fungal infections from free-text computed tomography (CT) scans (see Appendix 7).

∞   Ananda-Rajah, M.R., McBryde, E.S., Buising, K.L., Redl, L., MacIsaac, C., Cade, J. & Marshall, C. (2010). The role of general quality improvement measures in decreasing the burden of endemic MRSA in a medical-surgical intensive care unit. *Intensive Care Med, 36*(11), 1890–1898 (see Appendix 8).

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Finally, to my husband and children, my *raison d'etre*: without you, none of this would have been possible and I am joyful to be returning to your arms.

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List of Abbreviations

ABC   Activity-based costing

AFS   Antifungal stewardship

AH   Alfred Health

AML   Acute myeloid leukaemia

AMS   Antimicrobial stewardship

AUC   Area under the curve

BAL   Bronchoalveolar lavage

BSI   Blood stream infection

CAP   Community-acquired pneumonia

CCI   Charlson Co-morbidity Index

CDC   Centers for Disease Control and Prevention

CDSS   Computerised decision support system

CER   Comparative effectiveness research

CLABSI   Central line associated blood stream infection

CNS   Central nervous system

COPD   Chronic obstructive pulmonary disease

CT   Computed tomography

DDD   Defined daily dose

DRG   Diagnosis-related group

EAFT   Empiric antifungal therapy

ECIL   European Conference on Infections in Leukaemia

EFT   Equivalent full time

EHR   Electronic health record

FN	False negatives
FP	False positives
FOB	Fiberoptic bronchoscopy
GCA	Global Comparative Aspergillosis study
GIT	Gastrointestinal disease
GLM	Generalised linear models
GM	Galactomannan
GVHD	Graft-versus-host disease
HAI	Hospital-acquired infection
HEPA	High efficiency particulate air-filtration
HICPAC	Healthcare Infection Control Practices Advisory Committee
HRCT	High resolution Computed Tomography
HSCT	Haematopoietic stem cell transplant
IA	Invasive aspergillosis
ICAAC	Interscience Conference on Antimicrobial Agents and Chemotherapy
ICD	International Classification of Diseases
ICU	Intensive care unit
ID	Infectious diseases
IDSA	Infectious Diseases Society of America
IFD	Invasive fungal disease
IMD	Invasive mould diseases
IQR	Interquartile range
LDS	Latter Day Saints
LFTs	Liver function tests

L-AmB	Liposomal Amphotericin
LOS	Length of stay
MCVS	Multi-threaded Clinical Vocabulary Server
MDS	Myelodysplastic syndromes
MIC	Minimum inhibitory concentration
MRSA	Methicillin resistant *Staphylococcus aureus*
NCBT	Non-culture based tests
NHL	Non-hodgkins lymphoma
NHMD	National Hospital Morbidity Database
NHMRC	National Health and Medical Research Council
NHSN	National Healthcare Safety Network
NICU	Neonatal intensive care unit
NIS	National Inpatient Sample
NNIS	National Nosocomial Infections Surveillance
NLP	Natural language processing
NNIS	National nosocomial infection surveillance system
NNT	Number-needed-to-treat
NPV	Negative predictive value
PATH	Prospective Antifungal Therapy registry
PCR	Polymerase chain reaction
PK	Pharmacokinetic
PM	Peter MacCallum Cancer Institute
PPP	Purchasing power parity
PPV	Positive predictive value
RCT	Randomised controlled trial

RMH	Royal Melbourne Hospital
ROC	Receiver-operating-curve
SENIC	Study on the efficacy of nosocomial infection control
SOT	Solid-organ transplant
TDM	Therapeutic drug monitoring
TN	True negatives
TP	True positives
TPN	Total parenteral nutrition
UMLS	Unified Medical Language System
VA	Veterans Affairs
VAE	Vaccine adverse events
VAP	Ventilator associated pneumonia
VASQIP	VA Surgical Quality Improvement Program
VRE	Vancomycin resistant enterococcus
WHO	World Health Organization

Chapter 1: Introduction

The considerable health (Kontoyiannis, Marr et al. 2010; Pagano, Caira et al. 2010; Lortholary, Gangneux et al. 2011) and economic burden (Ananda-Rajah, Cheng et al. 2011; Menzin, Meyers et al. 2011) of invasive mould diseases (IMDs), in conjunction with their evolving epidemiology among an expanding population of immunocompromised patients, is a compelling argument for their surveillance. Patients with haematological malignancies and haematopoietic stem cell transplant (HSCT) recipients carry the greatest burden of invasive fungal diseases (Kontoyiannis, Marr et al. 2010; Pagano, Caira et al. 2010; Lortholary, Gangneux et al. 2011). Mould species are now the predominant fungal pathogens in this population, with invasive aspergillosis (IA) being most common (Kontoyiannis, Marr et al. 2010; Pagano, Caira et al. 2010; Lortholary, Gangneux et al. 2011).

For reasons that are poorly described in large epidemiological studies, the incidence of IMDs is highly variable, ranging from 8% to 42% in patients with acute myeloid leukaemia (AML) and HSCT recipients (Kontoyiannis, Marr et al. 2010; Neofytos, Lu et al. 2013). Short-term mortality has fallen from historical rates of 80% to 90% (Lin, Schranz et al. 2001) but remains unacceptably high at 38% to 43% (Nivoix, Velten et al. 2008; Neofytos, Horn et al. 2009; Nucci, Nouer et al. 2010; Nicolle, Benet et al. 2011; Steinbach, Marr et al. 2012). For patients who survive the short term, IMDs may adversely

affect long-term leukaemia cure due to changes or modification to subsequent chemotherapy treatments (Even, Bastuji-Garin et al. 2010).

Several authorities and professional societies believe that surveillance of IMDs should be the standard of care (Ellis, Marriott et al. 2000; Writing Group of the British Committee on Standards in Haematology 2008; Tomblyn, Chiller et al. 2009; Yokoe, Casper et al. 2009) and some jurisdictions have made nosocomial IA a notifiable disease (Fourneret-Vivier, Lebeau et al. 2006). IA may be nosocomially acquired (Oren, Haddad et al. 2001; Warris, Klaassen et al. 2003; Asmundsdottir, Erlendsdottir et al. 2008; Chang, Cheng et al. 2008; Hernandez-Castro, Arroyo-Escalante et al. 2009) as critical periods of immunosuppression (i.e., granulocytopenia) often correspond to periods of hospitalisation when acquisition is possible, but health care related outbreaks are often recognised too late to uncover an environmental point source (Cooley, Spelman et al. 2007; Kainer, Reagan et al. 2012; Bell and Khabbaz 2013). Recent guidelines advocate routine surveillance in addition to 'enhanced surveillance of microbiologic, pathologic and radiologic data' during periods of hospital construction (Tomblyn, Chiller et al. 2009), which, due to ageing hospital infrastructure, is often an ongoing activity in many hospitals. However, guidelines provide scant advice as to how surveillance should be implemented in hospitals.

Monitoring IMDs is important for:
- defining their burden

- informing and evaluating choice of preventative or management strategy

- tracking contemporary epidemiological data in response to changing therapeutic advances, host or environmental factors

- recognising sporadic but catastrophic health care related outbreaks.

At present, surveillance of IMDs is not routinely performed in many centres for a variety of reasons, including cost and the absence of a readily available laboratory prompt (such as a positive blood culture). Traditional surveillance methods involving clinical review in conjunction with laboratory-based and/or administrative methods are resource-intensive tasks requiring the synthesis of data from multiple sources (radiology, clinical, laboratory) (Kontoyiannis, Marr et al. 2010; Lortholary, Gangneux et al. 2011; Nicolle, Benet et al. 2011) followed by the application of complicated case definitions (De Pauw, Walsh et al. 2008). Laboratory-based surveillance for IMDs is subject to significant underreporting because conventional culture and histopathology are poorly sensitive, with microbiology for *Aspergillus* and hyaline moulds positive in 50% or fewer of cases (Denning, Marinus et al. 1998), compounded by patients at times being too unwell to undergo invasive diagnostic procedures. Non-culture based tests (NCBTs) such as GM are limited by variable penetration in hospitals, delayed turn-around time and a reduced sensitivity in the presence of concomitant antifungal therapy given for either treatment or as prophylaxis (Maertens, Groll et al. 2011).

Although administrative data is readily available, it is inaccurate for IMD surveillance due to missed or miscoded data (Chang, Burwell et al. 2008). Further, coding data is collated several weeks after patient separation and therefore does not allow real-time detection nor does it provide information on place of acquisition and time of onset. Thus, traditional methods of surveillance using either clinical review, laboratory-based methods or administrative data are costly, labour intensive, error prone and subject to variable case ascertainment and classification (Chang, Burwell et al. 2008; Kontoyiannis, Marr et al. 2010). Indeed, epidemiological studies using these traditional methods are characterised by high operational costs and finite life spans due to the burden of case ascertainment, data collection and data entry (Kontoyiannis, Marr et al. 2010).

Case finding is one of the most challenging barriers to implementation of IMD surveillance in hospitals. For surveillance in general, the primary screening method is critically important in order to minimise the burden of case finding and maximise case capture. However, for IMDs the optimal screening method is not well defined. CT has several attributes that lends itself to screening for IMDs. CT is a key diagnostic modality for IMDs stipulated in consensus guidelines (De Pauw, Walsh et al. 2008) and pulmonary involvement is present in 90% to 100% of patients with IA (Kontoyiannis, Marr et al. 2010; Pagano, Caira et al. 2010; Lortholary, Gangneux et al. 2011; Nicolle, Benet et al. 2011). It is a non-invasive test, widely available and promptly performed when IMD is suspected, with results reported within hours rather than days. However, extracting meaning from CT reports has up until now not been possible.

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Within the hospital setting, clinical reports are a rich source of patient-level information but their use is limited by their free-text, narrative form. Natural language processing (NLP) is a computational method for processing human language that has been applied for the detection of a variety of medical conditions, including pneumonia (Hripcsak, Friedman et al. 1995; Mendonca, Haas et al. 2005), tuberculosis (Knirsch, Jain et al. 1998), medical adverse events (Melton and Hripcsak 2005), vaccination adverse events (Hazlehurst, Naleway et al. 2009), tumours (Imai, Aramaki et al. 2007) and their progression (Cheng, Zheng et al. 2009). To date, NLP has not been used for the detection of IMDs from CT reports. Improved methods of case finding of IMDs is a major element of this thesis. The work herein will describe the development of a classifier that uses NLP, based on machine-learning methods, to flag CT reports supportive of IMDs. As a high-throughput technology, it has the potential to identify CT reports suspicious for IMD, thereby not only facilitating surveillance of IMDs but making it real-time, feasible, sustainable and network-wide.

This thesis, drawing on recent clinical studies, will argue the case for surveillance of the more diagnostically challenging mould diseases and discuss barriers to implementation of surveillance in hospitals. The specific research aims of this thesis are as follows:

- To determine the median hospitalisation cost, lengthof stay (LOS) and consumption of costly antifungal treatment attributable to IFD from a

hospital perspective in high-risk haematology patients using actual hospital costs.

- To determine the relative effectiveness and safety of azole antifungal prophylaxis with particular attention to voriconazole/posaconazole compared to fluconazole/itraconazole in AML/MDS patients undergoing intensive chemotherapy over a 12 year period at the Royal Melbourne Hospital.

- To determine the relative effectiveness and safety of intermittent liposomal amphotericin prophylaxis in haematology-oncology and HSCT patients over 7 years from January 2003 at the Royal Melbourne Hospital.

- To outline the controversies surrounding the use of posaconazole and provide practical clinical recommendations on the role of posaconazole for either treatment or prophylaxis of IFDs.

- To provide clinical recommendations on the design, implementation and monitoring of an antifungal stewardship programme in hospitals.

- To develop a NLP classifier using machine-learning techniques, as a means of enabling real-time biosurveillance of IMDs in patients with haematological malignancies.

Chapters 2 to 5 will review pertinent literature. Specifically, Chapter 2 will describe the current epidemiology of IMDs from recent single and multicentre studies, interpretation of reported incidence rates and reasons for their variability. Chapter 3 will detail the onerous work of surveillance, including controversies surrounding current case definitions for IMDs. Chapter 4 will

document the economic impact of fungal diseases from a health care system perspective. Chapter 5 will discuss the role of automated surveillance systems and NLP, citing key examples from a variety of medical conditions and their relevance to IMDs. Chapter 6 contains results of 3 original research studies and 2 papers elaborating clinical practice recommendations. In detail, Chapter 6 includes the attributable hospitalisation cost of an invasive fungal disease (IFD) in haematology-oncology patients (Ananda-Rajah, Cheng et al. 2011); the effect of changes in azole antifungal prophylaxis on local fungal epidemiology at a major Victorian transplant centre (Ananda-Rajah, Grigg, Downey et al. 2012); a discussion of antifungal prophylaxis strategies currently used at a major Victorian transplant centre focusing on the optimisation of posaconazole (Ananda-Rajah, Grigg et al. 2012) and evaluation of intermittent liposomal amphotericin (Ananda-Rajah, Grigg et al. 2011) and finally closes with a paper on antifungal stewardship which expands findings from an earlier study demonstrating that antifungal drugs comprise a major component of hospitalisation cost (Ananda-Rajah, Cheng et al. 2011) and makes practice recommendations for their oversight (Ananda-Rajah, Slavin et al. 2012). Chapter 7 describes development of a classifier based on machine learning techniques for detection of IMDs using NLP of CT reports from 3 major Victorian hospitals, including the 2 state-wide transplant centres (Ananda-Rajah, Martinez et al. 2012). Finally, a glimpse into the future that leverages the text analytic tool will be explored in Chapter 8.

With increasingly more data being digitally collected in the health care encounter (Larson 2013) or becoming available in databases comes the

opportunity to collect, analyse and exchange health care information. Text analytical tools are a means of unlocking patient-level data for a variety of applications, including data-driven analysis, clinical decision support and knowledge discovery. In clinical mycology, identifying patients at risk for IMDs is the start, but information technology using text analytics and an infrastructure that supports the exchange of data between institutions (Hibbert, Gibbs et al. 2007; Kosmider, Jones et al. 2008; Field, Kosmider et al. 2010) has the scope to deliver translational benefits well beyond surveillance alone.

Chapter 2: Navigating the Epidemiology of Invasive Mould Diseases—Definitions, Denominators and the Impact of Diagnostics

2.1 Fungal Epidemiology: Regional Variation Is the Hallmark

Current studies demonstrate that there is a wide regional variation in the incidence of IFDs in patients with haematologic malignancies ranging from 2% to 48% (Marr, Carter et al. 2002; Lionakis, Lewis et al. 2005; Pagano, Caira et al. 2006; Auberger, Lass-Florl et al. 2008; Malagola, Peli et al. 2008; Cordonnier, Pautas et al. 2009; Hahn, Stifel et al. 2010; Hammond, Marty et al. 2010; Vehreschild, Ruping et al. 2010; Ananda-Rajah, Grigg, Downey et al. 2012; Auberger, Lass-Florl et al. 2012; Neofytos, Treadway et al. 2013). Inter-institutional and regional variability in incidence rates, summarised in Table 2.1, can be attributed to several factors, including patient heterogeneity, differences in clinical (e.g., cytotoxic chemotherapy regimens) or transplantation practices (Kontoyiannis 2010), variable adoption of antifungal prophylaxis (Pollack, Heugel et al. 2011), logistical issues that determine access to diagnostic tools such as NCBTs (Maertens, Theunissen et al. 2005; Girmenia, Micozzi et al. 2010; Morrissey, Chen et al. 2013) or bronchoscopy services (Kontoyiannis 2011), climatic factors (Panackal, Li et al. 2010) or

differences in infection prevention practices (Weber, Peppercorn et al. 2009; Yokoe, Casper et al. 2009; Alangaden 2011).

Table 2.1 Fungal epidemiology from single and multicentre studies, 2010-2013

Patients	Possible IFDs	Probable/ proven IFDs	Lung involvement of IMDs	IFD consensus criteria	Denominators	Incidence rates	Antifungal prophylaxis	Study type	Single or multi-centre study	Duration	Country	Comments	Reference
AML newly diagnosed, n=254	95.4% of IMDs, n=103	Probable 0.9% of IMDs, n=1; proven 3.7% of IMDs, n=4	104 of 108 IMDs	2008	Patients	48.4% overall, IMD 42.5%, invasive candidiasis 5.5%	No unit policy but 7.9% (n=20) received prophylaxis either fluconazole, n=9; voriconazole, n=7; caspofungin, n=4	Retrospective	Single	2004-2010	US	IMDs were overwhelmingly in the possible category	Neofytos, Lu et al. 2013
Variety of haematological malignancies and autologous HSCT recipients, n=146	Possible IFDs, n=16	Probable/ proven IMDs, n=30	All 27 cases of IA had lung involvement	2002	Neutropenic episodes, n=220	21.8% (48/ 220)	Oral polyene; secondary prophylaxis with voriconazole if history of IA	Non-randomised prospective study	Single	2006-2007	Italy	No allo-HSCT recipients; Persistent neutropenic fever or clinical suspicion for IFD triggered an intensive diagnostic work-up (GM for 3 consecutive days but analysed twice weekly, CT chest and investigations as indicated)	Girmenia, Micozzi et al. 2010

Patients	Possible IFDs	Probable/ proven IFDs	Lung involvement of IMDs	IFD consensus criteria	Denominators	Incidence rates	Antifungal prophylaxis	Study type	Single or multi-centre study	Duration	Country	Comments	Reference
Variety of haematological conditions; acute leukaemia 68%, n=27	Not reported	Probable/ proven IFDs, n=27	85%, 23/27	2008	Courses of posaconazole prophylaxis, n=202	13% (27/ 202)	Posaconazole v fluconazole or itraconazole in historical cohort	Retrospective, case-control	Single	2001-2004 vs 2008-2010	Austria	Breakthrough IFD defined as occurrence ≥4 days after initiation of posaconazole prophylaxis; Exclusively non-*Aspergillus* moulds—i.e., *Mucormycetes* in 55% and yeasts in 45%	Auberger, Lass-Florl et al. 2012
AML, newly diagnosed, n=159	Not reported	Probable/ proven IFDs and IA	All cases of probable IA involved the lungs	2002	Number of patients	Breakthrough IFDs: 3.9% (3/ 77) vs 19.5% (16/ 82) & breakthrough IA: 2.6% (2/ 77) vs 13.4% (11/ 82) for posconazole vs historical group respectively	Posaconazole vs topical polyene prophylaxis	Prospective, case-control study using historical cohort	Single	2003-2005 vs 2006-2008	Germany	Breakthrough IFD not defined	Vehreschild, Ruping et al. 2010

Patients	Possible IFDs	Probable/proven IFDs	Lung involvement of IMDs	IFD consensus criteria	Denominators	Incidence rates	Antifungal prophylaxis	Study type	Single or multi-centre study	Duration	Country	Comments	Reference
AML, newly diagnosed; posconazole, n=99 vs topical polyene, n=58	10.3% (control) vs 7.1% (posaconazole)	Probable/proven IFDs: 51.7% (control group) vs 23.2% (posaconazole group); IMDs: 48.3% (controls) vs 16.2% (posaconazole)	IA was the most common IFD (40 of 53, 75.5%). All 27 cases of IA had a documented pulmonary involvement at chest CT	2008	Number of patients	All IFDs: 62.1% (controls) vs 30.3% (posaconazole)	Topical polyene prophylaxis vs posaconazole	Retrospective case-control study	Single	2006-2007 vs 2007-2010	Italy	No specially filtered rooms. GM assay retained major role in diagnosis of IA even in patients on posaconazole. Diagnosis of IA confirmed by GM in 76% of controls vs 87% of posaconazole patients	Girmenia, Frustaci et al. 2012
Acute leukaemia (AML 67.9%, ALL 26.8%, transformed MDS 5.4%) & HSCT patients (autologous n=43, allogeneic n=138); Total n=211	Possible IMDs n=4; inclusion of possible increased incidence from 14.3% to 21.4% in acute leukemia group only	Probable/proven IMDs, n=18	Majority of IMDs localised to lungs but figures not stated	2008	Number of patients	Acute leukemia 14.3%; allo-HSCT 7.2%, auto-HSCT 0%	Fluconazole	Retrospective study	Single	2007-2009	Netherlands	No specially filtered rooms; no IMDs in autologous HSCT patients	Janssen, van der Bruggen et al. 2011

Patients	Possible IFDs	Probable/ proven IFDs	Lung involve- ment of IMDs	IFD consensus criteria	Denominators	Incidence rates	Antifungal pro- phylaxis	Study type	Single or multi- centre study	Duration	Country	Comments	Reference
All patients admitted to a haematology service, n=4078	Not reported	Probable/ proven cases of IA, n=127	93% (118/ 127) had lung involvement	2008	Occupied bed days reported in favour of numbers of patients	1.6/ 1000 over- all; AML 1.9/ 1000; ALL 1.3/ 1000 patient days; incidence per risk group: AML 4.4% (91/ 2078 patients); ALL 2.2% 919/ 850 patients)	Posaconazole prophylaxis introduced 2007	Prospec- tive obser- vational study	Single	2004- 2009	France	Specially filtered rooms (HEPA) in- troduced 2005	Nicolle, Benet et al. 2011
Acute leukaemia newly diag- nosed, AML 76%, ALL 24%, MDS 18%; n=231	Not reported	Probable/ proven cases, n=24 at 100 days after diag- nosis of acute leukaemia; equal numbers of yeast and moulds	6 of 11 patients with IMDs had lung involve- ment	2008	Number of patients	10.4% at 100 days after acute leukaemia di- agnosis	No	Retrospec- tive obser- vational study	Single	2004- 2006	US	Low rate of IFDs relative to many series in patients with acute leukaemia undergoing intensive induction chemo- therapy with similar numbers of mould and yeast infections	Hammond, Marty et al. 2010
Variety of pa- tients: HSCT, SOT, HIV, solid tumour, haema- tological malig- nancy., surgical and general medicine, n=6845 evalu- able patients	Not reported	All IFDs, n=7526; Prob- able 11.6%; proven 88.3%	Not stated	2002	Registry therefore no denominator reported	No	No	Prospec- tive	Multi- centre, 25 sites	2004- 2008	US	*Candida spp* most common pathogen (73.4%), IMDs (17.6%); IA most commonly seen in HSCT recipients (49.5%) and patients with haematological malignancies (35.2%)	Azie, Neofytos et al. 2012

Patients	Possible IFDs	Probable/ proven IFDs	Lung involvement of IMDs	IFD consensus criteria	Denominators	Incidence rates	Antifungal prophylaxis	Study type	Single or multicentre study	Duration	Country	Comments	Reference
HSCT recipients; n=15,820 (autologous HSCT 59%)	Not reported	Probable/ proven IFDs, n=983 in 875 patients comprising IA (43%), invasive candidiasis (28%), and zygomycosis (8%).Incidence of non-*Aspergillus* mould infections was very low (12-month cumulative incidence, 0.3%)	Not stated	2002	Number of transplant patients	Cumulative incidence 12 months from HSCT: 3.4% overall (range 0.9 to 13.2%); IFD incidence lowest among autologous HSCT recipients, 12-month CI of 1.2%. 12-month CIs for MRD, URD and MMR donors were 5.8%, 7.7%, and 8.1% respectively: IFD incidence 3.1% to 20.6% for 6 of the largest sites contributing >20 of the highest risk MMR HSCT	No data	Prospective	Multi-centre, 23 transplant centres	2001-2006	US	Active surveillance but not all case-patients and denominator data was prospectively captured (periodic audits and coding data used)	Kontoyiannis, Marr et al. 2010
Febrile episodes in a variety of	Possible IFDs: 72	Probable/ proven IFDs:	>90% of patients had lung	2008	Registry therefore no	NA	Proven/ probable IMDs in	Hema e-Chart,	Multi-centre,	2007-	Italy	GM played a major role in diagnosis of	Nosari, Caira et al.

Patients	Possible IFDs	Probable/proven IFDs	Lung involvement of IMDs	IFD consensus criteria	Denominators	Incidence rates	Antifungal prophylaxis	Study type	Single or multi-centre study	Duration	Country	Comments	Reference
patients with haematological malignancies undergoing chemotherapy; Fever due to IFD analysed in this series. N=147 patients. AML in 81.6%, >90% neutropenic	of 147 (49%)	75 of 147 (51%) with yeast (n=23) to mould (n=52) ratio of 1:2.2; non-*Aspergillus* moulds rare being 2%	involvement. All possible IFDs and 48/52 (92%) with probable/proven IFDs had lung involvement		denominator reported		29.7% of patients receiving active mould active prophylaxis (itraconazole in n=18, caspofungin in 1 case) & in 39.7% of patients not receiving active anti-mould prophylaxis	prospective	26 haematology units	2009		IA being positive in 75% (27/35) of cases with IA. GM positivity lower in patients with probable/proven IFD on mould active prophylaxis (78.8% in 33 patients not on mould active prophylaxis vs 52.6% in patients on mould active prophylaxis with either itraconazole or caspofungin)	2012
Variety of patients: HSCT, SOT, HIV, solid tumour, haematological malignancies, surgical and general medicine, n=424	Not reported	Probable/proven IA in 393 adults. Proven IA in 15%	92.9% lung. Classical CT signs of nodule, halo and/or cavitation absent in 18% with probable/proven IA	2002	Number of admissions per hospital; numbers of HSCT and SOT recipients	Median incidence 0.271/1000 admissions (range 0.072-0.910). Overall incidence: 8.1% (84/1043) & 0.9% (18/2010) in allogeneic and autologous HSCT patients respectively	Not reported	Prospective	Multi-centre, 12 acute hospitals	2005-2007	France	Inter-institutional variability noted. No seasonal variation in incidence of IA. Underlying haematological conditions in 78%. Major host factors: acute leukaemia 34.6%, allo-HSCT 21.4%, chronic lymphoproliferative conditions (an unexpected finding) in 21.6%—i.e., 35% of haematological associated IA occurred in patients	Lortholary, Gangneux et al. 2011

Patients	Possible IFDs	Probable/ proven IFDs	Lung involvement of IMDs	IFD consensus criteria	Denominators	Incidence rates	Antifungal prophylaxis	Study type	Single or multi-centre study	Duration	Country	Comments	Reference
												with chronic lymphoproliferative disorders of which 67% occurred during second-line therapies	
AML, IA only, n=140	Not reported	Probable/ proven IV, n=140	Lung involved in 90% of cases	2002	Registry therefore no denominator reported	No	72% of 140 on prophylaxis; 67% on itraconazole	Prospective	Multi-centre, 21 haematology units	2004-2007	Italy	Post-induction aplasia the highest risk period. Of the 140 cases of IA, 60% occurred after first induction chemotherapy, 3% after consolidation in patients achieving a complete remission, 36% after treatment for refractory or relapsed AML	Pagano, Caira et al. 2010

2.1.1 Variations in Incidence Reflect Variations in Practice: Single Centre Experiences

A large single centre retrospective observational study reported substantially higher than expected incidence rates for IMDs among 254 adult patients with newly diagnosed AML (Neofytos, Lu et al. 2013). Over a 6-year period ending in 2010, a total of 48.4% (123/254) of patients developed IFD, of which 42.5% had IMD and 5.5% were diagnosed with invasive candidiasis. Among patients with IMDs, 4 (3.7%) were proven, 1 (0.9%) was probable, and the overwhelming majority (95.4%) were considered possible due to the absence of microbiologic confirmation (De Pauw, Walsh et al. 2008). Notably, during this study period antifungal prophylaxis was not routinely used but it is unclear whether the results of this audit prompted a reconsideration of that practice.

At this centre, the decision against using routine antifungal prophylaxis was somewhat puzzling in light of the fact that surveillance of IA using NCBTs was not routine either (Neofytos, Lu et al. 2013). The reliance on conventional diagnostics (culture, microscopy, histopathology and radiology) raises the possibility that the reported rates of IMDs at this centre may have been an underestimate of the true prevalence. Conversely, the reliance on radiologic findings in this study to establish a diagnosis of IMD may have overestimated the true incidence of disease because radiologic features are not pathognomonic for IMDs (Marom and Kontoyiannis 2011).

At this centre, like others (Dignan, Evans et al. 2009; Ananda-Rajah, Grigg, Downey et al. 2012) an early diagnostic approach was guided by suggestive

radiologic findings rather than NCBTs. However, the low recovery of fungal pathogens accounting for the 4 probable/proven IFDs seems unusual for a tertiary centre over a 6-year period, but no information on detection effort such as frequency or timing of lung sampling was provided. The 48% incidence rate of IFDs (Neofytos, Fishman et al. 2013) is not dissimilar to the 36% originally reported in patients receiving high-dose cytarabine-based induction chemotherapy for AML in the era prior to antifungal prophylaxis (Bow, Loewen et al. 1995). However, unlike that early study (Bow, Loewen et al. 1995), a predominance of mould infections rather than invasive candidiasis was seen and is consistent with the shift from *Candida* to moulds species, which has been attributed to the introduction of azole prophylaxis (Pagano, Caira et al. 2007; Ananda-Rajah, Grigg, Downey et al. 2012).

In contrast, another centre that does not use mould-active prophylaxis changed this policy after uncovering a higher than expected rate of IFDs among patients with AML (Girmenia, Micozzi et al. 2010). This was a non-randomised prospective study from 2006 to 2007 that assessed the feasibility of an intensive diagnostic work-up (3 consecutive GM assays and chest CT scan), as opposed to routine screening in patients meeting standard criteria for starting empiric antifungal therapy (i.e., fever refractory to broad-spectrum antibiotics). Consecutive adult patients with a variety of haematological malignancies who underwent chemotherapy or autologous HSCT and developed neutropenia lasting at least 7 days were eligible. Patients did not receive systemic prophylaxis but instead were given topical polyene prophylaxis with oral amphotericin B daily. Of 146 patients, 49 (34%) developed possible/probable

or proven IFDs, which complicated 22% (48/220) episodes of neutropenia. Serum GM was positive in 88.9% of cases of IA and all 27 cases had documented pulmonary involvement by chest CT.

Despite results supporting the use of an intensive diagnostic approach (no undiagnosed cases of fungal infection and no excess mortality with the additional benefit of a reduction in antifungal drug costs), this centre subsequently administered mould-active prophylaxis to their patients with AML (Girmenia, Frustaci et al. 2012). This was in light of the high incidence of IFD in their centre (i.e., IFD complicating 21.8% of 220 neutropenia episodes equating to 49 IFDs in 46 patients, see Girmenia, Micozzi et al. 2010), highlighting the value of prospective surveillance even if in the context of a clinical trial (Girmenia, Micozzi et al. 2010).

Despite the introduction of posaconazole prophylaxis in patients with AML, a higher than expected breakthrough rate of IFD was encountered in this same Italian centre. Breakthrough IFD rates were 51.7% in the historical cohort (n=58) on oral amphotericin B compared to 23.2% among the posaconazole group (n=99) (Girmenia, Frustaci et al. 2012). Of breakthrough infections on posaconazole, almost all pathogens (numbers not reported) remained susceptible to posaconazole *in vitro* possibly due to suboptimal serum levels, as therapeutic drug monitoring (TDM) was not performed. The absence of high efficiency particulate air-filtration (HEPA) filtered rooms may have been another variable contributing to the higher than expected breakthrough rates, emphasising the importance of general measures such as infection prevention

interventions in addition to specific measures such as antifungal prophylaxis. Alternatively, the incidence of breakthrough IFD at this centre may reflect an improved detection effort due to an intensive diagnostic strategy involving cyclical performance of GM serum testing and CT scanning described elsewhere (Girmenia, Micozzi et al. 2010) but this alone seems an unlikely explanation for the high incidence reported.

A small retrospective case-control study examined the effect of posaconazole prophylaxis introduced in 2008 to a single European centre (Auberger, Lass-Florl et al. 2012). Case-patients (n=95) from 2008 to 2010 with a variety of haematological conditions, 68% with acute leukaemia, were compared to a historical cohort (2001 to 2004) with similar underlying haematological diseases who were administered either fluconazole or itraconazole prophylaxis. Using course of prophylaxis as the denominator, the incidence of breakthrough probable or proven IFDs (defined as occurring after 4 or more days of posaconazole prophylaxis) was 13% (27/202) among cases and 12% (62/520) among a historical cohort receiving either fluconazole or itraconazole prophylaxis.

Incidence rates are infrequently reported according to course of prophylaxis as courses may not necessarily reflect independent periods of risk. Therefore, using the more common denominator of patient numbers revealed a breakthrough IFD incidence of 23/95 (24%), after excluding 4 patients diagnosed with IFD prior to initiation of posaconazole prophylaxis. Of concern, among the 62 microbiologically confirmed infections

(probable/proven IFDs), non-*Aspergillus* moulds predominated with *Mucormycetes* in 55% and yeasts (inclusive of *Candida* species, *Trichosporon asahii* and *Geotrichium capitatum*) in 45% raising the possibility of selection pressure induced by prophylaxis with a broad-spectrum anti-mould agent. An alternative explanation may be suboptimal drug exposure in patients due to a lack of posaconazole TDM. This may have been relevant because 17% of patients had severe (≥grade II) graft-versus-host disease (GVHD) (site not specified) requiring corticosteroids ≥1 mg/kg/day, both of which are well-recognised risk factors for IFDs (Baddley 2011).

In contrast, the Cologne group reported a low breakthrough rate of probable/proven IFD among 77 patients on posaconazole prophylaxis while undergoing high-dose cytarabine-based induction chemotherapy for AML (Vehreschild, Ruping et al. 2010). Patients on posaconazole prophylaxis from 2006 to 2008 had a breakthrough IFD rate of 3.9%, compared to a historical cohort (2003 to 2005) with a rate of 19.5% while receiving topical polyene prophylaxis. Absorption concerns did not appear to limit the effectiveness of posaconazole and it was well tolerated with no premature discontinuations due to intolerance documented (Vehreschild, Ruping et al. 2010).

A single centre retrospective study from the Netherlands compared IFD incidence rates in 56 patients receiving intensive chemotherapy for acute leukaemia (comprising AML, 67.9%; ALL, 26.8%; transformed MDS, 5.4%), in addition to 43 autologous HSCT and 138 allogeneic HSCT recipients from 2007 to 2009 (Janssen, van der Bruggen et al. 2011). This centre used

fluconazole prophylaxis but not HEPA filtration nor GM screening. Incidence rates for probable/proven IFDs for acute leukaemia, allogeneic HSCT and autologous HSCT were 14.3%, 7.2% and 0% respectively for each patient group (Janssen, van der Bruggen et al. 2011). Inclusion of possible cases affected the acute leukaemia group only, increasing the incidence from 14.3% (8/56) to 21.4% (12/56) overall. *Aspergillus* species were the most frequently detected pathogens with *Zygomycete* species, *Scedosporium* species, and an unidentified mould also isolated (Janssen, van der Bruggen et al. 2011). Thus, the inclusion of possible cases may greatly affect institutional incidence rates as has is evident elsewhere (Neofytos, Lu et al. 2013).

A prospective surveillance study from a French centre documented the changing incidence of IA from 2004 to 2009 among all haematology-oncology patients (Nicolle, Benet et al. 2011). These authors reported patient days at risk as the denominator and found that IA incidence was 1.6 per 1000 patient days (95% CI: 1.4, 1.9) overall with a slightly linear decrease (16% per year) observed during the study period. IA incidence was 1.9 per 1000 patient days (95% CI: 1.5, 2.3) among AML patients and 1.3 per 1000 patient days (95% CI: 0.8, 2.0) among ALL patients. Incidence decreased in the AML subset (-20% year; 95% CI: -6%,-36%, p=0.005), whereas it did not change among patients with ALL (-19% per year; 95% CI: -5%, +9%, p=0.19) or in patients with other haematologic diseases (+7% per year; 95% CI: -23% +41%, p=0.64). No information on outcomes in HSCT recipients was provided. The denominator cited patient days at risk but in fact reflected hospitalisation days rather than neutropenia days, the latter better reflecting the period of risk in

patients with acute leukaemia. Of note, the incidence of IA in ALL patients was not dissimilar to patients with AML and in contrast to patients with AML, did not decrease over time.

The more frequently reported cumulative incidence or attack rate (Fourneret-Vivier, Lebeau et al. 2006; Kontoyiannis, Marr et al. 2010; Azie, Neofytos et al. 2012) using patient numbers as the denominator showed a reduction in IA incidence among AML patients from 4.9% in 2004 to 2007 to 3.3% in 2008 to 2009 (p=0.04) following the introduction of posaconazole prophylaxis in 2007 (Nicolle, Benet et al. 2011) consistent with other reports (Vehreschild, Ruping et al. 2010; Ananda-Rajah, Grigg, Downey et al. 2012). At this centre, other measures such as specially filtered rooms (HEPA) introduced in 2005, may have contributed to the reduction in IA incidence seen (Nicolle, Benet et al. 2011). No changes in detection practice occurred over the study period with twice weekly GM screening and early CT scanning being standard practice. The original posaconazole prophylaxis trial (Cornely, Maertens et al. 2007) reported an IA event rate in the posaconazole group of approximately 1%, whereas the event rate in this study from 2008 to 2009 was 3.3% in patients with AML (i.e., an absolute reduction of 1.6% versus 6.0% in the RCT) highlighting the differences in clinical effectiveness outside the protocol-driven biases of clinical trials.

A retrospective study (2004 to 2006) from a single centre in the US described IFD incidence among 231 patients with newly diagnosed acute leukaemia comprising patients with AML 76%, ALL 24% and myelodysplastic

syndromes (MDS) 18% (Hammond, Marty et al. 2010). This centre did not use antifungal prophylaxis but instead tested serum GM and beta-D-glucan 1 to 2 times weekly at the onset of febrile neutropenia as part of an IFD surveillance strategy. At the conclusion of follow-up 6 months after study closure, 31 patients developed IFD (31/231, 13.4%), of whom 24 (24/31, 77%) developed IFD in the first 100 days after the diagnosis of acute leukaemia. Variable risk over time was seen with the cumulative probability of developing IFD being 5.9% at 30 days and 11.1% at 100 days after the diagnosis of acute leukaemia but risk persisted with 7 patients diagnosed with IFD beyond 100 days. These 7 patients were actively undergoing chemotherapy at the time of IFD with 4 patients having relapsed disease. Not unexpectedly, patients who failed initial induction were significantly more likely to develop IFD than those who did not have evidence of persistent leukaemia [14/65 (21.5%) versus 15/148 (10.1%), p=0.03]- lack of disease control being a recognised risk factor for IFD (Pagano, Caira et al. 2010; Pagano, Akova et al. 2011). In the absence of systemic antifungal prophylaxis, there was an equal proportion of yeast and mould infections (11 patients each) occurring within the first 100 days after leukaemia diagnosis (Hammond, Marty et al. 2010).

2.2 Reported Rates Either Underestimate or Overestimate the True Prevalence of Mould Diseases

The distinction between possible and probable/proven IMD is important from a surveillance perspective as these entities represent different degrees of diagnostic certainty. In brief, patients with probable/proven IMDs have a

positive microbiological indicator that is either culture or non-culture based (PCR [polymerase chain reaction] is not recognised as a valid diagnostic test for IMDs in current definitions [De Pauw, Walsh et al. 2008]) or histopathological in nature. Patients with possible IFDs lack microbiological confirmation but instead meet clinical and radiologic criteria suggestive of IMD after the exclusion of alternative diagnoses (De Pauw, Walsh et al. 2008). Thus the true burden of IMD may be either overestimated with the inclusion of possible cases or underestimated with their exclusion. The majority of published rates commonly report only probable and proven cases as these represent a high degree of diagnostic certainty. However, possible cases, while infrequently reported (Ananda-Rajah, Grigg, Downey et al. 2012; Neofytos, Treadway et al. 2013) are important from a health care perspective as these patients consume similar resources—i.e., diagnostics and antifungal drugs, as probable or proven cases. As previously seen, possible cases may in fact constitute the overwhelming majority of infections in some settings (Neofytos, Treadway et al. 2013).

Without improved diagnostics the true burden of IMD in patients with haematological malignancies will be underestimated (Hoenigl, Valentin et al. 2010). This hypothesis was recently tested in a small pre- and post-surveillance study over 7-month intervals in 2007 and 2010 following the introduction of twice weekly GM surveillance in patients with haematological malignancies and HSCT recipients (Hoenigl, Salzer et al. 2012). Incidence rates were reported using myelosuppressive courses/hospitalisations as the denominator. The overall incidence rate of IFDs was similar between each period being

27/690 (4.9%) and 24/729 (3.8%) but the introduction of twice weekly GM testing in 2010 increased the diagnosis of proven/probable IFDs 5-fold, with a concomitant decrease in possible IFD diagnoses (proven 7% to 8%, probable 4% to 58% and possible 89% to 38% over respective intervals) (Hoenigl, Valentin et al. 2010). Systemic antifungal prophylaxis (either posaconazole, itraconazole or fluconazole) is poorly described in this study but appeared to be low with 17% (117 of 690) of courses in 2007 receiving antifungal prophylaxis (Hoenigl, Zollner-Schwetz et al. 2011).

2.3 Characterising Populations at Risk for IFDs: Contribution of Multicentre Studies

Multicentre observational studies can highlight trends in fungal epidemiology in response to changing clinical or therapeutic practices. In the absence of denominator data, clinical registries do not provide incidence rates but provide a contemporary picture of fungal epidemiology in a broad population of patients.

The PATH (Prospective Antifungal Therapy Alliance) registry captured probable/proven IFDs from diverse patient groups (e.g., general medicine, haematological malignancy, HSCT, solid-organ transplant [SOT], solid tumour, HIV, or surgical specialties) across 25 centres in North America from 2004 to 2008 (Azie, Neofytos et al. 2012). Because the registry closed in 2008, IFDs were defined according to 2002 (Ascioglu, Rex et al. 2002) rather than the revised 2008 consensus criteria (De Pauw, Walsh et al. 2008). Given its

closure in 2008, the effect of a major change in clinical practice with the introduction of posaconazole, which was licensed for prophylaxis in 2007 following phase III trials (Cornely, Maertens et al. 2007; Ullmann, Lipton et al. 2007) may not have been appreciated.

Despite these limitations, a staggering number of patients were evaluable: 6845 patients with 7526 IFDs (proven: n=6647, 88.3%; probable: n=876, 11.6%; unidentified: n=3, 0.04%) (Azie, Neofytos et al. 2012). Invasive candidiasis was the major IFD in medical (n=3713, 79.8%) and surgical (non-transplant) patients (n=2111, 90.7%), and in those with solid tumours (n=983, 89.2%), while IA was more frequently seen in HSCT recipients (n=274, 49.5%) and haematologic malignancy patients (n=475, 35.2%). Among the moulds isolated, *Aspergillus* species accounted for 72% (1001 of 1385 mould isolates).

The distribution of *Aspergillus* species was relatively similar in all groups except for HSCT recipients and haematologic malignancy patients. Among haematology-oncology patients many *Aspergillus* species were unclassified (44.6% and 48.5% respectively), suggesting that non-culture based methods such as GM might have been used more frequently to diagnose IA in these patients. Indeed, the GM was used in almost half of IA (41.5%, n=399) cases and contributed to the diagnosis of a significant number of moulds other than *Aspergillus* (66%, n=35). Non-*Aspergillus* moulds that share cross-reacting antigens include *Penicillium* species, *Paecilomyces* species, *Alternaria* species, *Cladosporium herbarum*, *Acremonium species*, *Alternaria alternata*, *Fusarium oxysporum*, *Wangiella dermatitidis*, *Cryptococcus neoformans*, *Geotrichum*

capitatum, *Histoplasma capsulatum*, *Rhodotorula rubra*, and, rarely, *Mucormycetes* (Swanink, Meis et al. 1997; Dalle, Charles et al. 2005; Giacchino, Chiapello et al. 2006; Cummings, Jamison et al. 2007; Borras, Rosello et al. 2010).

For mucormycosis, culture and histopathological diagnosis supported the diagnosis in the vast majority of cases (culture in 82.6%, histopathology in 66.9%) because this disease usually demands more aggressive diagnostic investigations. In contrast, the beta-D-glucan test was used in a mere 0.5% of cases of invasive candidiasis (n=24) and IA (n=5). Regarding diagnostic modalities, 25.1% of patients with IA in the PATH alliance were diagnosed using the GM assay and/or biopsy results without culture isolation of *Aspergillus*—emphasising the difficulties in achieving organism recovery of these infections.

Short-term survival at 90 days varied significantly based on underlying patient category (Azie, Neofytos et al. 2012). Lowest survival was seen in HSCT recipients (37.5%) followed by 48.4% in patients with haematologic malignancy and approximately 75% in patients with HIV/AIDS, non-transplant surgical patients and SOT recipients, underlining the fact that that host variables strongly influence clinical outcomes.

2.3.1 Burden of IA is Greatest in Patients with Haematological Malignancies: PATH Registry

Closer examination of the clinical characteristics of 960 patients with probable/proven IA extracted from the PATH registry was revealing (Steinbach, Marr et al. 2012). The most frequent underlying disease was haematologic malignancy (n=464 [48.3%]), of which 268 patients (27.9%) underwent HSCT comprising allogeneic grafts in 72.8%. That IA was more commonly seen in allogeneic than autologous HSCT recipients is consistent with surveillance data from the TRANSNET cohort (Kontoyiannis, Marr et al. 2010). Similarly, the median day post-HSCT that IA was diagnosed was 97 days, which is similar to the median of 99 days found in the TRANSNET surveillance report of 425 cases of IA (Kontoyiannis, Marr et al. 2010). Among patients with haematologic malignancies, IA most commonly complicated AML (144/464, 53.7%) followed by NHL (79/464, 17%), myeloma (79/464, 17%) and ALL (56/464, 12.1%).

For ALL and AML, the association was slightly lower than an Italian registry, which reported that 69% (213/310) of IA occurred in patients with AML and 14% in patients with ALL (Pagano, Caira et al. 2006). That patients with ALL, myeloma and NHL accounted for 46% of the total burden of cases among patients with haematologic malignancies is notable as these are poorly studied groups in comparison to the higher risk patient groups with AML and HSCT recipients.

Overall 12-week survival was not dissimilar in patients with haematologic malignancy and HSCT recipients being 59.6% and 62.4% respectively. Among HSCT recipients, better survival was seen among autologous (71.3%) compared to allogeneic (59.7%) recipients. Of note, 15.1% (145/960 patients) were censored due to loss of follow-up-highlighting the difficulties in capturing even short-term outcomes. The TRANSNET study reported 12-week all-cause mortality rates of 57.5% and a 1-year mortality of 74.6% among HSCT recipients. These studies demonstrate the still significant mortality associated with IFDs despite improvements from historical mortality rates of 80% to 90% (Lin, Schranz et al. 2001).

2.3.2 Italian Multicentre Studies

Several of the observations from the PATH registry were confirmed by an Italian multicentre observational study (Nosari, Caira et al. 2012). In the Hema e-Chart Registry, adult and paediatric patients admitted to 26 Italian haematology units with a new diagnosis of haematological malignancy (acute or chronic leukaemia, Hodgkin's or non-Hodgkin's lymphoma, MDS, multiple myeloma, autologous or allogeneic HSCT recipients) were prospectively registered from 2007 to 2009 into a web-based surveillance system designed to study the infectious epidemiology of febrile events (Pagano, Caira et al. 2010). A subset of patients with fungal diseases was further analysed (Nosari, Caira et al. 2012). Possible IFDs were included resulting in 147 haematological patients, with 72 possible, 35 probable and 40 proven IFDs. Again, a high reliance on GM testing was seen with >75% (27/35) of probable cases diagnosed on GM detection alone. The majority of patients with IFDs had

AML (81.6%) and >90% (133/147) were neutropenic (absolute neutrophil count <0.5X109/L) at the time of symptom onset. Arguably, the registry was skewed towards this population as the trigger for entry was a febrile event in patients with a newly diagnosed haematological malignancy.

Mould-active prophylaxis, while not widely used (present in 39% of 147 patients), was associated with a lower diagnostic yield. Among 33 patients receiving either no prophylaxis or fluconazole, 26 of 33 (78.8%) with probable/proven infections were GM positive, whereas among 19 patients with probable/proven infections diagnosed while on mould-active prophylaxis (itraconazole or caspofungim), only 10 (52.6%) were GM positive.

A prospective registry study from 21 haematologic divisions in Italian hospitals captured 140 cases of proven/probable IA in patients with AML from 2004 to 2007 (Pagano, Caira et al. 2010). All centres performed GM testing twice weekly but whether it was triggered by episodes of fever and neutropenia or as part of routine screening is uncertain. IFDs were defined according to earlier 2002 criteria (Ascioglu, Rex et al. 2002). These investigators used attributable mortality at 120 days to assess outcome, a now outdated endpoint given difficulties in teasing out the competing risks of underlying disease, illness severity, host or treatment-related variables. Of the 140 cases of IA, 85 (60%) occurred after first-line induction chemotherapy, 4 (3%) after consolidation in patients who had obtained complete remission and 51 (36%) after treatment for refractory or relapsed AML. The lung was the most common site involved (126/140; 90%). The overall mortality rate on day 120 was 33% (47/140).

Multivariate analysis confirmed that recovery from neutropenia and AML stage (relapsed/resistant disease having a worse prognosis than AML in remission) were independent prognostic factors for mortality again emphasising the importance of underlying illness severity on treatment outcomes.

During this era, 72% of patients received systemic antifungal prophylaxis with either fluconazole or itraconazole but it was largely ineffective. Approximately two-thirds of patients (67%) developed IA despite prior anti-mould prophylaxis using itraconazole, highlighting the poor effectiveness of this agent for prophylaxis.

2.3.3　French Multicentre Studies

A prospective multicentre surveillance project encompassing 12 acute care French hospitals identified proven/probable IA cases irrespective of underlying disease (Lortholary, Gangneux et al. 2011). This study highlighted the burden of IA in patient groups beyond the well-recognised AML and HSCT populations. Because the study spanned 2005 to 2007, all cases were defined according to 2002 consensus criteria (Ascioglu, Rex et al. 2002). Notably, of 424 cases identified, patients with chronic lymphoproliferative disorders (i.e., lymphoma, myeloma, chronic myeloid leukaemia and others) were a major risk group comprising 21.6% overall, along with patients who had acute leukaemia (34.6%) and allogeneic HSCT (21.4%). Among patients with haematological malignancies, 67% (57/85) of IA had received second-line therapies for malignancy relapse/non-control, suggesting that treatment intensification or

cumulative immune suppression are risk factors for IA. IA was less commonly seen in non-haematology cancer patients with solid tumours (4.3%), SOT recipients (8.7%), systemic inflammatory conditions on high-dose steroids (4.6%) or chronic respiratory diseases (2.3%).

This surveillance study attempted to better define inter-institutional variation by adjusting incidence rates according to patient throughput and number of transplants performed between sites. According to patient admissions per hospital, IA incidence ranged from 0.072 to 0.91 with the overall median incidence of IA being 0.271/ 1000 admissions, without any significant temporal trend or seasonality observed. Differences in these wide incidence rates are presumably due to variations in local clinical or infection control practices, case-mix or patient recruitment but were not further explored in this study.

Other observations were concordant with established epidemiology. Patients with haematological malignances were the highest risk group, accounting for 78% of the total number of cases of IA. Among the 393 adults, 92.9% had lung involvement. For patients with acute leukaemia, IA complicated the induction phase of chemotherapy in 68% (93/136) confirming that it is one of the highest risk treatment phases along with treatment for refractory or relapsed disease (Pagano, Caira et al. 2010; Lortholary, Gangneux et al. 2011). The consolidation phase of therapy was another high-risk period, identified for 27% of acute leukaemia patients, in contrast to other studies that have shown this to be a period at considerably lower risk for IFD (Lewis, Hall et al. 2010; Pagano,

Caira et al. 2010; Lortholary, Gangneux et al. 2011; Ananda-Rajah, Grigg, Downey et al. 2012).

In the subgroups analysis, the incidence was 8.1% among allogeneic HSCT recipients (Lortholary, Gangneux et al. 2011), which is within the range of previous reports (Pagano, Caira et al. 2007; Garcia-Vidal, Upton et al. 2008) with 70% occurring late post-transplant (i.e., >100 days) as reported elsewhere (Kontoyiannis, Marr et al. 2010; Steinbach, Marr et al. 2012). For autologous HSCT, the 0.9% incidence is concordant with the TRANSNET experience (Kontoyiannis, Marr et al. 2010).

Microbiological confirmation using direct examination and culture of clinical specimens was used in a high proportion of patients in this study (Lortholary, Gangneux et al. 2011). Direct exam and culture of clinical specimens was performed in 325 (82.7%) of patients with direct exam being positive in 56% (182/325) of those patients sampled. Culture was positive for 76% of patients overall but lowest in patients with acute leukaemia (53%, 50/95) compared to >88% for the other groups. Although not discussed, the lower culture isolation from patients with acute leukaemia may be a consequence of delayed sampling procedures in patients already exposed to antifungal therapy, as has been described elsewhere (Shannon, Andersson et al. 2010). *A. fumigatus* (79.7%) was the most commonly isolated species. Serum GM detection was a useful diagnostic tool in this setting with 2 positive results recorded in 197 of 345 (57%) patients overall with positivity ranging from 69% in acute leukaemia and allogeneic HSCT to 40%, 26% and 0% in the chronic lymphoproliferative

disorders, SOT and patients with chronic respiratory disease respectively (p $<10^4$). The poor yield of GM in non-neutropenic patients may be a due to differences in pathophysiology of IA between neutropenic and non-neutropenic patients (Stergiopoulou, Meletiadis et al. 2007).

In this study, the 12-week mortality in patients with acute leukaemia was 37.8%, which is consistent with the 33% reported from Italy (Pagano, Caira et al. 2010) and 40.6% among patients with haematological malignancies in the PATH registry (Steinbach, Marr et al. 2012). The 56% overall mortality in allogeneic HSCT recipients is close to the 57.5% rate in the TRANSNET study (Kontoyiannis, Marr et al. 2010) but higher than the 37.6% reported in the PATH Alliance registry (Steinbach, Marr et al. 2012).

2.3.4   TRANSNET

The most comprehensive surveillance study of IFDs to date was undertaken by the TRANSNET consortium, consisting of 23 transplant centres across North America. These centres collectively accounted for 20% of the 80,000 HSCTs performed nationally over the study period. IFDs from HSCT and SOT recipients were captured prospectively from 2001 to 2006 (Kontoyiannis, Marr et al. 2010). Among 875 HSCT recipients, 983 probable or proven IFDs were identified. Mould infections predominated, comprising IA (43%), unspecified moulds, including *Fusarium* and *Scedosporium* (16%) and zygomycosis (8%) with invasive candidiasis accounting for 28% of IFDs. Non-albicans *Candida* species accounted for almost 70% of invasive candidiasis cases consistent with the shift in epidemiology that has been observed since the introduction of azole

prophylaxis (Pagano, Caira et al. 2006). The incidence of non-*Aspergillus* mould infections was very low at ≤0.3%, 12 months following transplant.

Of interest, cumulative incidence 12 months following transplant was only 3.4% (range by site 0.9 to 13.2%), an unexpectedly low figure in light of the population studied. On closer inspection, this low incidence can be explained by that fact that over half (59%) of the denominator of 15,820 patients were the lowest risk group—namely, autologous transplant recipients who had the lowest incidence of IFD (1.2%) among all transplant types. In contrast, the higher risk allogeneic HSCT recipients had rates of IFD ranging from 5.8% in matched-related, 7.7% in unrelated and 8.7% in mismatched-related donor transplants. By strength of numbers, this study was able to stratify risk of IFD according to transplant category: autologous versus allogeneic and within subtypes of allogeneic transplant also.

Incidence rates varied widely among TRANSNET hospitals. The 6 largest study sites, who each contributed >20 mismatched-related allogeneic HSCT recipients, demonstrated a cumulative incidence ranging from 3.1% to 20.6%. Similarly, among 17 sites contributing >20 unrelated allogeneic transplants each, 12-month cumulative incidence was 0 to 14.3%. The investigators acknowledged that there was variability between sites regarding the intensity of diagnostic investigations pursued, which may have accounted for the some of the inter-institutional variability observed but this was not explored in detail. Similarly, other clinical practice factors such as receipt of antifungal prophylaxis would have also affected reported incidence rates but was not

captured. Overall mortality 12 months from IFD onset was uniformly poor being 75% for IA, 72% for zygomycoses and 67% for invasive candidiasis, demonstrating that outcomes for invasive candidiasis are not dissimilar to IMDs.

Given the length of the study, some information on trends was available according to IFD type. The cumulative incidence 12 months following transplant was stable for invasive candidiasis in the 9 consecutive subcohorts of patients from 2002 to 2005. In comparison, the incidence of IA increased steadily from 0.6% in the subcohort that received transplants during the period January–April 2003, to 2.8% in the subcohort that received transplants during the period May–August 2004 falling to lower levels in the last 2 subcohorts. It was conjectured that the increase in IA incidence may reflect changes in transplant related practices (types of transplants, immunosuppression used) performed at high-risk sites, or improvements in the diagnostic tools used for IMDs but again, this degree of detail was not captured. It is notable that the incidence of IFDs did not decrease and in fact appeared to increase transiently especially in centres managing a higher risk (i.e., ≥40% allogeneic transplants) patient population (see Figure 2.1).
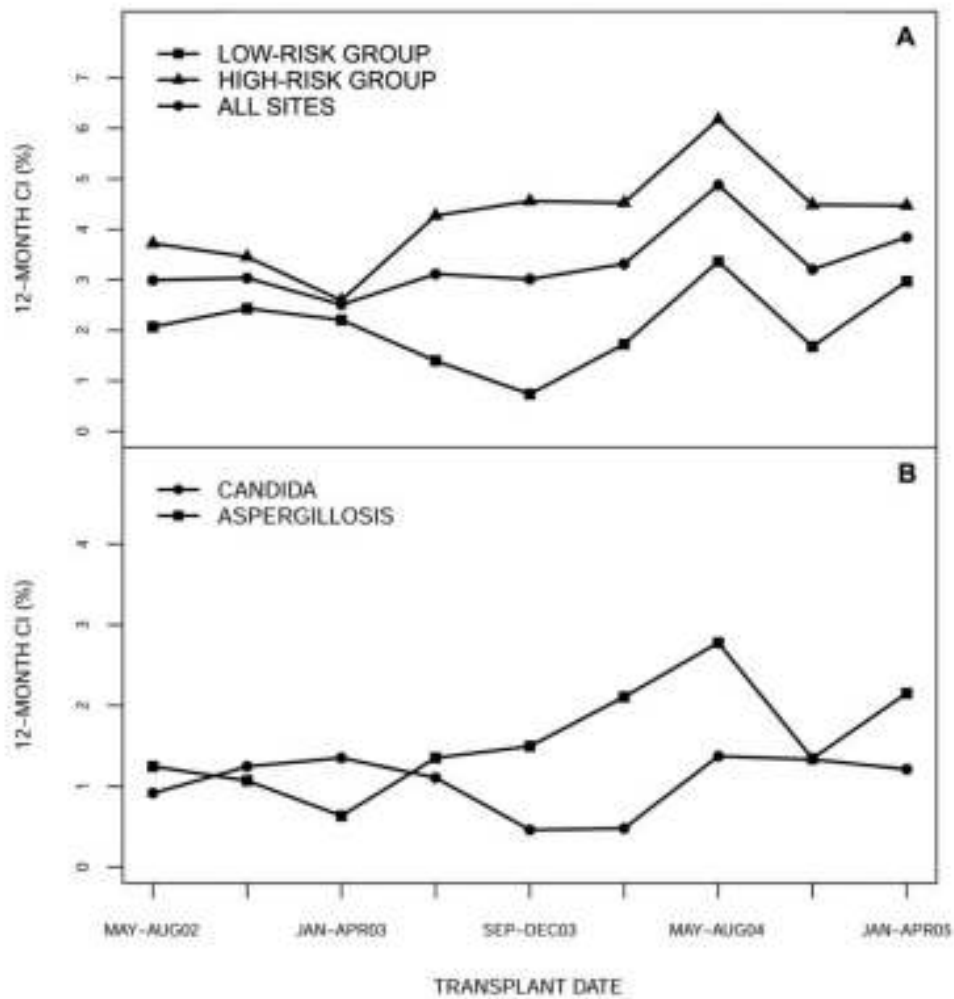
Figure 2.1: Trend in 12-month cumulative incidence (A) for first IFD among each of 9 subcohorts in the TRANSNET cohort, as determined by transplantation date, and stratified by inclusion of the transplant centre into high-risk (>40% allogeneic HSCT recipients) or low-risk (<40% HSCT recipients) groups and (B) for *Candida* and *Aspergillus* infections.
(Kontoyiannis, Marr et al. 2010)

2.4 Emerging Mould Infections

While IA remains the leading cause of mould infection in patients with haematological malignancies (Pagano, Fianchi et al. 2008), infection due to a heterogenous group of uncommon opportunistic fungi is being reported with

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increasing frequency (Bethge, Schmalzing et al. 2005; Kontoyiannis, Lionakis et al. 2005; Naggie and Perfect 2009; Chen, Blyth et al. 2011; Low and Rotstein 2011; Miceli and Lee 2011; Park, Pappas et al. 2011; Skiada, Pagano et al. 2011; Parize, Rammaert et al. 2012; Petrikkos, Skiada et al. 2012). It is unclear as to whether this represents a true increase in disease incidence or reflects improved detection but recent data would suggest the former.

Invasive mucormycosis is the second most common mould infection in patients with haematological malignancies with an incidence ranging from 0.1% to 2.5% in different series (Fukuda, Boeckh et al. 2003; Pagano, Caira et al. 2006; Pagano, Caira et al. 2007; Garcia-Vidal, Upton et al. 2008; Neofytos, Horn et al. 2009; Petrikkos, Skiada et al. 2012; Neofytos, Lu et al. 2013). A recent multicentre French study using administrative data reported an annual increase in the incidence of zygomycosis of 24% per year, in a decade from 1997 to 2006 (p<0.001) (Bitar, Van Cauteren et al. 2009). Possible explanations for this increase include: improvements in clinical management translating into longer survival at-risk following transplant (Pongas, Lewis et al. 2009) and a heightened clinical vigilance for this infection resulting in a more timely and aggressive diagnostic work-up.

The TRANSNET consortium identified 169 non-*Aspergillus* mould infections comprising, 105 *Mucorales*, 37 *Fusarium* species and 27 *Scedosporium* species in 169 patients of which nearly three-quarters (73.4%) were HSCT recipients (Park, Pappas et al. 2011). The 12-month cumulative incidence for mucormycosis was 0.29% among HSCT recipients. As with overall IFD

incidence, mucormycosis incidence among HSCT recipients varied widely between institutions being 0.08% to 0.69% (i.e., 0 cases in 3 sites to 31 or 18.3% of all cases from one site). An increasing incidence was seen over the surveillance period (2003 to 2004 compared to 2002), which was not due to increased numbers of allogeneic transplants performed nor surveillance artefact from improved detection methods because other uncommon mould infections did not increase during this period also (see Figure 2.2) (Park, Pappas et al. 2011).
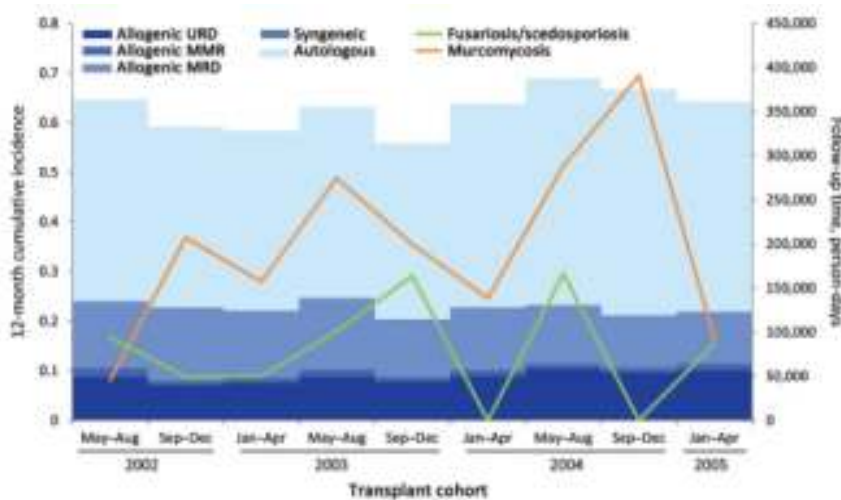
Figure 2.2: Changes in 12-month cumulative incidence for invasive *Mucorales* **infections, compared with** *Fusarium* **and** *Scedosporium* **infections, reported in the TRANSNET cohort, US 2001 to 2005. Changes in the underlying haematopoietic cell transplant population, by transplant type, is shown for comparison. URD (unrelated donor); MMR (mismatched-related donor); MRD (matched-related donor).**
(Park, Pappas et al. 2011)

A recent retrospective French study from 2005 to 2007 identified 101 cases of mucormyosis from administrative and reference laboratory records (Lanternier, Dannaoui et al. 2012). Patients with haematological malignancies had the

highest prevalence in accordance with the results of 2 multicentre studies performed in the same period, which showed that 62% and 44% of patients with mucormycosis had haematological malignancies (Pagano, Valentini et al. 2009; Skiada, Pagano et al. 2011). Haematological malignancies accounted for 50% of underlying disease followed by diabetes in contrast to older series that showed diabetes to be the predominant risk factor (Roden, Zaoutis et al. 2005) again emphasising the changing epidemiology of this infection over time.

Prophylaxis with voriconazole has been implicated in the emergence of mucormycosis (Imhof, Balajee et al. 2004; Siwek, Dodgson et al. 2004; Trifilio, Singhal et al. 2007). However, the increase in mucormycosis was evident before the introduction of voriconazole (Kontoyiannis, Wessel et al. 2000; Marr, Carter et al. 2002) and there was no association between breakthrough mucormycosis and voriconazole prophylaxis in a recent randomised clinical trial of allogeneic HSCT recipients at moderate risk of IFDs (Wingard, Carter et al. 2010). Further, among 179 cases of invasive mucormycosis reported in 4 different case series, 69 were breakthrough infections of which, only 12% occurred after voriconazole prophylaxis (Ambrosioni, Bouchuiguir-Wafa et al.; Pagano, Offidani et al. 2004; Pagano, Valentini et al. 2009; Ruping, Heinz et al. 2009). A recent multicentre study conducted in Belgium from 2000 to 2009 confirmed these single centre observations with no association seen between an increasing incidence of mucormycosis and the prophylactic or therapeutic use of voriconazole (Saegeman, Maertens et al. 2010; Saegeman, Maertens et al. 2010).

While the incidence of non-*Aspergillus* moulds is low, being <0.3% among HSCT recipients 12 months from transplant, mortality rates are high being 56.6% at 90 days in the TRANSNET cohort. Several recent excellent reviews (Quan and Spellberg; Caira, Trecarichi et al. 2011; Chen, Blyth et al. 2011; Petrikkos, Skiada et al. 2012) have covered the clinical, epidemiological and therapeutic aspects of these emerging moulds. All agree that further prospective multicentre surveillance studies are necessary, noting that RCTs may not be feasible nor informative given the rarity of these infections.

2.5   What Effect Does Surviving an IFD Have on Leukaemia Prognosis?

Few studies have examined the effect of IFD on leukaemia prognosis. A recent small retrospective French case-control study of patients with acute leukaemia compared 28 patients with proven/probable IFD who were alive 4 weeks after IFD onset to 78 control subjects matched on key demographic and clinical variables (Even, Bastuji-Garin et al. 2010). Delays in receipt of chemotherapy course occurred in 57.1% of cases and 20.5% of control subjects (p=0.001). This delay was a median of 11 days among cases and 4.5 days in control patients (p=0.0058). The chemotherapy schedule was changed in 68% of cases and 24.4% (p<0.001) of control patients.

There was no significant difference in overall survival (censored at 30 months after study inclusion) and event-free survival (i.e., defined as survival without leukaemia relapse or fungal death) between cases (HR 1.28, 95% CI 0.74–

2.22) and controls (HR 1.30, 95% CI 0.71–2.39). However, for the subset of 11 patients with proven IFD, event-free survival was lower when compared to controls on multivariate analysis (HR 3.4 [95% CI 1.6–7.2], p=0.001). Despite this study being underpowered for survival, it showed that patients who survive IFD encounter significant changes, including delays, drug changes or dose reductions in subsequent chemotherapy therapy. This, in turn, at least for patients with proven fungal disease, may adversely affect survival without leukaemic relapse or fungal related death.

2.6   Summary

The increasing prevalence of cancer and advances in therapeutic practices has resulted in an expanding population at risk for IMDs. More widespread use of antifungal prophylaxis and a longer period of survival at risk have seen the emergence of uncommon fungal pathogens, adding further complexity to clinical management. Since an early consideration of a widening differential of fungal pathogens and initiation of appropriate therapy affects clinical outcomes, the monitoring of epidemiological trends is important because it informs clinical decision making. Due to suboptimal diagnostic tools effective management of these infections is often dependent on clinical acumen which is akin to pre-test probability. Fungal epidemiology especially at an institutional level is an integral element of clinical acumen. Knowledge of local fungal epidemiology, risk factors for acquisition and tissue invasion and the timely and appropriate initiation of antifungal therapy influence clinical outcomes.

However, for multiple reasons, clinical practice is influenced by outdated or fragmented epidemiologic information.

All recent studies demonstrate a wide regional and institutional variability in incidence rates likely due to differences in local practices or factors (Pollack, Heugel et al. 2011). These include use of antifungal prophylaxis, variable diagnostic intensity reflecting the frequency and timing of investigations (Girmenia, Micozzi et al. 2010, (Neofytos, Lu et al. 2013), infection control practices (e.g., filtered rooms, hand hygiene compliance), preference for reporting clinical (i.e. possible) or microbiologically confirmed (i.e. probable/proven) IMDs or geoclimatic factors (Panackal, Li et al. 2010).

Multicentre studies provide an important reference for the current epidemiology and incidence of IMDs but due to limitations in data collection are unable to explain the striking variations in regional epidemiology observed.

Reasons for regional variation are better ascertained by single centre studies, which provide greater detail on case-mix, treatment-related factors, preventative strategies and diagnostic modalities at a patient-level. Thus, single and multicentre studies are complementary towards understanding fungal epidemiology. However, all studies, while striving to provide contemporary insights, fall short due to significant publication/reporting delays. For example, antifungal prophylaxis with posaconazole (Vehreschild, Ruping et al. 2010; Nicolle, Benet et al. 2011; Ananda-Rajah, Grigg, Downey et al. 2012; Girmenia, Frustaci et al. 2012; Hoenigl, Raggam et al. 2012; Steinbach, Marr

et al. 2012) may have contributed to a decrease in IA incidence but at a population level this trend has not yet been described.

Regional variability in the incidence of IMDs is the hallmark of recent epidemiological studies. IMD incidence varies according to underlying haematologic disease being between 4% and 42% in acute leukaemia patients (see Table 2.1) and for IFDs, between 8% and 20% in HSCT recipients (Caira, Girmenia et al. 2008; Kontoyiannis, Marr et al. 2010). Further, studies reporting only microbiologically confirmed infections (i.e., proven/probable IMDs) likely underestimate the true burden of IMDs given the exclusion of possible cases and the fact that current culture and histopathological methods are not highly sensitive. Falling autopsy rates only compound difficulties in establishing true IFD prevalence (Lewis, Cahyame-Zuniga et al. 2013). Interpretation of reported incidence rates is further complicated by inconsistent denominators and numerators (with the inclusion of possible cases being important), incomplete information on preventative strategies such as antifungal prophylaxis or specially filtered rooms, lack of clear definitions on what constitutes breakthrough infections in patients administered antifungal prophylaxis and a lack of information on detection effort/diagnostic aggressiveness.

Details regarding which diagnostic modalities are used (e.g., NCBTs, CT scan, lung sampling) and the frequency of their use (i.e., whether they are used as screening tools in high-risk patients or only when there is clinical suspicion of disease) is important. These represent measures of detection effort for IMDs

and will influence the diagnosis and thus reported incidence of IMDs. In the TRANSNET cohort, the diagnosis of IFD (including invasive candidiasis) among HSCT recipients was proven in 56% of cases (Kontoyiannis, Marr et al. 2010), whereas it was 88.3% in the PATH registry cohort (Azie, Neofytos et al. 2012). The latter group reported that the use of GM assay (GM in serum and/or bronchoalveolar lavage) contributed to 73% of IA diagnoses in HSCT recipients (Azie, Neofytos et al. 2012) but its contribution to diagnosis in the TRANSNET cohort is not stated.

Importantly, without highly sensitive diagnostic tools or an aggressive diagnostic approach employing the timely use of lung sampling, studies reporting only microbiologically confirmed proven/probable IMDs underestimate (Hoenigl, Valentin et al. 2010) true prevalence. The converse may apply for those studies that report possible cases because a subset of these patients may not have an IMD because radiological features are not specific for IMD. Despite these limitations, patients with possible IMDs are important from a health care standpoint because they consume similar resources (i.e., antifungal drugs, diagnostics) to patients with higher degrees of diagnostic certainty and are representative of real-world practice. It is worth noting that for possible IMDs, studies citing older criteria (Ascioglu, Rex et al. 2002) may tend to overestimate true IMD incidence compared to studies using the stricter, updated definitions for IMDs (De Pauw, Walsh et al. 2008).

Patients with haematological malignancies carry the greatest burden of IMDs. Although the majority of research has focused on selected groups, specifically

patients with AML and HSCT recipients, it is clear that patients outside these high-risk categories, including patients with heavily treated chronic lymphoproliferative disorders (Lortholary, Gangneux et al. 2011) or myeloma (Nucci and Anaissie 2009), have a substantial burden of IFD that is currently underappreciated.

While improvements in short-term mortality of IA, the most common IMD, are encouraging, it remains substantial. The case-fatality rate for invasive pulmonary aspergillosis has progressively decreased from 86% in a review of 1223 cases from 1972 to 1995 (Denning 1996) to 60% in studies published from 1995 to 1999 (Lin, Schranz et al. 2001) and to 33% to 43% in more recent reports (Nivoix, Velten et al. 2008; Nucci, Nouer et al. 2010; Lortholary, Gangneux et al. 2011; Steinbach, Marr et al. 2012). This consistent survival benefit has coincided with the introduction of better diagnostics (HRCT, NCBTs), more effective antifungal agents and better supportive care (Gooley, Chien et al. 2010). Little is known about the effect of IMD on a long-term leukaemia cure, but limited data would suggest that it may adversely affect leukaemia prognosis due to modifications or delays in curative chemotherapy (Even, Bastuji-Garin et al. 2010; Michallet, Benet et al. 2012).

Choice of denominator for reporting purposes is very important. Commonly used denominators are patient numbers and hospitalisation or myelosuppressive courses noting that cancer patients typically have multiple hospitalisations/treatment cycles. A patient-level approach reporting IMD according to numbers of patients obviates the assumption that periods of risk

are independent episodes, which may not be the case when the cumulative of effects of immunosuppression (a poorly quantified entity) are taken into account (Pagano, Akova et al. 2011). By reporting rates at the patient-level in specific patient groups (acute leukaemia undergoing intensive chemotherapy, myeloma patients, autologous versus allogeneic HSCT recipients), a 'risk per patient' rather than risk per chemotherapy cycle emerges. This may be more informative to clinicians when deciding on preventative strategies for specific patients starting their cancer treatment journey.

The variability in inter-institutional incidence of IMD and demand for contemporary data means that centres should become familiar with their local epidemiology, ideally through prospective surveillance in order also to keep pace with increasingly complex therapeutic practices. Interpreting epidemiology should take into account multiple variables, including transplant practices, geography, seasonality, host and diagnostic practices between centres, bearing in mind that this level of detail can not be captured in multicentre studies. Perhaps a new paradigm is needed? An investment in a data infrastructure with automated data collection (Nguyen, Moore et al. 2011; Nguyen, Moore et al. 2012; Rolka, Walker et al. 2012) could deliver the breadth of multi-site studies with the depth of single centre experiences, thereby delivering contemporary, prospectively collected epidemiological data with patient level detail (Pagano, Caira et al. 2009).

Chapter 3: The Work of Surveillance: Barriers and Challenges

3.1   Introduction

Surveillance is a core activity of infection prevention programs in hospitals. The overriding goal of surveillance is to reduce the morbidity and mortality of adverse health related events such as nosocomial infections (Tokars, Richards et al. 2004). Surveillance is defined as 'the ongoing, systematic collection, analysis, interpretation and dissemination of data regarding a health related event for use in public health action to reduce morbidity and mortality and to improve health' (German, Lee et al. 2001). The Study on the Efficacy of Nosocomial Infection Control (SENIC) and several subsequent studies have shown that institutions with active surveillance programs have lower rates of nosocomial infections (Haley, Culver et al. 1985; Jarvis 2003).

Surveillance systems require the following basic elements: a clear case definition, a defined population and mechanisms for reporting, analysing and disseminating the data. The standard approach to surveillance is for trained infection control staff to identify and report infections based on specific definitions and surveillance methods. However, conventional surveillance is labour and time intensive, approaches to case finding may be variable between institutions, inter-observer variability in applying case definitions is a common problem despite training of staff (Klompas 2010; Lin, Hota et al. 2010) and the

uniform intensity of effort necessary to ensure complete high quality data collection is difficult to sustain over time (Bolon, Hooper et al. 2009). Because of these limitations there is a growing interest in alternative surveillance methods that deliver data quality while minimising cost and effort thereby allowing resources to be directed towards prevention rather than data collection.

Automated or electronic surveillance of infectious diseases is the process of obtaining information from inter-related electronic databases for identifying infection distributions within a particular setting (Wright, Perencevich et al. 2004). With increasing amounts of electronic data routinely collected during health care encounters, the role of automated surveillance is being increasingly explored (Klompas, Haney et al. 2008; Leal and Laupland 2008; Klompas and Yokoe 2009; Lazarus, Klompas et al. 2009; Lin, Hota et al. 2010; Murff, FitzHenry et al. 2011; Elkin, Froehling et al. 2012). Automation of surveillance activities is consistent with the CDC's desire to streamline surveillance practices using the best available technology (Rolka, Walker et al. 2012).

Using patient level data in existing hospital databases is central to modernising surveillance practices (Rolka, Walker et al. 2012) but there are challenges that need to be addressed. These include access to data sources, standardisation of data elements, data messaging using secure methods and developing the tools necessary for data analysis and feedback of meaningful outcomes to end-users (Tokars, Richards et al. 2004; Rolka, Walker et al. 2012).

The challenges and shortcomings of conventional surveillance of IMDs will be discussed further and opportunities for innovation and improvement will be highlighted.

3.2 Traditional Methods of Surveillance: Clinical Review, Administrative Data, Laboratory-based Processes

Although several authorities have called for surveillance of IMDs (Ellis, Marriott et al. 2000; Tablan, Anderson et al. 2004; Writing Group of the British Committee on Standards in Haematology 2008) and some jurisdictions have made nosocomial IA a mandatory reporting requirement in hospitals (Fourneret-Vivier, Lebeau et al. 2006), the most effective and efficient method for surveillance remains unanswered. Traditional surveillance methods involve prospective or retrospective case finding, laboratory reporting or the use of administrative data- all of which have significant shortcomings.

3.2.1 How Long Does Manual Bedside Review Take?

Few studies have quantified the work of surveillance in the immunocompromised host population. A German study prospectively gathered information on the occurrence of nosocomial infection among patients with haematologic disease (Dettenkofer, Ebner et al. 2003). They recorded all nosocomial infections acquired by 351 HSCT recipients over a 54-month period at a single centre during their period of hospitalisation. Neutropenia was a major risk period being associated with 72% of infections. Nearly two-thirds

of infectious episodes (68%) were blood stream infections (BSIs) or pneumonia.

Given the high clinical burden associated with these infections, a follow-up study was performed targeting only BSIs and pneumonia complicating neutropenia as a means of minimising the time and labour costs of surveillance (Dettenkofer, Wenzler-Rottele et al. 2005). This study involving neutropenic patients undergoing HSCT from 18 hospitals in Germany, Austria and Switzerland found a wide variation in time required to perform surveillance—i.e., data collection, documentation and analysis. Duration of surveillance ranged from 2.1 to 5 hours per 10 beds per week possibly due to differences in the expertise of infection control staff. It is noteworthy that even targeted surveillance of 2 conditions with the greatest clinical burden (i.e., pneumonia and BSI) was not substantially easier, taking on average 3.5 hours per week, compared to their earlier study (Dettenkofer, Ebner et al. 2003) encompassing all infections, which required 5 hours per 10 beds per week (Dettenkofer, Wenzler-Rottele et al. 2005).

3.2.2 Screening for Mould Diseases: Where Should Surveillance Start?

An observation pertinent to surveillance of IMDs was made in the surveillance study of nosocomial infections in immunocompromised haematology patients (Dettenkofer, Wenzler-Rottele et al. 2005). In 70% of pneumonia cases, no pathogen was isolated prompting the authors to advocate the use of chest imaging findings (chest radiography and CT) in combination with clinical symptoms as a means for case ascertainment (Dettenkofer, Wenzler-Rottele et al. 2005). Their qualification that clinical signs may be muted in neutropenic

patients (Carlisle, Gucalp et al. 1993; Legrand, Max et al. 2012) only adds weight to the role of radiological features to support the diagnosis of pneumonia. Similar observations were noted in a smaller prospective study from a single centre documenting nosocomial infections in patients with haematological malignancies (Engelhart, Glasmacher et al. 2002). Again, BSIs and pneumonia were the most common infections accounting for 43% and 34% respectively of the 44 nosocomial infections identified over the 8-month surveillance period. No aetiologic agent was isolated in the majority of pneumonias (being identified in only 5 of the 15 cases) partly due to the early institution of empiric therapy. Therefore, the diagnosis of pneumonia was primarily based on radiographic and clinical features (Engelhart, Glasmacher et al. 2002).

These studies provide lessons relevant to the surveillance of IMDs. Because IMDs predominantly affect the sino-pulmonary tract (see Table 2.1) it seems reasonable in this population to focus attention on chest and/or sinus imaging findings when screening patients for these infections.

3.2.3 Multidisciplinary Teams, Complex Case Definition and Multiple Data Sources Make Surveillance for Mould Diseases Burdensome for Hospitals

Active prospective surveillance of IMDs is a burdensome activity. A prospective study of IA from a French centre described the performance of case ascertainment in detail (Nicolle, Benet et al. 2011). Data was collected on standardised forms with multidisciplinary validation of IA cases by experts

using standardised but complex international definitions (De Pauw, Walsh et al. 2008). Case ascertainment relied on multiple data sources, including survey of haematologists, prospective surveillance of health care associated infections in addition to notifications from the mycology laboratory. Multidisciplinary meetings were held monthly consisting of at least 1 clinician, 1 mycologist and 1 infection control preventionist and this effort was sustained over the 6-year study period (Nicolle, Benet et al. 2011).

Similarly, an earlier French study over a 3-year period from 2000 described the process by which a 2005 bed tertiary transplant centre undertook epidemiological IA surveillance as is mandatory in France (Fourneret-Vivier, Lebeau et al. 2006). A multidisciplinary validation committee composed of infection control physicians, microbiologists and clinicians used multiple sources of data for IA case finding. Laboratory notifications of positive microbiological indicators such as culture, histopathology or NCBTs were sent to the clinician who only reported cases *with suggestive radiological features* such as the halo sign, air-crescent or a positive histological result. Clinical data, including host characteristics, microbiological and histopathological diagnoses were collected by the clinician and the microbiologist and all cases were reviewed on a monthly basis by the multidisciplinary committee who classified cases according to consensus criteria (Ascioglu, Rex et al. 2002). Notably, this cumbersome process was part of routine hospital operations but the authors pointed out that no standardisation of epidemiological surveillance exists in France or elsewhere.

Of interest, at this centre, the incidence of nosocomial IA (proven and probable cases) was 0.6 cases/100 000 patient days (95% CI 0.2–1.0) for the whole hospital and 0.17 cases/1000 patient days (95% CI 0.02–0.32) in the haematology units (Fourneret-Vivier, Lebeau et al. 2006). Although the haematology unit had the most cases of any single unit [n=32 of 74 (43%)], the majority of cases [n=42 of 74 (57%)] were found in other units such as intensive care, respiratory medicine, infectious diseases and internal medicine underlining the burden of IA in non-haematological patients. This unexpected distribution of cases prompted the authors to suggest that the entire hospital should be considered for surveillance with special attention paid to high-risk units, but there was no discussion as to how this should occur (Fourneret-Vivier, Lebeau et al. 2006).

The original TRANSNET publications (Kontoyiannis, Marr et al. 2010; Pappas, Alexander et al. 2010) provided another perspective on the burdensome nature of active prospective IFD surveillance. Investigators received information from attending clinicians, participated in clinical rounds and reviewed clinical microbiology, serology, medical, and pathology records on a weekly basis. At each site, data were entered onto standardised forms that were forwarded to the coordinating centre. A data review committee reviewed each case to determine validity and inclusion into the study. Additional information from a single TRANSNET participating centre provides greater detail (Chang, Burwell et al. 2008). At this site, TRANSNET investigators received information from attending physicians and pharmacists, participated

in clinical rounds and infection control meetings, and identified cultures positive for *Aspergillus* species from the microbiology database.

Despite these rigorous efforts, TRANSNET investigators also used ICD-9 codes after January 2004, 3 years after study commencement, to capture cases missed by the aforementioned methods (Kontoyiannis, Marr et al. 2010). Further, an internal audit of a subset of randomly selected HSCT recipients from study sites who were not identified as having an IFD revealed a small number of additional IFD cases (<5% of the total TRANSNET cases) (Kontoyiannis, Marr et al. 2010). Thus, despite best efforts on behalf of multidisciplinary teams, using multiple data sources at considerable expense, cases were still missed.

Similar concerns in ensuring complete case capture of patients with IFDs were raised by PATH registry investigators (Steinbach, Marr et al. 2012). This was a passive reporting model with each of the 25 participating centres encouraged to enrol all consecutive patients with IFD. However, there was variability in the screening process at each centre with one centre contributing 22% of cases while another contributed less than 1% (range 2 to 213 patients per site) and complete case capture even at high-enrolling centres could not be assured (Steinbach, Marr et al. 2012).

3.2.4 Summary: Challenges Faced by Hospitals Implementing Surveillance of Mould Diseases

The experiences from France and elsewhere, illustrate some of the challenges faced by hospitals for IMD surveillance:

- No standardised method for conducting epidemiological surveillance exists.

- It is costly to perform, being a highly labour and time intensive process.

- Targetted surveillance of key clinical syndromes such as pneumonia has a marginal benefit on reducing the time spent on case ascertainment and data collection (Dettenkofer, Wenzler-Rottele et al. 2005).

- Pneumonia is a major infectious complication in haematology-oncology patients and attention to chest imaging findings is important for its detection given the poor yield from microbiological investigations.

- Multiple sources of data (e.g., laboratory alerts, radiological features, survey of attending clinicians, coding data) are required for complete case capture.

- Classification of cases requires adjudication by a multidisciplinary team using complex case definitions that were principally intended for clinical trial recruitment (Ascioglu, Rex et al. 2002; De Pauw, Walsh et al. 2008). The complexity of these definitions makes them prone to misclassification errors requiring in practice, the need for teams of experts to adjucate the presence of disease.

- The burden of IMDs, in particular IA, has a wide distribution not only affecting patient groups with well-recognised risk factors (i.e., intensive chemotherapy for AML or HSCT recipients) but patients with chronic

lymproliferative disorders (Lortholary, Gangneux et al. 2011) and non-haematological patients in whom the burden of disease is currently underappreciated due to the lack of surveillance in these groups (Fourneret-Vivier, Lebeau et al. 2006; Pappas, Alexander et al. 2010; Lortholary, Gangneux et al. 2011).

In summary, active surveillance of IMDs is a painstaking and costly process requiring case ascertainment from multiple data sources and involving the application of complicated definitions by clinical experts.

3.3 Laboratory Notifications and Administrative Data for Fungal Surveillance: Readily Available Data Sources with Significant Limitations

3.3.1 Poor Sensitivity of Current Diagnostic Tests Make Laboratory-based Surveillance Unsuitable for Mould Diseases

IMDs lack an easily identifiable laboratory prompt because conventional culture/histopathology has a low yield and patients may be too unwell to undergo invasive diagnostic procedures. For *Candida*, non-invasive tests such as blood cultures are negative in approximately 50% and 30% of patients with biopsy-proven disseminated and single-organ candidiasis respectively (Berenguer, Buck et al. 1993). This means that blood sampling will miss *Candida* infection in up to 50% of patients with documented disease.

Arguably, monitoring IA is more challenging than invasive candidiasis due to the lack of a reliable laboratory alert (Ostrosky-Zeichner 2012). Diagnosis of IA is based on a constellation of clinical, radiologic and laboratory features (when available). Negative blood cultures are the rule for IA even in the case of disseminated disease (Barnes and Marr 2007), hence positive microbiological evidence relies on either culture, histopathology and NCBTs such as GM and PCR (Horvath and Dummer 1996; Barnes 2008). The sensitivity rates of sputum, BAL and tissue cultures for the diagnosis of pulmonary IA have ranged between 15% to 69%, 0% to 67%, and 30% to 52% respectively (Bodey, Bueltmann et al. 1992; Reichenberger, Habicht et al. 1999; Tarrand, Lichterfeld et al. 2003).

The use of more sensitive diagnostic tests such as GM and/or molecular assays may significantly increase diagnostic yield and hasten the diagnosis of IA (Pfeiffer, Fine et al. 2006) but have a diminished sensitivity in the presence of concomitant mould-active antifungal therapy (Marr, Balajee et al. 2004). A meta-analysis of 27 reports of serum GM demonstrated an overall sensitivity of 71% and a specificity of 89% when studied against proven cases of IA in mostly patients with haematological malignancy and/or HSCT recipients (Pfeiffer, Fine et al. 2006). Similarly, a meta-analysis of 16 studies of PCR-based assays demonstrated sensitivity for 2 positive results of 75% and a specificity of 87% in patients with probable/proven IA (Mengoli, Cruciani et al. 2009). However, PCR-based tests for *Aspergillus* are not yet standardised.

On the occasion when histopathologic analysis is performed, it may not be possible to distinguish *Aspergillus* species from other filamentous fungi (Hope, Walsh et al. 2005). Further, failure to identify the fungal organism does not necessarily denote an absence of disease (i.e., poor test sensitivity) due to factors such as sampling error or fastidious growth characteristics of the organism (Hope, Walsh et al. 2005; Barnes and Marr 2007). For bronchoscopy, variation in technique such as volume of lavage fluid instilled or methods of fluid recovery (Albelda, Talbot et al. 1984; Reichenberger, Habicht et al. 2002; Bergeron, Porcher et al. 2012) also affect diagnostic yield. Species discrimination, which is important for choice of antifungal treatment, typically requires culture isolation (Wengenack and Binnicker 2009), which for *Aspergillus* species may take several days to weeks (Hope, Walsh et al. 2005). These factors are responsible for the fact that microbiology for *Aspergillus* and hyaline moulds is positive in <50% of IMD cases (Denning, Marinus et al. 1998).

3.3.2 Diagnostic Aggressiveness is a Process Measure That Affects Reported IMD Incidence Rates

Establishing a diagnosis of IMD is dependent on diagnostic intensity reflecting the frequency and timing of investigations such as NCBTs, HRCT or lung sampling. Diagnostic yield of investigations for IMDs is highly dependent on their timing. For patients with suspected IMDs, fiberoptic bronchoscopy (FOB) is an important investigation for isolation of fungal organisms but the diagnostic yield of this invasive procedure diminishes with delays in referral and the initiation of empiric antifungal therapy. This was recently confirmed in

the largest case series of HSCT patients (n=501) who underwent FOBs (n=598) for investigation of new pulmonary infiltrates in the first 100 days post-HSCT (Shannon, Andersson et al. 2010).

The overall yield of bronchoalveolar lavage (BAL) for clinically significant pathogens (fungal, bacterial and viral) was 55%. This is notable in light of the near universal use of concomitant antimicrobial therapy, suggesting that it is still worthwhile performing BAL despite the institution of antimicrobial treatment. Timing of FOB was critical to recovery of the aetiological organism with FOBs performed within the first 4 days of symptom onset associated with a 2.5 fold greater yield compared to late examinations (p<0.0001). Although diagnostic yields were lower for patients with GVHD, neutropenia and diffuse infiltrates, as has been described elsewhere (Gruson, Hilbert et al. 2000; Boersma, Erjavec et al. 2007), it was still 2 to 4 fold higher if FOB was performed early (Shannon, Andersson et al. 2010).

Supporting early FOB exam was its association with improved short-term survival. Late examinations were associated with a higher 30-day and 100-day pulmonary mortality irrespective of FOB guided adjustments in antimicrobial therapy (see Figure 3.1) (Shannon, Andersson et al. 2010). The 30-day pulmonary mortality among patients with a positive diagnosis of infection was 6% compared to 14% among those undergoing late FOBs (p=0.0366). The most frequent infectious diagnoses leading to death were fungal, polymicrobial and multi-drug resistant pneumonias. Together, these pneumonias accounted for 53% of fatal pneumonias at 30 days and were more common in the late

FOB group (64 versus 24%, p=0.0004). These pathogens were also the most frequent cause of all fatal pneumonias at 100 days following FOB, accounting for 57% of deaths in this group of patients.

Thus, FOB should be regarded as a key diagnostic tool rather than a default intervention when HSCT patients appear to be failing empiric therapy as delays compromise its diagnostic utility, which in turn may affect survival. This study also highlights the effect of those unquantifiable institutional factors such as differences in diagnostic aggressiveness and logistical issues on IMD detection. Clinicians need to consider the diagnosis, order the appropriate investigations that need to be done in a timely fashion, recognising that some key diagnostic tools like NCBTs may not be available on-site (Ellis, Marriott et al. 2000)-all these factors affect microbiological confirmation and subsequent IMDS reported rates.
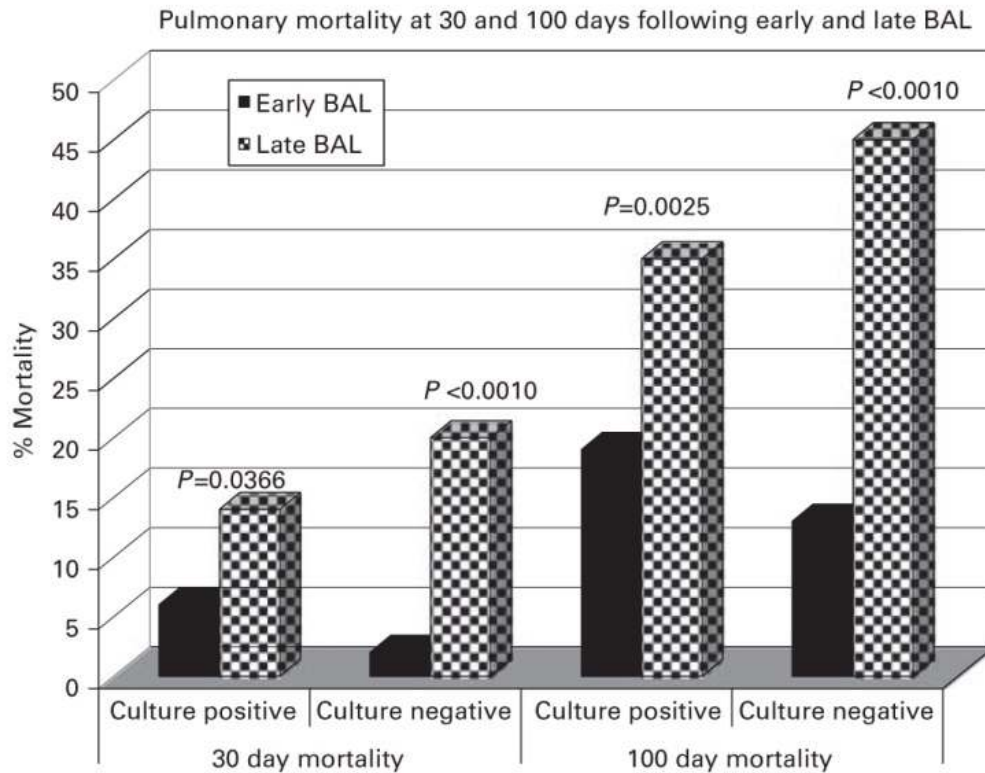
Figure 3.1: Pulmonary mortality at 30 and 100 days following early and late bronchoalveolar lavage (BAL). Significantly lower mortality rates were observed when a diagnosis of infection was confirmed by early FOB (black bars) compared to late examinations (checkered bars). Early culture-negative FOBs were also associated with lower mortality rates compared to late culture-negative exams. These findings were true for both 30- and 100-day mortality rates.

(Shannon, Andersson et al. 2010)

The effect of changes in diagnostic practices was explored in a retrospective study from a large US centre of HSCT recipients from 2000 to 2009 (Neofytos, Treadway et al. 2013). The overall rate of IMD was low being 0.2% (2 of 874) and 3.8% (42 of 1109) in autologous and allogeneic HSCT recipients respectively. Rates of IMD and IA among HLA-matched unrelated and haploidentical allogeneic HSCT recipients increased from 0.6% annually to 3.0% (p=0.003) and 2.0% (p=0.04) after 2005 respectively (see Figure 3.2),

coinciding with the introduction of routine bronchoscopy in patients with new respiratory tract symptoms and abnormalities on CT. Importantly, these rates likely underestimate the true incidence because the use of GM was limited until late 2009 and diagnosis until then was based on non-antigen culture based tests (Neofytos, Treadway et al. 2013).
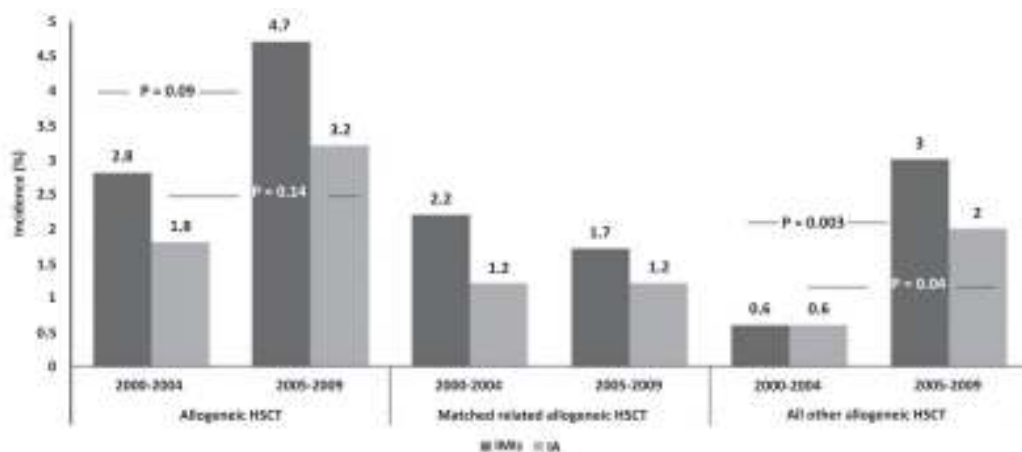
Figure 3.2: Rates of IMDs overall and IA by type of haematopoietic stem cell, between 2000 to 2004 and 2005 to 2009. Sites of infections were not mutually exclusive. Patients could have >1 site infected. HSCT, haematopoietic stem cell transplant; MR, matched-related.
(Neofytos, Treadway et al. 2013)

3.3.3 Summary: Suboptimal Tests and Variability in Diagnostic Practice Limit the Benefit of Laboratory-based Surveillance for IMDs

For many reasons microbiological diagnosis of IMDs is difficult. Several factors, including the poor sensitivity of current diagnostic tests, a reluctance to subject high acuity patients to potentially risky invasive procedures, variation in the availability of diagnostic resources and differences in diagnostic

aggressiveness, affect microbiological yield, rendering laboratory-based surveillance of IMDs subject to significant underreporting.

3.4 Administrative Data: A Readily Available Source of Data but Unsuitable for Hospital Surveillance of Moulds Due to Its Poor Sensitivity and Retrospective Nature

3.4.1 Coding Data and IA

Although administrative data has inherent limitations, it is appealing for surveillance purposes as it is a readily available, easily accessible and routinely captured source of data. Few studies have examined the validity of coding data for fungal surveillance. Chang et al. (2008) compared case ascertainment of probable/proven IA in SOT and HSCT recipients using ICD-9 codes to active prospective surveillance at a site participating in the TRANSNET network. Over a 5-year period, 64 cases of proven/probable IA were identified from ICD-9 codes, of which only 16 (25%) satisfied consensus criteria (Ascioglu, Rex et al. 2002) for proven/ probable IA. An additional 3 patients were identified using methods employed by TRANSNET. However, of the 67 cases in total, 48 (72%) did not met consensus criteria for probable/proven IA, had alternative diagnoses or no infection. Individual codes had poor to modest sensitivities ranging from 32% [95% CI, 13%-57%] to 63% [95% CI, 38%% to 84%] but sensitivity improved when codes were combined (84%, 95% CI, 60%-97%).

Despite this improved sensitivity, the combination of codes was poorly predictive of probable/proven IA with a positive predictive value (PPV) of 30% (95% CI, 18%-44%). For allogeneic HSCT recipients, coding data alone underestimated 1-year cumulative incidence rates being 3.2% (6 of 184) when, after pooling methods, it was actually 4.8% (9 of 184) (Chang, Burwell et al. 2008).

The authors believed that coding data may be a useful method of IA surveillance. However, it could be argued that for an infrequent event, coding data alone is not a suitable screening tool given its sensitivity, at best, of only 84% would result in many missed cases (Chang, Burwell et al. 2008). It is likely that misclassification errors occurred as codes are usually not assigned by clinicians but rather non-medical administrative staff who may not be able to interpret all the relevant information in the medical record. Additionally, coding data does not allow for real-time surveillance being collated several weeks after the clinical encounter nor provide information on place of onset (e.g., location within the hospital) or whether the IMD pre-dated hospitalisation or was hospital-acquired (Bahl, Thompson et al. 2008; Stevenson, Khan et al. 2008).

3.4.2 Coding Data and Candidaemia, a Fungal Infection with an Indisputable Laboratory Prompt

A small single study from an Australian centre confirmed the poor sensitivity of coding data for fungal surveillance (Nguyen and Reid 2005). This study focused on fungal BSI, specifically candidaemia and cryptococcal BSI, which

should be more easily detected than IA given the presence of a positive blood culture. The study compared discharge codes at 2 hospitals with a pathology database over a 6-year period. A high degree of underreporting was found, with a mere 42% (25 of 60 cases) of pathology database cases assigned an appropriate code despite evidence of infection being found in 97% (58 of 60) of the medical records. Location of documentation in the medical record influenced the likelihood of code assignment. If the infection was documented in the front sheet of the medical record it was more likely to be coded appropriately (80% versus 29%). The odds ratio of the fungal BSI being coded if it appeared on the front sheet was 10 [95% CI: 2.5 to 39.2] in contrast to 0.1 (95% CI: 0.0 to 0.5) if it was mentioned in the progress notes (Nguyen and Reid 2005).

An additional limitation identified by this study was the poor specificity of all the codes with one exception, for BSI. Accordingly, a search for fungal BSI using discharge codes would have revealed many cases that were not blood borne. It is concerning that hospital discharge data even for a condition with an unmistakeable electronic signal such as BSI was inaccurate because in Australia coding data is linked to hospital reimbursement.

3.4.3   Manual Chart Review for Case Ascertainment is Time Consuming

The authors of this study commented on the considerable time required for manual data collection, which in this retrospective audit took approximately 45 minutes per record (Nguyen and Reid 2005) in contrast to the average of 14 minutes spent by coders (Dimitopoulos, Bennett et al. 2001). We concur with

their experience regarding the time imposition associated with case ascertainment using administrative coding data and manual chart review. In our own experience chart review took on average 45 to 60 minutes per case for studies included in this thesis (Ananda-Rajah 2011; Ananda-Rajah, Cheng et al. 2011; Ananda-Rajah, Grigg, Downey et al. 2012; Ananda-Rajah, Martinez et al. 2012).

3.4.4 Summary: Limitations of Administrative/Coding Data

Coding data has several limitations:

- poor validity with misclassification errors common

- modest to poor sensitivity making coding datasets unsuitable as screening tools

- being retrospective in nature, it is always collated several weeks after patient separation and therefore unsuitable for real-time surveillance

- case ascertainment is time consuming

- coding data does not distinguish between proven, probable or possible IMDs according to consensus definitions (De Pauw, Walsh et al. 2008)

3.5 Traditional Surveillance Methods: Unsustainable Beyond the Scope of Research Projects and Unfeasible Long Term

Traditional surveillance methods are both resource-intensive and subject to variability in case ascertainment. In addition, they are characterised by high operational costs and finite life spans with the high cost of data collection/entry a major drawback. Indeed, the TRANSNET surveillance study required

considerable government and industry support from Merck, Astellas, Pfizer, Schering-Plough Research Institute and Enzon (Kontoyiannis, Marr et al. 2010). Similarly, a recent Australian multicentre randomised controlled trial comparing a diagnostic driven approach for the diagnosis of IA to standard care in allogeneic HSCT recipients required a total of $2.5M for research personnel comprising a data manager (1.0EFT) dedicated to data collection/entry for 5 years, and research nurses at 0.5EFT at 3 sites and 1.0EFT at 2 sites for 4 years for follow-up tracing (Morrissey, Chen et al. 2013).

The Australian Candidaemia Study, a prospective laboratory-based surveillance project involving 50 centres from 2000 to 2005 across Australia, required 30% of the total of $1.1M in funding solely for manual data collection/entry and still resulted in incomplete data capture for variables such as mode of acquisition and risk factors (Chen, Slavin et al. 2006). Of 1095 patients with Candidaemia identified from laboratory surveillance, demographic and clinical data, including co-morbid conditions and risk factors, were available for 1005 (91.7%) episodes and outcome data for 857 (78.3%) (Chen, Slavin et al. 2006).

The TRANSNET surveillance study provided clinically meaningful insights but it also illustrated some of the major barriers and challenges of active prospective fungal surveillance: high cost; questionable sustainability as evidenced by its closure; reporting delay, being published 4 years after its closure in 2006; timeliness because it documented a period prior to the

licensure of posaconazole prophylaxis (for HSCT patients with GVHD, see Ullmann, Lipton et al. 2007) and therefore did not capture the effect of this practice change at a population level. Despite TRANSNET being a comprehensive active prospective surveillance program incomplete case capture was addressed by periodic audits and review of coding data to capture missed cases and determine denominator data respectively (Chang, Burwell et al. 2008; Kontoyiannis, Marr et al. 2010).

3.6 Fungal Surveillance and Risk Adjustment: Is the Additional Burden of Data Collection on Hospitals Worthwhile?

Standard approaches to surveillance involve case finding or notifications (nominator data) and applying denominators to calculate rates. In the haematology-oncology population appropriate denominators include patient days, myelosuppressive chemotherapy courses or neutropenia days (see Table 2.1). Risk adjustment is performed because hospitals and patient populations vary and risk adjustment accounts for this variability by adjusting for the most important confounding factors such as neutropenia or other clinical risk factors (e.g., transplant versus non-transplant patients) (Tokars, Richards et al. 2004; Kanerva, Ollgren et al. 2010); transplant type (e.g., autologous versus allogeneic) or subcategories within allogeneic transplantation (e.g., unrelated versus matched-related versus mismatched-related donor types) (Kontoyiannis, Marr et al. 2010). Risk adjustment is important when making inter-facility comparisons ('benchmarking'), when making data publicly available and when

tracking rates within an institution over a long period of time because it partially controls for changes in patient characteristics, clinical practice, preventative interventions or infection control practices (Ram, Gafter-Gvili et al. 2009; Kanerva, Ollgren et al. 2010).

Few clinical mycology studies have examined the appropriate methodology for performing IMD surveillance, let alone examining the merit of risk adjustment. Neutropenia days acknowledges that the majority of nosocomial infections in the haematology-oncology population develop during the neutropenic period (Engelhart, Glasmacher et al. 2002; Dettenkofer, Ebner et al. 2003; Dettenkofer, Wenzler-Rottele et al. 2005). Although IMDs have a second peak coinciding with the onset of GVHD in HSCT recipients, adjusting for this variable has not been attempted. A small study from an Israeli centre surveyed infectious episodes of bacterial and fungal aetiology, occurring during the neutropenic period among haematology-oncology and HSCT patients (Ram, Gafter-Gvili et al. 2009).

In a similar pattern to other studies, surveillance required a multidisciplinary team. Research nurses received information from attending physicians, pharmacists and used microbiology data. Suspected fungal cases were classified according to consensus criteria (De Pauw, Walsh et al. 2008) by a single physician expert. Incidence was assessed using the number of patients, admissions, hospital days and neutropenia days in the following patient subgroups: acute leukaemia, patients undergoing induction chemotherapy for acute leukaemia, allogeneic HSCT, autologous HSCT and other patients.

Throughout the 12-month surveillance period, 159 patients had 356 admissions totalling 3546 hospital days and 778 neutropenia days. Of 79 infectious episodes, 17 were bacteraemias, 5 were possible/probable/proven fungal episodes and 34 were episodes of fever of unknown origin. For IFDs, although the absolute number was small (n=5), a wide variability in incidence according to clinical risk was evident: incidence among all admissions was 1.4%, among patients with acute leukaemia it was 6.5% but highest during induction chemotherapy (19%) (Ram, Gafter-Gvili et al. 2009).

Similarly, incidence rates per 1000 neutropenia days for all admissions, patients with acute leukaemia and patients undergoing induction chemotherapy for acute leukaemia were 7, 10 and 18 respectively (see Table 3.1). Like other studies (Engelhart, Glasmacher et al. 2002; Dettenkofer, Ebner et al. 2003; Gupta, Singh et al. 2009) neutropenia days was the most discriminative denominator. Phase of treatment such as induction chemotherapy was another useful discriminating variable consistent with observations elsewhere (Pagano, Caira et al. 2010).

Table 3.1: Use of Different Denominators for Infection Surveillance

Reporting in Haematology-oncology Patients

	Optional denominators	All febrile episodes	Bacterial episodes		Fungal infections	
			MDI	Bacteremia	All IFI	Proven + probable IFI
No. of episodes in all patients		79	8	17	5	3
	100 admissions (n=356)	22	2	4.80	1.4	0.8
	100 patients (n=159)	50	5	11	3	2
	1000 hospital days (n=3546)	22	2	5	1	1
	1000 neutropenia days (n=778)	100	10	22	7	4
No. of episodes in AL		27	0	5	4	2
	100 AL admissions (n=61)	44	0	8	6.5	3.3
	100 AL patients (n=24)	NA	0	21	17	8
	For 1000 hospital days (n=1011)	27	0	5	4	2
	For 1000 neutropenic days (n=392)	69	0	13	10	5
No. of episodes in induction of AL		14	0	2	4	2
	100 inductions for AL admissions (n=21)	66	0	10	19	10
	100 inductions for AL patients (n=21)	66	0	10	19	10
	1000 hospital days (n=475)	29	0	4	8	4
	1000 neutropenic days (n=221)	63	0	9	18	9

AL = acute leukemia, MDI = micobiological documented infections, IFI = invasive fungal infections

(Ram, Gafter-Gvili et al. 2009)

3.6.1 Risk Adjustment According to Stem Cell Transplant Category

Reporting incidence according to type of transplant is also important as revealed by the TRANSNET study (Kontoyiannis, Marr et al. 2010). Reflecting the greater degree of immune impairment, IFDs were more common in allogeneic HSCT patients compared to autologous recipients. The aggregate 12-month cumulative incidence of IFDs at 12 months was 1.2% after autologous HSCT, but 5.8%, 7.7% and 8.1% among recipients of matched-related, unrelated and mismatched-related donors respectively (see Figure 3.3).

This is because the HLA-disparity between donor and recipient, which is predictive of the risk and severity of GVHD, is one the major determinants of IA.
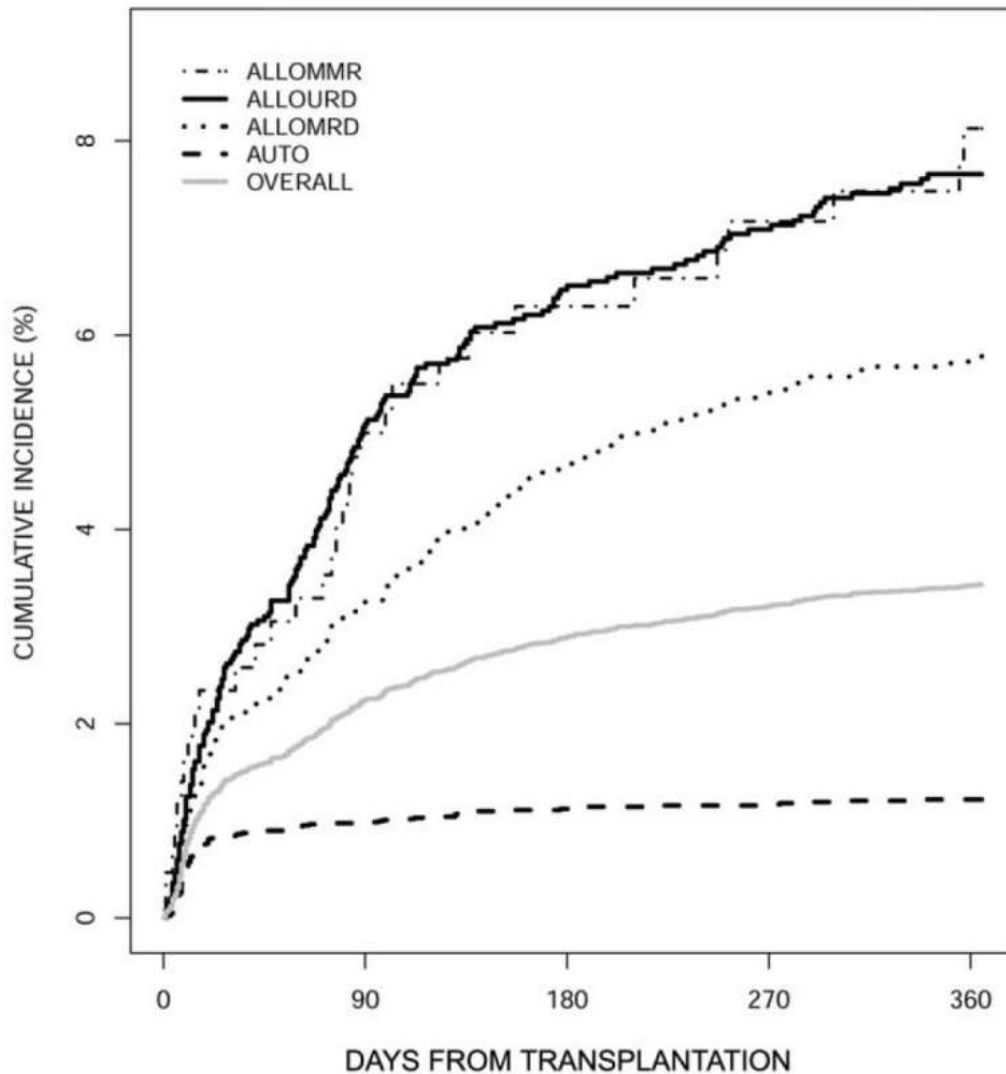
Figure 3.3: Cumulative incidence curves for any IFD among HSCT recipients in the TRANSNET cohort, stratified by type of HSCT. ALLOMMR (allogeneic mismatched-related donor); ALLOMRD (allogeneic MRD); ALLOURD (allogeneic unrelated donor); AUTO (autologous)

(Kontoyiannis, Marr et al. 2010).

3.6.2   Summary: Risk Adjustment

In reference to hospital-acquired infections, it has been suggested that the best set of adjusting variables should be objective, simple, discriminating and widely available (Sax and Pittet 2002). For haematology-oncology patients, neutropenia days fulfil these criteria but are not easily collected as they are not routinely captured by administrative systems. When adjustment variables such as neutropenia days are to be collected for the entire population at risk rather than the fraction of patients who develop the infection, manual data collection incorporating this variable imposes an unreasonable demand for hospitals (Tokars, Richards et al. 2004).

For IMDs, unanswered questions regarding risk adjustment include the following: if the number of IMDs in a given unit is low, is risk adjustment worthwhile? How great a difference must risk adjustment make in what number of institutions to justify the data collection burden at all institutions? What is the time burden of collecting data for risk adjustment and how else could this time be used? Electronic means of data capture would obviate these concerns but is dependent on developing the information extraction tools and gaining access to hospital information systems.

3.7 What Recommendations Do Practice Guidelines Offer for Fungal Surveillance?

3.7.1 Surveillance of Nosocomial Mould Infections is Easier Said Than Done

A number of environmental measures are advocated by practice guidelines to minimise exposure of immunocompromised patients to opportunistic moulds within the hospital environment especially during periods of construction or renovation (Tablan, Anderson et al. 2004; Tomblyn, Chiller et al. 2009; Weber, Peppercorn et al. 2009; Yokoe, Casper et al. 2009). Ageing hospital infrastructure means that construction and renovation is an ongoing activity and in urbanised environments is a common occurrence around hospitals also. During hospital construction, consensus guidelines from the CDC and professional societies recommend surveillance for cases of health care associated IMDs in immunocompromised patients conferring it a IB recommendation—i.e., strongly recommended for all hospitals and viewed as effective by experts because of strong rationale and suggestive evidence (Tomblyn, Chiller et al. 2009).

3.7.2 What Constitutes Nosocomial Acquisition of Mould Infection?

Consensus recommendations acknowledge that the incubation period for IA is unknown (Tomblyn, Chiller et al. 2009) precluding a definition of what constitutes nosocomial IA (Hajjeh and Warnock 2001). In cancer patients, disease attribution is further complicated by their frequent health care encounters making it difficult if not impossible to determine if exposure to

Aspergillus spores occurred during hospitalisation or within the community. One definition that is frequently used considers IA as nosocomially acquired if it occurs after 1 week of hospitalisation or within 2 weeks of hospital discharge (Patterson, Zidouh et al. 1997). This is a conservative time frame, with recent evidence from a prospective survey of acute leukaemia patients at a French hospital suggesting that the incubation period of IA was between 10 to 35 days noting that incubation is contingent not only on exposure, but also on degree and duration of the immunological defect which pre-disposes to subsequent tissue invasion (Nicolle, Benet et al. 2011).

An update to the CDC/HICPAC Guidelines for Preventing Opportunistic Infections Among HSCT Recipients (2000) recommends that health care facilities during periods of construction or renovation track all cases of invasive mould infection regardless of time to onset after admission because clinical encounters with hospitals are frequent and the incubation period of IA is unknown (Tomblyn, Chiller et al. 2009). It confers a BIII recommendation— i.e., B: Moderate evidence for efficacy, or strong evidence for efficacy, but only limited clinical benefit—supports recommendation for use. Should generally be offered. III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. These guidelines state that cases of IMD with onset of symptoms ≥7 days after hospital admission are more likely to be hospital-acquired (Tomblyn, Chiller et al. 2009).

Recent consensus guidelines have intentionally relaxed the case definitions by endorsing clinically documented and microbiologically confirmed IMDs with the inclusion of proven, probable, and possible cases in the surveillance case definition (Tomblyn, Chiller et al. 2009). Accordingly, these guidelines broaden supportive evidence for IMD to include culture, histology, host factors, NCBTs, and clinical (including radiology) data (BIII). Whether NCBTs include non-standardised methods such as PCR is not explicitly stated but the inclusive nature of these guidelines suggest that positive PCR, although not raising diagnostic certainty beyond the possible category (De Pauw, Walsh et al. 2008), may be appropriate for inclusion of clinical cases for surveillance.

3.7.3 A Note of Caution When Attributing IMD to Nosocomial Acquisition: A Subset of Patients at Admission Will Have Subclinical Disease

It is possible that a subset of patients have IMD at presentation raising the issue of identifying these patients at the outset for early targeted treatment. A recent observational study from France reported the presence of IA at admission in 11% of hospitalised haematology-oncology patients of whom 76% had AML. However, this is likely an underestimate of the true incidence as diagnostic investigations were clinician initiated rather than protocol-driven (Nicolle, Benet et al. 2011). Subclinical IA was present in a subset of patients in the posaconazole registration trials as evidenced by a positive serum GM which was returned in 4% each of posaconazole (12/304) and comparator groups (13/298) with AML/MDS (Cornely, Maertens et al. 2007) and in 7% (21/301) and 10% (10/299) of posaconazole and fluconazole patients respectively

(Ananda-Rajah, Slavin et al. 2012) with severe GVHD (Ullmann, Lipton et al. 2007). Thus, the presence of subclinical IMD at hospital admission further confounds disease attribution as being nosocomially acquired or not.

3.7.4   Routine Versus Outbreak Detection of Mould Diseases: Outbreaks Cannot Be Recognised in the Absence of Baseline Surveillance Data

These guidelines appropriately recommend that a case cluster, identified as an increase in the number of cases or in the incidence of IMD among HSCT recipients, should trigger an investigation for environmental sources of mould exposure (Tomblyn, Chiller et al. 2009). Implicit is the assumption that hospitals are aware of their baseline incidence in real-time for outbreaks to be reliably identified. However, in general this is not the case because continuous prospective surveillance of IMDs is not routinely performed in many hospitals.

Unfortunately these guidelines provide no methodology to guide hospitals in performing either 'routine surveillance for cases of IMD, including IA (BIII)' or 'enhanced surveillance of microbiologic, pathologic, and radiologic data to identify trends suggesting an environmental mould source (BIII)' during periods of construction (Tomblyn, Chiller et al. 2009). Based on experiences from France, where IA surveillance is a mandatory requirement for hospitals, a dedicated active prospective surveillance program is a resource-intensive endeavour requiring the commitment of multidisciplinary teams (Fourneret-Vivier, Lebeau et al. 2006). In the absence of clear guidelines it is largely left up to hospitals to implement these programs within their capabilities.

3.7.5 British Guidelines: Benefits of Surveillance Beyond Infection Prevention

The need for active surveillance is a key aspect in the control and prevention of nosocomial IA as recommended by experts. However, prevention of nosocomial IMDs should not be the sole motivation for surveillance. The British Committee for Standards in Haematology in recognising the evolving epidemiology of IFDs in patients with haematological malignancies recommended that continuous prospective collection of incidence rates from centres would be useful for many purposes among them, clinical risk stratification and for informing choice of management strategies based on changes in fungal pathogens over time (Writing Group of the British Committee on Standards in Haematology 2008). This authority emphasised that it should be as contemporary as possible being 'regularly and frequently updated' (BIII) and reported according to diagnostic certainty as defined in consensus criteria. Like other guidelines, the many elements required to make continuous prospective fungal surveillance a reality in hospitals are easier said than done.

3.7.6 Summary: Practice Guidelines

- Professional societies and experts recommend continuous prospective surveillance of IMDs not only for case cluster detection during periods of hospital construction and renovation but also to track epidemiological trends.

- Construction and renovation activities both internal and external to hospitals are an ongoing activity making prospective surveillance of nosocomial IMDs an important task.

- Knowledge of local baseline incidence is required to reliably identify outbreaks but is dependent on a dedicated comprehensive surveillance program.

- Practice guidelines recommend continuous prospective surveillance in hospitals but fail to provide guidance regarding its implementation.

- Comprehensive surveillance of clinically documented and microbiological documented cases using all available diagnostic modalities requires a coordinated response from a multidisciplinary team.

- A dedicated comprehensive surveillance program for IMDs is a major commitment for health care facilities but should be regarded as an investment in improved safety and quality of health care to patients.

- Surveillance for nosocomial mould infections is complicated by the fact that the incubation period of opportunistic moulds, in particular *Aspergillus*, is unknown; a subset of patients will have subclinical disease at presentation and clinical encounters between patients and health care facilities are frequent.

3.8 Case Definitions for IFD Diagnosis: A Cornerstone for Clinical Research with Limitations for Surveillance

Difficulties in reliably establishing the diagnosis of IFDs prompted expert groups such as the EORTC/MSG to formulate case definitions for clinical or epidemiological research (Ascioglu, Rex et al. 2002; De Pauw, Walsh et al. 2008). The EORTC/MSG revised definitions for IFD (De Pauw, Walsh et al. 2008) and their earlier iteration (Ascioglu, Rex et al. 2002) stipulate 3 levels of diagnostic certainty comprising possible, probable and proven categories. These guidelines were created for clinical trials of therapeutic agents for IFDs rather than as guides to clinical practice (Writing Group of the British Committee on Standards in Haematology 2008; Partridge-Hinckley, Liddell et al. 2009; Wingard, Carter et al. 2010) to ensure that patients enrolled in trials truly have IFD.

The inclusion of possible cases in consensus definitions recognises the difficulties in obtaining timely and objective proof of IFD in sick patients with significant co-morbidities. However, to meet the category of possible IFD a reasonable search for alternative conditions must have been made. In practice, possible infections may have the highest burden as evidenced at one major US centre where they comprised >90% of infections (Neofytos, Lu et al. 2013).

While current fungal diagnostics remain suboptimal, the need for definitions will persist. Hsu et al. (2011) recently characterised an ideal fungal detection platform: good sensitivity, the ability to provide species level discrimination,

multiplex capacity for a broad array of fungal pathogens and the ability to distinguish between disease and colonisation. None of our current diagnostics meet these criteria and most fall short on several levels. Indeed, it is the lack of sensitive and timely diagnostics combined with the high morbidity and mortality of IFDs, which motivated the introduction of empirical antifungal therapy in patients with neutropenia and persistent fever of unknown origin (Segal, Almyroudis et al. 2007).

The complexity of consensus guidelines (De Pauw, Walsh et al. 2008) for fungal diagnosis limits their application to fungal surveillance. With greater than 30 host, clinical and mycological criteria, they are prone to subjective errors in interpretation. Classification errors are a well-recognised problem even for personnel trained at applying surveillance case definitions for other complex conditions such as central line associated blood stream infection (CLABSI) or ventilator associated pneumonia (VAP) (Hota, Harting et al. 2010; Lin, Hota et al. 2010; Klompas 2012). For clinical mycology trials, convening expert panels for adjudication of potential cases is the norm (Cornely, Maertens et al. 2007; Kontoyiannis, Marr et al. 2010; Lortholary, Gangneux et al. 2011; Nicolle, Benet et al. 2011) again emphasising the difficulty in defining what constitutes an IFD.

3.9 Radiographic Features of IMDs are Key Diagnostic Criteria

These criteria that have steadfastly informed the conduct of clinical research are not without controversy. Wingard et al. (2010), in a prophylaxis trial comparing fluconazole to voriconazole in allogeneic HSCT recipients at moderate risk for IFD, adopted a more liberal approach with the inclusion of patients with suggestive clinical features (fulfilling the EORTC/MSG criteria for possible IFD) but without an alternative aetiology as evidenced by negative bronchoscopy. These patients categorised as 'presumptive IFDs' were regarded as representative of routine clinical practice where clinicians are compelled to escalate treatment based on radiographic abnormalities suggestive of IA while the diagnostic work-up proceeds. Radiographic criteria took precedence over non-specific clinical signs or symptoms in this trial highlighting the importance of this diagnostic modality. However, radiographic features were hierarchical being subdivided into (1) major criteria: for lungs (new halo sign, air-crescent sign, or cavity), and for sinuses (radiological evidence of erosion of sinus walls, extension to neighbouring structures, or destructive changes of skull base) and (2) minor criteria defined as any new infiltrate not fulfilling major criteria or pleural effusion (Wingard, Carter et al. 2010).

The distinction between some radiographic features being more suggestive of IMD than others has been scrutinised recently. Nucci et al. (2010) argued that the radiographic features of IA (dense well-circumscribed lesion, air-crescent sign or cavity) promulgated by the EORTC/MSG guidelines are too restrictive,

lacked sensitivity, were non-specific being associated with other conditions (Bruno, Minniti et al. 2007), observer dependent, transient (Caillot, Couaillier et al. 2001), weighted for more advanced disease as they are based on studies performed prior to the introduction of NCBTs (Kuhlman, Fishman et al. 1985; Herbrecht, Denning et al. 2002) and potentially misleading in the context of immune reconstitution where cavitation may signify neutropenic recovery rather than clinical failure (Caillot, Couaillier et al. 2001).

They argued their case in a case-control study that compared mostly myeloma patients (91%) undergoing cytotoxic chemotherapy of whom 83 'controls' had EORTC/MSG defined probable/proven IA with the classical radiologic features (De Pauw, Walsh et al. 2008) to 42 probable 'cases' who lacked these pre-specified radiologic features but were GM positive. From a clinical standpoint, case and control patients had similar rates of culture recovery of *Aspergillus* species (29% for cases, 19% for controls); clinical response, with a 90-day survival of 64% for cases versus 52% for controls (p=0.27) and similar GM/beta-D-glucan kinetics in response to antifungal therapy, suggesting that those patients lacking pre-specified radiographic features as defined by the EORTC/MSG guidelines (De Pauw, Walsh et al. 2008) most likely had IA. The salient difference being that case-patients had radiographic features at study inclusion not classically associated with IA such as diffuse consolidations, ground-glass infiltrates and pleural effusions.

Importantly, 11 case-patients on serial imaging performed a median of 2 weeks later, had developed dense, well-circumscribed consolidations and/or

macronodules, suggesting that this category at study entry may represent an earlier stage of infection. It is doubtful that a single small study (Nucci, Nouer et al. 2010) will force a major shift in guideline recommendations but it does highlight the shortcomings of current radiographic criteria notwithstanding the acknowledgement in the consensus definitions that IA may infrequently present as lobar or segmental consolidations and wedge-shaped infiltrates (De Pauw, Walsh et al. 2008).

The consensus guidelines were largely informed by the image dataset of 235 patients with probable or proven IA (Greene, Schlamm et al. 2007) enrolled in the Global Comparative Aspergillosis Study (1997 to 2000), which compared voriconazole to amphotericin B for the treatment of IA (Herbrecht, Denning et al. 2002). All patients had either positive histopathology or culture for *Aspergillus*, suggesting that they had a higher burden of disease or more advanced disease. It is worth noting that although macronodules ($\geq$ 1cm) were most common (95%), non-specific findings such as consolidations were evident in 30% of patients, air-bronchograms in 16%, clusters of small nodules (<1cm) in 11%, pleural effusions in 10%, ground-glass infiltrates in 8.9%, infarct shaped consolidations in 7.7%, and small airway lesions in 6.8% (Greene, Schlamm et al. 2007) (see Table 3.2).

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Table 3.2: Imaging Findings in Patients with Invasive Pulmonary

Aspergillosis

Imaging finding	No. (%) of patients (N = 235)
Macronodule (≥1 cm in diameter)[a]	222 (94.5)
Halo sign[b]	143 (60.9)
Consolidation[c]	71 (30.2)
Macronodule, infarct shaped	63 (26.8)
Cavitary lesion[d]	48 (20.4)
Air bronchograms	37 (15.7)
Clusters of small nodules (<1 cm in diameter)	25 (10.6)
Pleural effusion	25 (10.6)
Air crescent sign	24 (10.2)
Nonspecific ground-glass opacification	21 (8.9)
Consolidation, infarct shaped	18 (7.7)
Small-airway lesions[e]	16 (6.8)
Atelectasis	7 (3.0)
Hilar/mediastinal lesion	4 (1.7)
Pericardial effusion	2 (0.9)

NOTE. Patients may have >1 type of lesion.

[a] Includes macronodules with or without halo sign and infarct-shaped macronodules.

[b] A macronodule with a perimeter of ground-glass opacity.

[c] Includes infarct-shaped consolidations.

(Greene, Schlamm et al. 2007)

Importantly, all patients in the GCA trial had at least one abnormality at baseline, which according to trial protocol were for the lungs, a halo, air-crescent sign or new pulmonary lesions not attributable to other factors (Herbrecht, Denning et al. 2002). Trial protocol, in turn, was informed by an earlier radiographic study of 9 patients with acute leukaemia some of whom

had radiographic progression from halo to macronodules and cavitation (Kuhlman, Fishman et al. 1985). Not surprisingly given these trial inclusion criteria, 61% of patients from the GCA image substudy had at least one halo sign (Greene, Schlamm et al. 2007). Thus, Nucci et al. (2010) rightly take issue with the current weighting given to radiographic criteria in consensus guidelines as they are based on reports from 1985 to 1997 favouring the halo, macronodule or air-crescent sign. If we are to adopt a more liberal approach to the radiographic criteria of IMDs then the argument by Nucci et al. is interesting but needs to be confirmed by larger contemporary multicentre studies.

3.9.1 Do the Radiologic Features of IMD Vary with the Type of Immunosuppression?

It is possible that the radiologic manifestations of IMD may vary depending on the type of immunosuppression—e.g., neutropenic versus non-neutropenic patients such as corticosteroid treated patients. This may have implications for radiologic criteria used in definitions after considering that 45% of patients in the image dataset that informed those guidelines were neutropenic (Greene, Schlamm et al. 2007).

A small retrospective study of 66 patients with haematological malignances and proven or probable invasive pulmonary aspergillosis from 2002 to 2007 treated at a major US cancer centre attempted to find a CT correlate to specific types of immunosuppression (Milito, Kontoyiannis et al. 2010). Patients had a variety of risk factors, including neutropenia in 52%, HSCT in 45%, steroid

use in 44% and GVHD in 33%. There was no correlation between initial CT findings and risk category but the study was revealing in other aspects. Nodular lesions were the most common finding present in 82% overall and not substantially different between groups (neutropenia 74%, HSCT 87%, GVHD 95%, steroids 83%). Non-specific air space changes were common being present in 75% of patients as either segmental or lobar consolidations (39%), ground-glass opacities (12%), tree-in-bud changes in 21% and pleural effusions in 41% which were usually bilateral (88%). Alternative diagnoses are not a likely explanation for these non-specific features as study inclusion criteria were strict ensuring that patients with mixed infections—i.e., fungal, bacterial or viral pathogens, were excluded from analysis.

Patients in routine clinical practice, unlike experimental models, often have overlapping types of immune suppression. Thus, it is important that future large-scale studies further explore the question of CT correlates of invasive pulmonary aspergillosis according to degrees of immunosuppression as additional information may influence future revision of case definitions, which in turn will affect how IMDs are detected.

3.9.2 Summary: Traditional Surveillance Using Administrative Data, Clinical Review and Laboratory-based Methods

Arguably, IMDs are among the most cognitively challenging infections to diagnose even for clinicians at the bedside equipped with all available data. Laboratory-based surveillance is subject to significant underreporting because microbiological indicators of infection are often lacking due to inadequate or

unavailable diagnostic tools (Pfeiffer, Fine et al. 2006; Leeflang, Debets-Ossenkopp et al. 2008; Mengoli, Cruciani et al. 2009; Ostrosky-Zeichner 2012), concomitant antifungal therapy or patient acuity contraindicating invasive diagnostic procedures. Administrative data as a means of IMD detection is inherently inaccurate due to missed or miscoded data (Chang, Burwell et al. 2008) and does not allow real-time surveillance as it is collated several weeks after patient separation nor does it provide information on whether the infection was pre-existing or acquired during the clinical encounter.

In reality, no single method will be adequate for surveillance and complete case capture will require, as many studies have shown, the pooling of data from multiple sources. However, the choice of primary screening method is critically important in order to reduce the burden of case finding with adjunctive sources of data serving to augment the primary method. Although the optimal screening method for IMDs is undefined, the high frequency of pulmonary involvement (see Table 2.1) makes chest CT imaging a reasonable starting point for screening. However, with CT reports in a free-text unstructured form, extracting meaning from them is the next challenge.

Chapter 4: The Economic Impact of Invasive Fungal Diseases

4.1   Introduction

Constraints on health care expenditure demand that treatments must not only be efficacious but also cost-effective. Accurate estimates of cost are important because they underpin cost-effectiveness studies. The economic burden of IFDs on the health care system is substantial (Wilson, Reyes et al. 2002; Slavin, Fastenau et al. 2004; Menzin, Meyers et al. 2009). It is estimated that 64,480 patients are hospitalised with IFDs each year in the US contributing US$1.89 billion in additional annual hospital costs (Menzin, Meyers et al. 2009).

There is a growing literature on the economic burden of IFDs in patients with haematological malignancies and stem cell transplant recipients. However, studies are characterised by heterogeneity regarding methodologies used for cost determination, questionable generalisability between jurisdictions, differing outcomes reported (e.g., mean versus median costs) and variable cost categories. Attributable hospitalisation cost of IFD is more meaningful than gross costs but is difficult to determine because separating the effect of IFD from competing host and treatment-related variables is challenging.

Table 4.1: Hospitalisation costs of IFDs over the past decade, 2002-2012

Reference	Patient characteristics	Source	LOS	Findings	Methods	Country	Perspective	Study type	Duration
Wilson, Reyes et al. 2002	Variety of patients: HIV, cancer, transplant recipients	National Hospital Discharge Survey & Maryland Hospital Discharge Dataset 1994-1998—i.e., data from a single state only	Mean additional: IA, 19 days; candidiasis, 14 days	Incremental mean hospitalisation cost per patient for aspergillosis $36,867. For all IFDs, room charges 47%; Pharmacy costs 17%, laboratory costs 11% contribute to total hospitalisation cost. Traditional risk groups (HIV, cancer, transplant) accounted for 45% for all infections. Per risk group with IA: transplant $83 949; neoplasia $46,429; HIV $31,309; Inpatient costs accounted for 54% of total cost	Cost-to-charge ratios (1996)	US	Hospital	Retrospective case-control	1997, with costs projected to 1998
Slobbe, Polinder et al. 2008	AML/MDS n=269 patients, 80 patients with IA (possible n=32; probable/proven n= 48)	Prospective observational study	Mean LOS: possible IA, 91 days; probable/proven IA, 104 days; controls, 84 days	Probable/proven IA mean excess costs €15,280 (2007)	Microcosting data Patient-level data used. IA incidence 30% in patients who were routinely administered fluconazole prophylaxis	Netherlands	Hospital	Prospective case-control study	2002-2007
Kim, Nicolau et al. 2010	n=1603 patients with principal (34%) or secondary code for aspergillosis; 45% with malig-	National discharge coding data from 2200 hospitals	median LOS for total cohort 23 days	Median hospital cost $52,803 (2006); antifungals accounted for 7.2% of	Actual costs (2006), not charges; total hospitalisation costs	US	Hospital	Retrospective observational	2000-2006

Reference	Patient characteristics	Source	LOS	Findings	Methods	Country	Perspective	Study type	Duration
	nancy			total hospitalisation cost; inpatient mortality 36.7%; By ICD-9-CM code, median hospitalisation costs were $40 145 for HIV patients, $41 734 for non-haematological malignancy patients, $73 029 for haematological malignancy patients and $102 160 for patients with bone marrow transplant complications	reported				
Menzin, Meyers et al. 2011	Patients with IFDs in 80/9896 SOT & HSCT 111/4661 recipients respectively	Healthcare Cost and Utilisation Project Nationwide Inpatient Sample (data from approximately 20% of all inpatient stays from > 1000 institutions)	Aspergillosis associated with an additional 19.3 days	Aspergillosis associated with $55,400 (2007) mean excess costs overall and $51,655 in HSCT recipients only	cost-to-charge ratios (2007)	US	Hospital	Retrospective matched case-control study. Matching criteria for controls: age (10-year categories), sex, region, hospital type, year & transplant type	2004-2005
Slavin, Fastenau et al. 2004	Discharge diagnoses from public & private hospitals; Hospitalisations associated with Aspergillosis n=4583 & Candidiasis =57 758	NHMD, Victorian hospitals excluded	Mean LOS: aspergillosis, 12.2 days; disseminated candidiasis, 30.7 days	Mean hospitalisation costs (1999) for aspergillosis, $9 334 & disseminated candidiasis $33 274	'Per diem' or daily cost of hospitalisation (rather than actual costs calculated) used & multiplied by mean LOS for each infection	Australia	Hospital	Retrospective observational	1995-1999

Reference	Patient characteristics	Source	LOS	Findings	Methods	Country	Perspective	Study type	Duration
Dodds Ashley, Drew et al. 2012	Convenience sample of 200 patients with possible/probable/proven IFDs being either IA, invasive candidiasis, cryptococcosis or zygomycosis. Variety of underlying conditions—i.e., HIV, SOT, HSCT, neoplasia	Hospital costing and clinical databases. Electronic and medical charts	Mean LOS: all IFD patients 25.8 days v 18.4 days for controls; IA patients (n=58) 24.6 days v 17.1 days in controls	Mean excess hospital cost (2004-2005) for IFD cases $32,196 with non-pharmacy costs accounting for 63% & laboratory costs being 18% of the difference; $3996 (12%) attributed to systemic antifungal drugs	Patient-level data from a single academic centre. Cost-to-charge ratios used	US	Hospital	Retrospective matched case-control study. Controls matched based on admission to the same medical or surgical service, hospitalisation duration at least as long as the case-patient before IFD diagnosis, age within 10 years of the case-patient & primary co-morbid condition	2004-2005
Tong, Lau et al. 2009	Patients with a variety of underlying diseases. Hospital discharges associated with aspergillosis n=10,400	Nationwide Inpatient Sample & MedPAR file	Median (mean) LOS per aspergillosis patient was 10 (17.7) days	Median (mean) total hospital cost per patient with IA of $44 845 ($96 731);the median (mean) per patient ranged from $47 252 ($82 946) for HIV to $413 200 ($442 233) for HSCT recipients. Excess median cost for HSCT recipients & patients with haematological malignancies were $41,889 & $41,379 respectively. Pharmacy 30%, ICU 12% & laboratory 11% of total cost.	Cost-to-charge ratios (2003)	US	Hospital	Retrospective observational study	2003
Rieger, Cornely et al. 2012	Patients with newly diagnosed or relapsed AML or MDS; IFD	Chart review from a 5 centres	Mean excess LOS for cases 12 days	Mean incremental costs of €21 063 were dominated by	Patient-level data used. Detailed costing data from	Germany	Hospital	Retrospective matched case-control study. Controls matched for	2007

Reference	Patient characteristics	Source	LOS	Findings	Methods	Country	Perspective	Study type	Duration
	patients, n=36 (IA in 74%) and controls, n=72			cost for antifungal drugs (36%), hospital stay (32%) & blood products (23%)	hospitals not available. Therefore costs determined from multiple sources for primary patient care, ICU, mechanical ventilation, parenteral nutrition, diagnostics, systemic antifungal medication and concomitant medication			same underlying disease, age within 5 years, duration of neutropenia & intensity of chemotherapy regimen	

4.2 Determining Hospitalisation Cost from Administrative Data

4.2.1 International Studies

Studies using administrative data have largely focused on transplant recipients possibly because transplantation is a procedure that is reliably captured in administrative or coding datasets (Slavin, Fastenau et al. 2004; Menzin, Meyers et al. 2009; Kim, Nicolau et al. 2010; Menzin, Meyers et al. 2011). In a recent analysis using nationally representative coding data, Menzin et al. (2009) studied the excess mortality, lengths of stay, and costs attributable to IFDs in high-risk patients in the US. A total of 11,881 patients with IFDs were matched to uninfected control patients. Patients with IFDs had a significantly higher mortality rate (15% versus 5%), mean lengths of stay (LOS) (18.7days versus 7.3days) and mean costs ($44,726 versus $15,445) (p<0.001 for all comparisons) than did patients without IFDs. They found that patients undergoing transplant procedures had the highest rate of excess mortality, LOS, and costs compared with all other high-risk groups. Their findings corroborated earlier findings from administrative data now over a decade old, showing that transplant patients had the greatest cost burden compared with other high-risk populations (Dasbach, Davies et al. 2000; Wilson, Reyes et al. 2002).

An updated retrospective review by Menzin et al. (2011) re-examined the excess or attributable economic burden of IFDs in transplant patients in the US. This was a case-control study with subjects identified from a large

administrative database (2004 to 2005 Healthcare Cost and Ultilization Project Nationwide Sample) that contains discharge level information on 8 million hospitalisations reflecting approximately 20% of hospitalisations from >1000 US institutions. Cases were patients with ICD9-CM codes for transplant and IFD and uninfected controls were matched on the basis of age (within 10 years), sex, hospital region/type, year of hospitalisations (2004 or 2005) and type of transplant (heart, lung, kidney, liver, pancreas, allogeneic HSCT, autologous HSCT). Costs were derived by converting charges for each hospital stay using hospital-specific cost-to-charge ratios. Excess LOS and costs were assessed as the overall difference in means for the 2 cohorts. Among 9896 SOT patients and 4661 HSCT recipients, 0.8% SOT and 2.4% HSCT patients had an IFD with IA the most common infection. After adjusting for age, sex, race, region and co-morbid conditions by linear regression, patients with IFD had a 5-fold excess mortality ranging from 14 to 22%, an additional 19 hospital days (range 14 to 24 days) and $55,400 in excess costs (range $44,243 to $70,260) (Menzin, Meyers et al. 2011).

A recent study analysed administrative data from an earlier era (2000 to 2006) in the Premier Perspective Database to determine hospital outcomes and costs associated with IA (Kim, Nicolau et al. 2010). This is the largest clinical and financial database (with more than 130 million patient discharges reporting actual costs rather than costs derived from cost-to-charge ratios) from more than 2200 hospitals across the US (Kim, Nicolau et al. 2010). Patients with discharge ICD-9 codes of aspergillosis (n=1603, 45% of whom had some type of malignancy) who received at least 3 days of intravenous antifungal therapy

were identified and all costs were inflated to US$2006 using the medical care component of the consumer price index. Gross rather than attributable costs were reported with the median favoured over the mean. Median hospital costs were $52,803 and did not differ by year over the study period. Median LOS was 23 days. Intravenous antifungals accounted for 7.2% (range: 0.78–15.9%) of the cost of aspergillosis-related hospitalisation and overall, seems to have decreased compared to a 1998 study that showed that antifungal drug costs contributed 17% to hospitalisation costs (Wilson, Reyes et al. 2002). Crude mortality was 36.7% and was lowest in the last 2 years of the study (2005, 2006).

Although hospitalisation costs of IA were substantial, antifungal drugs accounted for only a small percentage of total costs associated with treatment. Initial antifungal choice was not independently associated with in-hospital crude mortality in a multivariate logistic regression model. In-hospital death was associated with significantly higher hospitalisation costs compared to patients who were discharged alive (median) $71,169 versus $41,267 (p<0.001). This difference was not driven by antifungal drug costs, which were equivalent between groups being $3379 for patients who died and $3074 for patients who were alive at discharge (p=0.108). Not unexpectedly, median hospitalisation costs increased with degree of immunosuppression likely reflecting increasing patient acuity being $40,145 for HIV patients, $41,734 for non-haematological malignancy patients, $73,029 for haematological malignancy patients and $102,160 for patients with bone marrow transplant complications (Kim, Nicolau et al. 2010).

The variability of cost with patient acuity is supported by an analysis of the National Inpatient Sample (NIS) conducted in 2003 which used cost-to-charge ratios to estimate hospital costs (Tong, Lau et al. 2009). From a dataset of 7.5 million hospital discharges representing 20% of US community hospitals, 10,400 aspergillosis cases were identified across 171 diagnosis-related groups (DRGs). This large dataset allowed an evaluation of the economic burden of aspergillosis in distinct patient subgroups as determined by DRGs. A separate database, the Medicare Provider Analysis and Review (MedPAR), from the Centres for Medicare and Medicaid Services was used to acquire hospital charge information on Medicare beneficiaries but the 2 datasets represented distinct patient populations. Each subgroup was compared to a control population consisting of patients within the same DRG or ICD-9-CM category who did not have a ICD-9-CM code for aspergillosis. Excess costs were the difference in median hospitalisation costs of the aspergillosis and control populations. Hospital costs were further categorised as pharmacy, accommodation, intensive care unit (ICU), laboratory, medical supplies and other groups (Tong, Lau et al. 2009).

This study is valuable for examining differences in health economic outcomes between sub-populations at risk for aspergillosis. Despite the inherent limitations of administrative data, Tong et al. (2009) found that IA had a median LOS that was 1.8 to 2.4 times higher and median total hospitalisation costs per admission that was 2.3 to 12.7 times higher than control patients. Among all patients, the mean total hospitalisation cost of patients with

aspergillosis ranked above the 90th percentile for all high-risk DRG categories. Among transplant patients, HSCT recipients with aspergillosis had the longest median LOS (48 days) and highest hospitalisation costs (median=$413,200) (Tong, Lau et al. 2009).

It is evident from this nationwide sample that although the number of incident cases is relatively small (36 per million per year in the US), aspergillosis affects a diverse patient population with 10,400 cases spread across 171 DRGs (Tong, Lau et al. 2009). Patients who are traditionally regarded as being at highest risk for aspergillosis assigned high-risk DRGs comprising HIV, haematological malignancy, chemotherapy, HSCT and reticuloendothelial immunity disorders and post-transplant coding categories comprised only 19% of aspergillosis hospitalisations. In contrast, the top 5 most common DRGs (i.e., infectious and parasitic complications, COPD, tracheostomy, respiratory conditions with ventilator support) comprised 44% of hospitalisations with none of them belonging to a recognisable high-risk (i.e., cancer or post-transplant) group (Tong, Lau et al. 2009).

According to patient subgroup, median excess hospitalisation costs associated with aspergillosis were $10,039 for HIV patients, $41,379 for patients with haematological malignancies, $40,297 for patients receiving chemotherapy and highest in HSCT recipients at $41,889 (Tong, Lau et al. 2009). Disproportionate increases in excess hospital costs (relative to patients from the same DRG subgroups but without aspergillosis) were seen across all high-risk DRGs being 820% for chemotherapy patients, 630% for patients with

haematological malignancy, 170% in HIV patients and 127% in HSCT recipients. Overall, the median (mean) LOS per case-patient was 10 (17.7) days and median (mean) total hospital charge in 2003 was $44,845 ($96,731). With respect to the total hospital cost for aspergillosis patients, pharmacy, ICU, and laboratory expenditures were the most significant contributors across the DRGs analysed. On average, pharmacy costs represented 30% of total expenditures, while ICU and laboratory costs represented approximately 12.2% and 11.8% respectively (Tong, Lau et al. 2009).

4.2.2   Australian Data

Few studies have examined the economic burden of IFDs in Australia. Slavin et al. (2004) used administrative data in 1995 to 1999, the era prior to the widespread use of potent antifungal drugs. In this study, hospitalisations complicated by *Aspergillus* or *Candida* were identified from discharge coding captured by the National Hospital Morbidity Database (NHMD). Unfortunately, study findings were limited by an absence of data from Victoria, the second most populous state. Included in the case ascertainment criteria was superficial candidiasis in addition to invasive and disseminated forms. Hospitalisation costs were determined by calculating the mean DRG *per diem* cost from a separate dataset, the National Hospital Cost Data Collection and multiplying these *per diem* costs to LOS reported in the NHMD. Thus, it appears that like Kim et al. (2010), actual costs of hospitalisation were not used but instead derived from DRGs estimated from a costing dataset separate from mycoses related hospitalisations. It is important to note that *per diem* costs may not reflect actual costs incurred because it assumes that costs are evenly

distributed across the hospitalisation, which is not necessarily the case in reality.

Curiously, in this study candidiasis had a substantially higher cost than IA (Slavin, Fastenau et al. 2004). This study could not distinguish between acute and chronic forms of aspergillosis. Over the 5-year study period, 4583 hospitalisations associated with aspergillosis and 57,758 hospitalisations with candidiasis were identified accounting for a total expenditure of $563 million adjusted to 1999 Australian dollars. Aspergillosis was associated with a mean LOS and hospitalisation cost of 12 days and $9334, while invasive and disseminated candidiasis respective outcomes were 17 days and 31 days with costs of $12,954 and $33,274. The higher costs associated with disseminated and invasive candidiasis were largely driven by longer LOS compared to aspergillosis. Even after accounting for the lower LOS, the hospitalisation cost of aspergillosis seems strikingly low. During this era, IA was associated with mortality rates of over 95% (Denning 1996) but early in-hospital death does not entirely explain these findings as in-hospital mortality of patients with aspergillosis from this dataset was only 8% (Slavin, Fastenau et al. 2004). This may be a shortcoming of administrative data, which does not capture out-of-hospital mortality or in-hospital death due to aspergillosis not listed as a primary or secondary diagnosis.

4.3   Patient-level Analyses

Administrative data is an efficient data source for burden of illness studies but patient-level analyses provide more detailed clinical information on factors influencing outcomes and cost. A recent Dutch study examined the attributable hospitalisation cost of IA in patients undergoing chemotherapy for AML-MDS (Slobbe, Polinder et al. 2008). Diagnostic practice was protocol-driven and therefore unchanged during the study period (2002 to 2007). After 5 days of persistent fever, patients underwent high resolution CT repeated 5 to 7 days later, bronchoscopy as indicated with GM on either serum or BAL fluid. Voriconazole was the treatment of choice from 2002 with conventional amphotericin used prior. Mean cost reported at patient-level included the first course of cytotoxic chemotherapy and all consecutive treatment episodes (i.e., remission-induction or consolidation chemotherapy and transplantation).

Microcosting methods were used, meaning that all diagnostic or therapeutic procedures rendered were itemised and costed according to official hospital reimbursement figures. Pharmacy drug acquisition costs were used for drugs administered. Bottom-up methods such as microcosting or activity-based costing (ABC) is the method of choice for most economic evaluations as costs are recorded at the patient-level by counting every activity performed and transforming them into monetary units (Jegers, Edbrooke et al. 2002). The cost of inpatient days were based on a *per diem* method with the unit price for hotel costs of ward or ICU stay per day multiplied by the LOS. Cost categories for in-hospital care included diagnostic costs (imaging, microbiology,

bronchoscopy, CT-guided lung biopsy), antifungal and antibiotic costs, costs of surgical treatment included lung resection, ICU and non-ICU ward costs and costs relating to transfusion of blood or blood products (Slobbe, Polinder et al. 2008).

The case group comprised 80 patients who developed IA from a total of 269 patients resulting in an IA incidence of 30% (Slobbe, Polinder et al. 2008)—a figure that is in the upper range reported in the literature (Vehreschild, Ruping et al. 2010; Auberger, Lass-Florl et al. 2012; Girmenia, Frustaci et al. 2012). It should be noted that at this centre, fluconazole was the antifungal of choice for prophylaxis. For the majority of patients (59 of 80, 74%) IA complicated chemotherapy for AML-MDS, with only 3 cases occurring during allogeneic transplantation. Overall mortality at 12 weeks after starting antifungal therapy was 22% for case-patients with no difference between probable/proven cases and possible cases of IA. Total mean IA related costs were €15,280 (2007) for patients with probable/proven IA compared to patients without IA (p<0.001). Mean medical costs were significantly higher for patients with probable/proven IA for all cost categories, including diagnostic procedures, medication and transfusion related costs. Further analysis revealed that attributable cost was sensitive to antifungal drug choice with 8 days of intravenous voriconazole treatment for IA increasing costs by €17,890 for probable/proven IA. Patients with probable/proven IA had a longer mean LOS than control patients (104 days versus 84 days, p<0.001) (Slobbe, Polinder et al. 2008).

Dodds Ashley et al. (2012) using patient-level data reported similar outcomes from a single US centre (Duke University Medical Centre, Durham, NC). In this case-control study 200 patients with ICD-9 discharge codes for either aspergillosis, candidiasis, cryptococcosis and zygomycosis from 2004 to 2005 were matched to 200 uninfected control patients with similar underlying conditions (Dodds Ashley, Drew et al. 2012). All cases underwent manual chart review to ensure that they met consensus definitions for possible, probable or proven IFD (according to modified Mycoses Study Group/European Organisation for Research and Treatment of Cancer [MSG/EORTC] definitions, December 2005 version 31). Importantly, this study attempted to take into account LOS prior to IFD onset by, including the duration of hospitalisation prior to IFD onset in the matching criteria for control patients.

Hospitalisation costs were determined by converting charges to costs using cost-to-charge ratios. Briefly, charges are billing parameters between US health care providers and payers and are not thought to truly represent the actual costs of delivering hospital-based medical care to patients (Meltzer 2001; Jegers, Edbrooke et al. 2002). Charges were assigned according to the following categories: systemic antifungal drugs, concomitant drugs, hospital room charge, laboratory testing, health care professional charges, radiology charges, procedural charges and other. After adjusting for race-ethnicity, sex, age and co-morbid illnesses, mean total hospital cost for cases was $32,196 more than for controls (95% CI $18,074–46,318, p<0.0001).

Non-pharmacy costs (such as ward costs and laboratory fees) accounted for the majority (63%) of this difference, and an additional $3996 or 14% of the difference was due to systemic antifungal drugs. Patients with invasive candidiasis most commonly received fluconazole or caspofungin while voriconazole, caspofungin or lipid formulations of amphotericin B were most commonly given to patients with IA. The high contribution of laboratory costs (18% of the difference) may be unique to this centre, which used GM assays and fluorescence *in situ* hybridisation assays for the rapid identification of *Candida* species. The mean length of hospital stay was longer for cases than controls (25.8 versus 18.4 days) (Dodds Ashley, Drew et al. 2012).

A recent German study addressed the question of attributable cost of IFDs in patients with AML-MDS from a hospital perspective (Rieger, Cornely et al. 2012). This was a multicentre retrospective case-control study of patients over a 10-month period in 2007. Detailed chart review was performed to determine resource utilisation because German hospitals do not have a system to obtain itemised costing at the patient-level. Control patients were matched on similar age, a comparable duration of neutropenia and intensity of chemotherapeutic regimen as case-patients. Resource utilisation data for the period of hospitalisation included mechanical ventilation, parenteral feeding, diagnostic procedures, systemic antifungal medication and cost-intensive medications such as antibiotics and immunosuppressive drugs (Rieger, Cornely et al. 2012).

The attributable cost of an IFD was the difference in costs between cases and matched controls. Costs were calculated as the quantity of each resource

consumed multiplied by the unit cost for each resource. A total of 108 patients were identified, of which 36 had IFDs (74% of whom had IA) matched to 72 control patients (Rieger, Cornely et al. 2012). The mean excess LOS for IFD patients was 12 days. Excess mean costs associated with IFD was €21,063 (p<0.05) with antifungal drugs accounting for 36% of the difference, hospital stay 32% and blood products 23%. Antifungal drugs in patients with IFDs included voriconazole in 81%, caspofungin in 75% followed by liposomal amphotericin in 31%. When control patients received antifungal drugs (89%), it was on an empiric basis and comprised voriconazole in 56%, fluconazole in 32%, caspofungin in 29% with liposomal amphotericin accounting for only 6% of prescriptions.

Antifungal drugs in both control and case-patients were a major cost driver. For example, mean costs of control patients who received systemic antifungal drugs was €32,361, whereas costs in control patients who did not receive antifungal drugs was €15,203 lower. These data demonstrate that in real-world clinical practice, overuse of antifungal drugs is common and often deviates from published evidence. Voriconazole was used empirically despite a lack of licensing for this indication. If ICU was required (for 39% and 13% of case and control patients respectively), mean costs per patient rose dramatically compared to patients who did not require ICU; for IFD patients (€65,347 versus €42,716) and control patients (€42,394 versus €28,749) (Rieger, Cornely et al. 2012).

All studies comparing economic outcomes in patients with and without IFDs consistently demonstrate that patients with IFD have prolonged hospitalisation, higher ICU requirements and higher excess hospitalisation costs than patients without IFDs (Tong, Lau et al. 2009; Kim, Nicolau et al. 2010; Ananda-Rajah, Cheng et al. 2011; Dodds Ashley, Drew et al. 2012). However, few studies have examined the effect of modifiable factors such as antifungal therapy on cost drivers such as LOS.

4.4   Effect of Treatment Strategy on Cost

A post-hoc analysis of the TRANSNET study attempted to examine the effect of antifungal treatment on specific economic outcomes such hospital LOS (Baddley, Andes et al. 2013). A subgroup of 361 patients with IA enrolled at 9 of the 23 transplantation sites were studied with associated antifungal treatment regimens retrospectively collected.

Factors found to be associated, on multivariate analysis, with increased LOS (defined as a LOS of 30 days or more) were also surrogates of illness severity. These included neutropenia (OR 3.05, $p<0.06$), malnutrition (OR 2.82, $p<0.037$) and prolonged ICU stay (OR 1.12, $p<0.001$). Receipt of voriconazole in the initial antifungal regimen (i.e., administered within 48 hours of IA diagnosis) was identified as a factor associated with reduced LOS (OR 0.41, $p<0.027$) after controlling for multiple co-morbidities.

The association between voriconazole and shorter LOS may reflect its suitability for oral de-escalation facilitating earlier discharge from hospital and is consistent with findings from Kim et al. (2010), who reported that voriconazole, amphotericin B lipid complex and caspofungin were associated with decreased LOS but only voriconazole was associated with reduced hospital costs. Receipt of combination therapy was not significantly associated with decreased LOS but the study may have been underpowered to evaluate this specific treatment approach. It is unclear if receipt of combination therapy is a marker of disease severity and therefore may be associated with increased LOS but the converse did not hold either (Baddley, Andes et al. 2013).

This study revealed that variation in treatment approaches to IA is the norm rather than the exception. There were 48 different regimens recorded for the treatment of IA with the mean length of treatment (115 days) in excess of the 6 to 12 weeks recommended by guidelines (Baddley, Andes et al. 2013). Voriconazole and amphotericin B were most commonly used and consistent with 2008 practice guidelines (Walsh, Anaissie et al. 2008) noting that TRANSNET closed in 2006. Combination antifungal therapy, which is not advocated by any current or previous published guidelines, was common being used as initial treatment in 36% of patients. The most frequent regimen was voriconazole plus caspofungin (22%) or a lipid formulation of amphotericin plus caspofungin (6%) (Baddley, Andes et al. 2013). This study supporting the favourable effect of voriconazole on LOS is preliminary and by no means conclusive but does highlight the need for further comparative effectiveness studies to identify potentially modifiable treatment-related variables under the

influence of clinicians, which may improve the health and economic outcomes of these infections (Baddley, Andes et al. 2013).

4.5   Summary

The economic burden of IFDs is substantial (Wilson, Reyes et al. 2002; Menzin, Meyers et al. 2009; Menzin, Meyers et al. 2011). Accurate estimates of cost underpin cost effectiveness analyses but studies are characterised by heterogeneity in cost determination methods or source data, questionable generalisability, differences in outcomes reported (e.g. median versus mean costs) and variable cost categories. Economic analyses based on clinical trial data, while usually comprehensive, are subject to selection bias as trial populations are not representative of the full spectrum of patients in clinical practice and sample size may be insufficient to dissect the influence of underlying disease on overall costs (Wenzel, Del Favero et al. 2005). Large administrative datasets overcome the problem of sample size but certainty of IFD diagnosis, details of antifungal treatment and host characteristics are often not available (Menzin, Meyers et al. 2009; Menzin, Meyers et al. 2011).

Cost determination methods for IFDs are highly variable with some studies reporting either gross hospitalisation costs (Slavin, Fastenau et al. 2004; Tong, Lau et al. 2009; Kim, Nicolau et al. 2010) or attributable costs using either patient-level (Slobbe, Polinder et al. 2008; Ananda-Rajah, Cheng et al. 2011; Dodds Ashley, Drew et al. 2012) or more commonly, administrative data because the latter is a routinely collected and readily available resource

(Wilson, Reyes et al. 2002; Tong, Lau et al. 2009; Menzin, Meyers et al. 2011). Studies from the US often use cost-to-charge ratios (Wilson, Reyes et al. 2002; Tong, Lau et al. 2009; Menzin, Meyers et al. 2011; Dodds Ashley, Drew et al. 2012) rather than actual costs. Where actual costs are reported they may in fact reflect per day or *per diem* costs multiplied by average LOS (Slavin, Fastenau et al. 2004), cost per unit (e.g., list costs for good/services rendered) (Rieger, Cornely et al. 2012), neither of which are as accurate as microcosting (Slobbe, Polinder et al. 2008) or activity-based costing (Barnett 2009; Ananda-Rajah, Cheng et al. 2011) methods (Jegers, Edbrooke et al. 2002).

Microcosting and activity-based costing are bottom-up methods that reflect itemised costs of goods or services delivered at the patient-level but this costing method is not widely available and tends to be institution specific. *Per diem* cost applies a single cost to each hospital day and therefore disregards the variations in resource consumption (e.g., drug and non-drug interventions, treatment or diagnostics) that occur with time (Dixon, McKeen et al. 2004). Studies tend to report mean (Wilson, Reyes et al. 2002; Slavin, Fastenau et al. 2004; Slobbe, Polinder et al. 2008; Menzin, Meyers et al. 2011; Dodds Ashley, Drew et al. 2012; Rieger, Cornely et al. 2012) over median (Kim, Nicolau et al. 2010; Ananda-Rajah, Cheng et al. 2011) costs, noting that the mean may overestimate cost because it is highly influenced by outlier patients.

Median cost is a more conservative measure but may not be as fiscally relevant from a hospital perspective because it is less influenced by those few outlier patients who consume the greatest resources. Costs are variable with gross

hospitalisation costs being US$52,803 (2006) (Kim, Nicolau et al. 2010) and US$44,845 (2003) (Tong, Lau et al. 2009), while attributable hospitalisation costs are US$55,400 (2007) (Menzin, Meyers et al. 2011), €15,280 (2007) (Slobbe, Polinder et al. 2008), US$32,196 (2004 to 2005) (Dodds Ashley, Drew et al. 2012). Excess LOS is uniformly prolonged ranging from 7 days (Dodds Ashley, Drew et al. 2012) to 20 days (Slobbe, Polinder et al. 2008).

Attributable cost is a more informative measure as it attempts to disentangle the effect of underlying disease, but these studies are few and those using patient-level data even fewer (Slobbe, Polinder et al. 2008; Ananda-Rajah, Cheng et al. 2011; Dodds Ashley, Drew et al. 2012). The cost of IFDs is largely borne by inpatient rather than ambulatory services, which contribute 54% towards total direct medical costs (Wilson, Reyes et al. 2002). However, the drivers of hospitalisation cost are conflicting with some studies citing LOS as the major contributor (Wilson, Reyes et al. 2002; Kim, Nicolau et al. 2010; Dodds Ashley, Drew et al. 2012) with antifungal drugs (7.2% in Kim, Nicolau et al. 2010) or pharmacy (30% in Tong, Lau et al. 2009; 17% in Wilson, Reyes et al. 2002) accounting for a smaller fraction of the difference. However, others have contested these estimates (Ananda-Rajah, Cheng et al. 2011).

Cost drivers are ideally derived from patient-level analyses rather than administrative coding data because the former captures detailed information on antifungal drug consumption, which are regarded as high cost items (de With, Steib-Bauert et al. 2005; Rieger, Cornely et al. 2012) poorly captured by administrative datasets. Importantly, measures of resource use alternative to

cost that are independent of country and inflationary pressures are needed if health economic studies are to have improved generalisability (Ananda-Rajah, Cheng et al. 2011).

Chapter 5: Automated Surveillance and Natural Language Processing

5.1 Making Continuous, Prospective Surveillance of IMDs Feasible: Technological Solutions

Practice guidelines advocate *routine* surveillance for clinical cases of IMDs in addition to '*enhanced surveillance* of microbiologic, pathological and radiological data', especially during periods of hospital construction (Tomblyn, Chiller et al. 2009; Yokoe, Casper et al. 2009). Ageing hospital infrastructure means that construction and renovation is an ongoing activity in many hospitals. Thus, compliance with guidelines and therefore best practice effectively translates into continuous prospective surveillance, which, as seen in other jurisdictions (Fourneret-Vivier, Lebeau et al. 2006; Nicolle, Benet et al. 2011), is a demanding task for hospitals.

We believe that prospective surveillance of fungal diseases in hospitals requires smarter use of technology to make it feasible, sustainable and cost-effective. Similar sentiments have been expressed following review of the CDC National Healthcare Safety Network (NHSN). The NHSN is the largest hospital-acquired infection (HAI) reporting system in the US, encompassing over 11,500 medical facilities. The HAIs tracked by the NHSN included CLABSI, catheter-associated urinary tract infections, VAP, surgical site

infections and *Clostridium* difficile infection. Importantly, IMDs are not included, which is a concerning omission in light of the largest reported fungal outbreak which is currently active in the US. The multistate fungal infection outbreak associated with contaminated steroid injections has affected 749 patients caused 61 deaths (as of 3 August 2013), with over 13,500 people exposed (Kainer, Reagan et al. 2012; Shoham and Marr 2012; Kontoyiannis, Perlin et al. 2013; Pappas, Kontoyiannis et al. 2013). It is unclear if IMDs will become notifiable conditions as a consequence of this outbreak as doing so will go some way towards protecting vulnerable populations from these rare but catastrophic system failures in the future.

5.2 Ideal Surveillance Model: the CDC's Perspective

An audit of the CDC's Division of Healthcare Quality Promotion Surveillance Branch made several salient observations regarding the challenges of surveillance largely in reference to HAIs but with implications for surveillance of IMDs. Legislative mandates to use the NHSN as the primary means for HAI reporting in an increasing number of states (30 states at present at www.cdc.gov/hai/state-based/tracking.html accessed on 20 July 2013) in the US has imposed significant pressures on the NHSN system. These quality and safety initiatives that incorporate process and outcome measures related to HAIs are linked to hospital reimbursement. As a result, increasing state participation is applying pressure on the NHSN to modernise all aspects of data management.

5.2.1 CDC Recommendation: Improving Data Collection from Health Care Systems Using Technology

The external panel reviewing the NHSN believed that upholding the standards of HAI surveillance, which are based on the principles of credible and valid epidemiologic data (i.e., data integrity and quality), requires investment in NHSN infrastructure, including the incorporation of emerging information technologies and embracing innovative technology solutions (CDC 2008).

The panel recognised that data collection and entry was a labour intensive task and called for greater attention to the development of efficient, user-friendly data collection methods in order to reduce the burden of surveillance and meet future demands on the system. Automating data collection was a key recommendation that cited information extraction from commercial systems in health care facilities as a critical step for the future expansion of the NHSN. In making this recommendation the CDC acknowledges that the burden of data collection and reporting on end-users tends to be underestimated by authorities.

Automated data collection is an important means for meeting the demands of increasingly complex health care systems dealing with high acuity populations. The panel cautioned that at present, the NHSN will not have adequate capacity to maintain pace with increased volume of the system without automated data collection, particularly in complex health networks that provide a high volume of services to populations with high acuity (CDC 2008).

The recommendations from the NHSN review have relevance to surveillance of IMDs: extraction of data from existing hospital systems, incorporation of best available technology to reduce the burdensome nature of fungal case ascertainment in order to keep pace with changes in an increasingly complex clinical environment.

5.2.2 CDC Recommendation: Exploiting Unstructured Data in Health Care

A greater reliance on technological advances in data collection, processing and analysis has been emphasised in the CDC's vision for public health surveillance into the next era (Rolka, Walker et al. 2012). The CDC acknowledges that we are entering a period where huge amounts of data will flow from initiatives such as electronic health records and other data not developed specifically for public health surveillance. They envisage that unstructured data like data in free-text format will become a major contributor to real-time surveillance because unstructured data tends to be delivered more quickly than traditionally sourced surveillance data (Rolka, Walker et al. 2012).

The domain of health informatics is informed by the provision of timely, relevant and high quality information delivered in a cost-effective fashion by leveraging computer science, information science or technology (Savel and Foldy 2012). The 3 elements of public health informatics are relevant to surveillance in general:

1. The study of complex systems.

2. Opportunities to improve efficiency and effectiveness of public health systems through innovative data collection or use of information.

3. The maintenance of processes and systems to achieve these goals (Savel and Foldy 2012).

A greater reliance on innovative technologies, the timely delivery of informative data and improved data collection harnessing unstructured or free-text data are recurrent themes in improvements to public health surveillance envisioned by the CDC (Savel and Foldy 2012)—these elements have relevance to surveillance of discrete conditions such as IMDs as will be discussed later in this chapter.

5.2.3 Requirements for Automated Surveillance According to the CDC

The CDC, a leading authority on public health surveillance, has outlined the key components of a public health surveillance system, which have applicability to surveillance of other conditions like IMDs. Following is an adaptation of these recommendations (Savel and Foldy 2012) to the task of IMD surveillance:

1. Planning and system design: identifying information and sources that best address a surveillance goal. For IMDs, chest imaging findings are an important source of data as identified in surveillance studies of nosocomial infections in patients with neutropenia (Engelhart, Glasmacher et al. 2002; Dettenkofer, Ebner et al. 2003) and recent epidemiological studies demonstrating that pulmonary involvement of IMDs occurs in >90% of patients (see Table 2.1).

2. Data collection: identifying bias associated with different collection methods (e.g., laboratory-based versus administrative or coding systems versus active or passive prospective reporting). For IMDs, clinical and microbiologically confirmed infections correspond to possible and probable/proven IMDs respectively (De Pauw, Walsh et al. 2008); laboratory-based surveillance for IMDs would result in significant underreporting and coding data is inherently inaccurate for case ascertainment and classification (Chang, Burwell et al. 2008). Identifying the appropriate use of structured data in EHRs compared to free-text unstructured information is important. Uptake of certified (rather than basic) EHRs in non-federal acute care hospitals has increased in the US from 72% to 85% from 2011 to 2012 (Murdoch and Detsky 2013). However, it is almost non-existent in Australian hospitals. Thus, in our setting and in those jurisdictions lacking comprehensive EHRs, unstructured data will be a major source of data for surveillance purposes.

3. Using technology to expedite high quality data entry in routine clinical practice.

4. Data management and collation refers to ways of sharing data across different computing/technology platforms, data linkage across hospital information systems and processes designed for identifying and addressing data quality problems. Because IMDs are typically diagnosed in acute care settings, access to data from hospital information systems would be necessary for case ascertainment.

5. Analysis: using appropriate statistical and visualisation tools to identify case clusters while leveraging high-performance computational resources for large data sets or complex analyses.

6. Interpretation: determining the utility of data linkage (combining datasets related by time, place, person or condition) or combining data from other sources for new perspectives and knowledge discovery.

7. Dissemination: finding the most appropriate display of information for end-users, this may include the use of visualisation applications.

8. Application to public health programs: streamlining the flow of surveillance data into information systems, which subsequently trigger interventions—i.e., linking surveillance to interventions. Access to timely, relevant and high quality surveillance data via a user-friendly interface with linkage to interventional programs such as clinical decision support, translates into meaningful actionable knowledge.

5.2.4   CDC Recommendation: Maximising Value from Existing Health Care Systems

The CDC have provided recommendations that address the transition from manual reporting using traditional sources of data to automated data collection for surveillance purposes (Savel and Foldy 2012).

- As much as possible existing systems should be used or modified.

- Existing data streams should be leveraged for multiple purposes.

- The expectation of delivering an ideal system can delay the important work of system change, therefore consideration should be given to small incremental steps rather than sweeping organisational changes.

- The combination of disparate sources and forms of information can provide a more complete picture of disease burden than singular sources of data.

The CDC identified the roles of information science and emerging technologies as possibly the most pressing issue that confronts the agency and its partners. Therefore, while progress in information technology has provided opportunities for improvements to the effectiveness and efficiency of surveillance, the CDC is aware of the practical realities governing the successful adoption of technology. Technology that addresses a clinical need and user requirements should have a higher priority than solutions that are technologically exciting (Thacker, Qualters et al. 2012).

In reference to public health informatics, the CDC questioned the sustainability of active surveillance using standard techniques such as manual chart reviews or manual data entry in the face of rising economic pressures on health care. Likewise, passive reporting is not ideal due to incomplete case ascertainment and reporting delays. Overcoming many of the limitations of traditional case finding relying on manual methods is informatics science and there is a growing body of published evidence outlining its role in health care for safety, quality and research initiatives as illustrated by the following studies.

5.3 Automated Surveillance of a Variety of Conditions and Their Lessons for IMDs

Electronic surveillance systems that meet some of the CDC's recommendations have been developed, but none as yet have focused on IMDs. However, lessons applicable to IMDs are appreciated.

5.3.1 Surveillance of Hospital Acquired Infections

Automated surveillance of HAIs was pioneered >20 years ago at the Latter Day Saints (LDS) hospital, Utah (Evans, Larsen et al. 1986). This hospital leveraged pre-existing EHRs by developing a medical decision logic system known as the Health Evaluation through Logical Processing (or HELP) system in a period of 2 years. With domain expertise from infectious diseases physicians they developed a knowledge base, which in combination with antimicrobial and microbiology inputs could identify patients with HAIs (urinary tract, surgical site, lower respiratory tract, bacteraemia, line related). Patients with HAIs were flagged if they were not receiving appropriate antibiotics or where less costly but equally efficacious alternatives were available or if they were receiving prolonged surgical prophylaxis (longer than 48 hours of cephalosporin antibiotics) without reasonable justification (Evans, Larsen et al. 1986).

Integration of data from multiple electronic hospital systems realised efficiency savings. During the 2-month pilot, the system was more cost-efficient and

accurate than manual surveillance. It identified 14% more HAIs and reduced labour by 65%, from 130 hours to 46 hours (Evans, Larsen et al. 1986). Prior to automation, the burden of manual surveillance was considerable with infection preventionists spending 130 hours on surveillance and 8 hours collating surveillance data for a summary report. In contrast, the system required 8.6 hours to prepare a similar report based on unverified computer alerts. With computerised alerts, physician reviewers took approximately 15 minutes to adjudicate each case for the presence of an HAI. Thus, inclusion of physician verification, which is not a routine step with standard surveillance, required 46 hours of surveillance and yet identified more patients and more sites of infection. Thus, automated surveillance was both cost saving and effective in identifying HAIs. Importantly, the system while targeting HAIs, did not address fungal diseases, which are also well-recognised as being nosocomially acquired (Tomblyn, Chiller et al. 2009; Weber, Peppercorn et al. 2009; Yokoe, Casper et al. 2009; Alangaden 2011).

During the 2-month pilot study at the LDS hospital, time saved in manual surveillance resulted in re-deployment of staff into other areas such as audits of patient care, in-service and educational activities. The real-time provision of data permitted more rapid responses with faster isolation of patients and feedback of surveillance data. Combined with clinical decision support functionality, the system flagged patients receiving inappropriate antibiotics, prolonged surgical prophylaxis (142 patients in one month) or antibiotics where cheaper alternatives were available (Evans, Larsen et al. 1986). The system identified 37 patients during the 2-month pilot who were receiving

inadequate or inappropriate antibiotic therapy and in 64 patients recommended an alternative or less costly antibiotic all of which were regarded as clinically relevant by an adjudication panel (Evans, Larsen et al. 1986).

5.3.2 Central line Associated Blood Stream Infection

Recently, a multicentre retrospective study comparing automated detection of CLABSI in 20 ICUs from 4 hospitals showed that it was both feasible and accurate, providing similar estimates as gold standard manual surveillance (Lin, Hota et al. 2010). Infection preventionists at each site performed manual surveillance of CLABSI using CDC definitions over 12-month periods. Rates were then compared to a computer algorithm that was applied retrospectively to the surveillance dataset using criteria adapted from CDC surveillance definitions. Across 41 time intervals from 2004 to 2007, median CLABSI rates as determined by infection preventionists were 3.3 and by computer algorithm were 9.0 infections per 1000 central line–days. Correlation between the computer algorithm and manual surveillance was weak with wide inter-institutional variation in correlations evident. For example, the medical centre with the lowest rate by traditional surveillance (2.4 infections per 1000 central line–days) had the highest rate by computer algorithm (12.6 infections per 1000 central line–days). The heterogeneity in reporting standards (as evidenced by the disparities between manual and computerised surveillance rates) pointed towards variations in the subjective interpretation of case definitions by infection preventionists. This study cast doubt on the validity of publically reported institutional rates currently based on manual reporting, which in some US states is linked to hospital reimbursement (Lin, Hota et al. 2010).

The computer algorithm used in the multicentre CLABSI study (Hota, Harting et al. 2010; Lin, Hota et al. 2010) relied on clinical data in EHRs. The algorithm evaluated laboratory-based blood culture results using step wise logic to make a determination regarding the presence or absence of CLABSI (Hota, Harting et al. 2010). Multiple sources of electronic data were used to drive the algorithm, including: microbiology of positive and negative blood culture results; patient census, including admission, discharge or transfer information and pharmacy dispensing to determine if vancomycin as a surrogate marker of CLABSI treatment, had been prescribed. At one hospital microbiology data was limited by free-text format but this was overcome with the application of natural language processing (NLP) which will be discussed later (Hota, Harting et al. 2010).

These investigators successfully translated existing manual surveillance case definitions to automated methods drawing on 3 specific areas of domain expertise: clinical, surveillance and informatics. In doing so, they illustrated the value of using multiple sources of data for electronic surveillance from 4 medical centres with diverse data environments. They overcame technical barriers, including major differences in the data availability, structure (e.g., in some cases using NLP to extract organisms from unstructured microbiology results), and SQL language type. A major challenge was the heterogeneity of local nomenclatures for describing microbiology data emphasising the broader need for data harmonisation across organisations. Uniform standards in

vocabulary and database schema would assist the broader development of electronic surveillance systems.

5.3.3 Ventilator Associated Pneumonia

VAP is another diagnostically challenging condition for which automated surveillance has been recently trialled using a computerised algorithm adapted from CDC case definitions (Klompas, Kleinman et al. 2008). Accuracy of the algorithm was compared to prospective clinician survey at 3 ICUs at a single US centre over a 3-month period. Of 459 consecutive patients who underwent mechanical ventilation, the algorithm applied to electronic data detected 20 patients all of whom satisfied standard CDC criteria (100% PPV). In contrast, prospective clinician survey detected 33 patients with possible VAP of whom only 17 met standard definitions resulting in a 52% PPV. Of the 21 cases of confirmed VAP detected by pooling both methods, the majority of cases (20/21, 95%) were identified by the algorithm and fewer (17/21, 81%) by clinician survey.

In adapting the CDC criteria for VAP, the key elements such as 1 radiographic criterion, 1 systemic criterion and 2 pulmonary criteria were retained while features not usually captured by EHRs were eliminated, including non-specific signs (e.g., crepitations, dyspnoea, cough). These were subsequently replaced with quantifiable outcomes as surrogates for clinical or microbiological criteria (e.g., radiologist opinion of chest radiograph findings; temperature and white cell count for systemic criteria; gram stain of respiratory secretions or changes in ventilator settings for pulmonary criteria) (Klompas, Kleinman et al. 2008).

In short, electronically available data became the surrogates of clinical criteria (Klompas, Kleinman et al. 2008). These ventilator change criteria served as an efficient means of rapidly screening large numbers of patients receiving mechanical ventilation with those patients meeting this specific criterion further evaluated to determine if they met the case definition. This hospital was somewhat unique, because a snapshot of ventilator settings was recorded on a daily basis into a database maintained by the respiratory department. It was this dataset that was subsequently interrogated for screening purposes with additional laboratory information sourced from hospital information systems (Klompas, Kleinman et al. 2008).

5.3.4 Detection of Hospital Outbreaks Using Local Adaptation of Public Health Surveillance Software

An attempt at whole hospital detection of infectious disease outbreaks was recently tested using a combination of 2 population-based epidemiologic surveillance software programs (Huang, Yokoe et al. 2010). WHONET-SaTScan software from the World Health Organization (WHO) Collaborating Centre for Surveillance of Antimicrobial Resistance originated from integration of software designed for public health surveillance (WHONET/BacLink and SaTScan). In this retrospective study at a US centre, the hybrid software (WHONET-SaTScan) was calibrated for laboratory-based outbreak detection. It was applied to a microbiology dataset containing patient identifiers, ward location, clinical service, collection date, specimen source, hospital admission date and antimicrobial susceptibility profiles. Cluster alerts detected

electronically by WHONET-SaTScan were compared to clusters identified by standard surveillance performed by infection preventionists. Manual reporting of case clusters by ICPs was based on known epidemiologic source, genetic clonality and rule-based criteria such as 3 or more nosocomial cases within a 2-week interval.

In this study, the automated cluster detection software (WHONET-SaTScan) identified all confirmed hospital outbreaks and demonstrated that traditional cluster detection spuriously identified outbreaks that were likely to reflect normal random variations rather than actual outbreaks. In other words, the statistical basis of cluster detection employed by the software was more accurate than rule-based criteria used by infection preventionists. Nearly all 59 clusters (95%) reported by the automated detection tool were deemed to be of interest to the adjudicating panel of hospital epidemiologists and 25% generated sufficient concern to prompt an active intervention or full scale intervention (Huang, Yokoe et al. 2010).

In addition, the automated tool was more comprehensive than traditional surveillance as it evaluated all pathogens rather than only multiply drug resistant organisms, such as methicillin resistant *Staphylococcus aureus* (MRSA) or vancomycin resistant enterococci (VRE), which were the focus of targeted surveillance by hospital infection preventionists (Huang, Yokoe et al. 2010). Of interest, two-thirds of identified clusters were due to gram negative or fungal pathogens that were not under routine surveillance (i.e., of 59 clusters identified, 53% were due to gram positive organisms, 36% were due to gram

negative organisms and 12% were due to fungi). Of the 7 fungal outbreaks, the majority (n=6) were due to *Candida* species and one was due to *Aspergillus fumigatus*. Validation will be required to determine if statistical alerts are indeed superior to rule-based criteria (i.e., traditional case surveillance case definitions) when prospectively partnered with clinical judgement to guide preventative interventions (Huang, Yokoe et al. 2010).

5.4   Commercial Automated Surveillance Systems

Commercial vendors started to take an interest in automated surveillance systems for HAIs in the 1990s and presently there are several market leaders in the US, including CareFusion's MedMined, AICE software, Hospira's Theradoc, Premier's SafetySurveillor-Infection Control, MEDITECH's Healthcare Information System, and MIDAS1 Care Management-Infection Control (Halpin, Shortell et al. 2011).

Experts have cautioned against acquisition of commercial systems (Classen 1994; Clayton, Narus et al. 2003) citing concerns with vendor longevity when hospitals typically require vendors to stay in business for ≥30 years (Clayton, Narus et al. 2003) and poor published evidence supporting their value (Chaudhry, Wang et al. 2006). Clinician-led development of automated surveillance systems rather than adoption of commercial systems is consistent with the CDC's recommendations that these systems be informed and driven by clinical need (Rolka, Walker et al. 2012). Despite the presence of several commercial systems many US hospitals have preferred to pay private

consultants or develop their own in-house systems (Wisniewski, Kieszkowski et al. 2003; Grota, Stone et al. 2010; Halpin, Shortell et al. 2011).

Indeed, a clinical champion from LDS and key developer of the HELP system (Evans, Larsen et al. 1986) stated that clinical information systems developed by linking existing departmental systems is 'the only viable means of creating a comprehensive integrated medical record in a relatively short time—i.e., 2 to 5 years' (Classen 1994). Thus, the integration of existing hospital systems and the application of complex data analysis techniques can yield enormous benefits in the area of HAI surveillance as echoed by the CDC (Savel and Foldy 2012).

5.5   Unlocking Data in Hospitals Using NLP

In hospitals, radiology and pathology reports are a rich source of clinical information but their use for clinical and epidemiological research is limited by their free-text, narrative form. NLP is a computational method for processing human language. Natural language refers to language used for human general purpose communication and is distinct from programming language used by computers. NLP has allowed rapid retrieval of data from electronic documents with an accuracy comparable to human interpretation (Meystre, Savova et al. 2008). As a high-throughput technology, it has been applied for detection of a variety of conditions from structured and unstructured documents. Structured data is information presented in a standard, predictable form that can be easily processed by a machine. Unstructured data includes free-text clinical

narratives/ reports representing the majority of patient-level information in hospitals.

5.5.1 Components of Natural Language

Computational methods that extract and organise information in text is a knowledge intensive and complex task. Natural language encapsulates a vast amount of expressiveness, variety, ambiguity and vagueness that a machine must process. For example, the same concept may be expressed multiple ways (CAP, community-acquired pneumonia); the same word may have different meaning depending on context (discharge from hospital versus wound discharge); relations among words may be ambiguous (e.g., no evidence of pneumonia versus pneumonia cannot be excluded); negation detection is difficult (e.g., no evidence of pneumonia versus the lung fields are clear); and the meanings of some expressions may lack specificity (e.g., may represent pneumonia or may be consistent with pneumonia).

Understanding textual language in clinical narratives requires several key elements. These include syntactic, semantic and domain-knowledge components. Syntax refers to the formal grammars that specify the relationship between units in text such as nouns, verbs, adjectives, and objects (Nadkarni, Ohno-Machado et al. 2012). NLP must ultimately extract meaning from text and this is addressed by semantics. Domain-knowledge is information related to the topic from a subject matter expert. Clinical NLP systems are often linked to a controlled clinical vocabulary whereby words are mapped to concepts (e.g., pneumonia, consolidation, CAP would all be mapped to the same

concept), while discharge from hospital would be mapped to a managment type concept and fever to a sign/symptom concept.

Clinical vocabularies such as the Unified Medical Language System (UMLS) Metathesaurus developed by the National Library of Medicine assigns a unique identifier to a concept, with synonymous concepts having the same identifier, allowing NLP systems to map a broad range of words in text to a specific concept. Sematic categories for concepts are also included in the UMLS such that fever for example, is assigned the category sign/symptom. Clinical vocabularies help improve access to clinical information because each concept is associated with a well defined and unique meaning thereby minimising variety and ambiguity.

5.5.2 Key Technical Aspects of NLP

There are 2 common approaches to NLP: rule-based or knowledge-based approaches and statistical or machine-learning based approaches. Rule-based systems use knowledge to develop a set of explicit decision rules. In contrast, statistical or machine-learning based systems use large annotated bodies of text (corpora) often labelled by domain experts to train machine-learning algorithms. These algorithms are subsequently used to build classifiers (Cohen and Hunter 2008; Nadkarni, Ohno-Machado et al. 2012). Machine-learning systems use algorithms that infer patterns from training datasets thereby permitting predictions on unseen or unlabelled data.

Learning can be supervised or unsupervised. In supervised methods, each item in the training set is labelled with the correct answer, whereas in unsupervised methods, the machine-learning system tries to recognise patterns automatically and automatically generates the most globally optimal solution to the problem (Cohen and Hunter 2008). Overfitting the model is a potential problem (i.e., the model may fit the training data almost perfectly but is poorly predictive at classifying unseen cases). In NLP, cross-validation is a well-recognised method for minimising the risk of overfitting. Cross-validation randomly partitions the training data into training and test sets to internally validate the model's predictions. The process of partitioning, training and validation are repeated over several rounds and the validation results are then averaged across rounds.

Statistical approaches perform better in practice because they learn from the most common cases in real data and improve with greater amounts of data representative of the condition of interest. However, handwritten rule-based and statistical approaches are probably complementary and may be combined (e.g., initial statistical processing being followed by a rule-based post processing step) (Nadkarni, Ohno-Machado et al. 2012).

5.6   NLP for Clinically Diverse Applications

NLP has been used successfully for detection of several conditions, including nosocomial pneumonia (Haas, Mendonca et al. 2005), medical adverse events (Melton and Hripcsak 2005), vaccine adverse events (Hazlehurst, Naleway et

al. 2009), tumours (Imai, Aramaki et al. 2007) and their progression (McCowan, Moore et al. 2006).

5.6.1 Post-operative Complications

Recently, 6 Veterans Affairs US hospitals participated in a NLP-based approach to detection of post-operative complications from a comprehensive EHR (Murff, FitzHenry et al. 2011). A group of 2974 surgical patients from 1999 to 2006 were randomly selected and linked to an administrative database. An impressive volume of clinical data was subsequently extracted from electronic sources, including narrative clinical notes (i.e., discharge summaries, progress notes, operative notes, microbiology reports, imaging reports and outpatient records), vital sign information, pharmacy data and laboratory results from the Veterans Health Information System and Technology Architecture. Post-operative complications studied were acute renal failure requiring dialysis, venous thromboembolism, sepsis, pneumonia or myocardial infarction—all of which are patient safety indicators collected by trained nurse reviewers as part of the VA Surgical Quality Improvement Program (VASQIP) (Murff, FitzHenry et al. 2011).

The NLP system employed for information extraction from free-text records was the Multi-threaded Clinical Vocabulary Server (MCVS, Elkin, Brown et al. 2006). MCVS has been installed at multiple organisations, including the CDC; the Department of Veterans Affairs; and several academic medical centres, including Mount Sinai School of Medicine, Mayo Clinic, and Johns Hopkins Health System. The system has been used for biosurveillance (Elkin,

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Brown et al. 2008) and for input into large-scale clinical research data warehouses (Brown, Speroff et al. 2006; Brown, Elkin et al. 2008). In this study (Murff, FitzHenry et al. 2011), the MCVS processor parsed free-text records from EHRs, identifying specific medical concepts and mapped these concepts to an ontology of medical concepts known as the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) terminology, which contains over 310,000 concepts (SNOMED-CT 2013, http://www.ihtsdo.org/snomed-ct). Handcrafted rules were designed for sentence strings or expressions not recognised by MCVS (Murff, FitzHenry et al. 2011).

The NLP approach was compared to patient safety indicators, which is an administrative discharge code based system. VASQIP confirmed events, as determined by nurse reviewers served as the reference standard (Murff, FitzHenry et al. 2011). NLP correctly identified 82% of acute renal failure cases compared with 38% for patient safety indicators. Similar results were obtained for venous thromboembolism (59% versus 46%), pneumonia (64% versus 5%), sepsis (89% versus 34%), and post-operative myocardial infarction (91% versus 89%). Thus, an NLP-based approach using a comprehensive EHR was superior to an administrative code based algorithm at detecting post-operative events (Murff, FitzHenry et al. 2011). However, with less than 2% of US hospitals having comprehensive EHRs (Jha, Bates et al. 2009) the query strategies used in this study would not be feasible in many hospitals.

5.6.2 Biosurveillance of Influenza

Biosurveillance of infectious diseases demands rapid detection and response. Biosurveillance has been defined by a US Presidential Directive to specifically relate to acute events such as a terrorist threat or an influenza epidemic (Thacker, Qualters et al. 2012). However, with a proliferation of modifying terms for surveillance (e.g., 'epidemiologic', 'active', 'passive', and 'sentinel', 'integrated', 'syndromic', 'laboratory-based', 'hospital-based') this definition has been criticised as being non-specific as it does not facilitate an understanding beyond the term surveillance alone (Thacker, Qualters et al. 2012).

NLP has been applied for influenza biosurveillance (Elkin, Froehling et al. 2012). A retrospective case-control study conducted at the Mayo Clinic compared data from the chief complaint field to data in the free-text whole encounter note of EHRs. The CDC's Biosense system currently uses text in the chief complaint field of EHRs. Briefly, Biosense is a CDC initiative established in 2004 in response to the anthrax bioterrorist attacks (Bradley, Rolka et al. 2005). The aim of this web-based system is to expedite recognition of bioterrorist attacks or disease outbreaks and to facilitate rapid response from public health authorities. It analyses clinical data from disparate sources, including chief complaint fields from outpatient encounters and emergency department visits.

The search strategy used by Biosense is based on key word searches for the occurrence of words or strings of text suggestive of influenza-like illness such

as 'fever' and 'cough', 'upper respiratory infections' or 'influenza-like illness' but it may miss related but less specific language such as 'pain on swallowing'. These investigators used NLP to extract concepts from the whole encounter note, which were then mapped to SNOMED-CT and compared these NLP extracted codes to information from the chief complaint field alone.

Like Murff et al. (2011), investigators used the MCVS system to parse the entire encounter note for key clinical variables, including history, physical findings, laboratory findings and radiology reports(Elkin, Froehling et al. 2012). Concepts from each section of the encounter note (history of the present illness; medical history; social history; review of systems; medications; allergies; physical examination; and impression, report, or plan) were coded to SNOMED-CT and classified as positive, negative or uncertain for the presence of an influenza-like illness. Cases were patients who tested positive for influenza virus (n=1203) on respiratory specimen swab and similar number of control patients (n=1455) who tested negative. Comparison between whole encounter note and chief compliant field showed that the NLP-based approach was superior. A fixed specificity of 0.4 (judged as appropriate in terms of false positives) resulted in a sensitivity of 89% using the whole encounter and 74% for the chief complaint field alone (p<0.001) (Elkin, Froehling et al. 2012).

5.6.3 Adverse Reactions to Vaccination

NLP has been used to detect relatively rare events such as vaccine adverse events (VAEs). Collaboration between the CDC and 8 large health maintenance organisations (Kaiser Permanente Northwest) used NLP to extract

information from comprehensive EHRs that were present at these sites (Hazlehurst, Naleway et al. 2009). Investigators compared standard automated methods that query EHR records for ICD codes assigned by clinicians and administrators against classification of encounters based on NLP of clinician text notes in the EHR (i.e., code-search versus text classification methods).

The text classification system used NLP (MediClass—'Medical Classifier') (Hazlehurst, Frost et al. 2005) and knowledge-based techniques to classify clinical encounters. Knowledge-based systems are rule-based criteria, which in this study, were clinical features that could be interpreted as possible VAEs (Hazlehurst, Naleway et al. 2009). MediClass retrieves clinical data, identifies medical concepts and maps them to the UMLS Metathesaurus (Humphreys, Lindberg et al. 1998). MediClass classifies items by running a rules engine using the identified concepts and their contexts. The NLP system was customised to detect VAEs by training it on a dataset of case-patients with clinical encounters (including all office visits, ED visits, and telephone encounters occurring within 7 days of the immunisation) coded as 'immunisation related' or assigned a diagnosis code of 'adverse effects of medical care' (Hazlehurst, Frost et al. 2005).

Against a reviewer confirmed gold standard of 248 cases, MediClass had a sensitivity of 75%, specificity of 97%, PPV of 89% and NPV of 92% (Hazlehurst, Frost et al. 2005). When MediClass was applied to a staggering 12,414 clinical encounters it identified 319 as containing possible VAEs. Manual review of these records revealed that 57% were true positives. After excluding encounters based on specific groups of diagnostic codes, PPV

increased to 64% without incurring a loss of sensitivity (i.e., missed notifications). This study demonstrates the possibilities of NLP as an efficient means of screening large linked databases in order to identify important but rare events (Hazlehurst, Frost et al. 2005).

5.6.4   Hospital-acquired Pneumonia in Neonates

Surveillance of bacterial pneumonia, like fungal pneumonia, is challenging and time consuming. Despite the presence of standardised CDC definitions for nosocomial pneumonia the case definition is complicated and prone to subjective errors of interpretation (Klompas 2010; Klompas, Magill et al. 2012). Like patients with haematological malignancies and suspected IMDs, obtaining appropriate specimens from neonates with suspected pneumonia is difficult emphasising the pivotal role of non-invasive tests such as chest imaging in establishing the diagnosis. In a National Institutes of Health funded study, patients with nosocomial pneumonia from 2 neonatal ICUs (NICUs) were prospectively identified by trained infection preventionists using standardised case definitions based on National Nosocomial Infection Surveillance System (NNIS) criteria (Mendonca, Haas et al. 2005). Like fungal surveillance, case ascertainment required multiple data sources, including review of microbiology and radiology reports, chart review and consultations with attending physicians and nurses. The electronic surveillance system using a NLP-based approach was applied retrospectively to this reference dataset of confirmed cases of nosocomial pneumonia (Mendonca, Haas et al. 2005).

The NLP system used in this study was MedLEE ('Medical Language Extraction and Encoding System). MedLEE is a general purpose natural language processor that is routinely used at this centre to parse and encode clinical reports. It has been evaluated for automating calculation of a severity score guideline for CAP that requires encoded data found in discharge summaries (Friedman, Knirsch et al. 1999), breast cancer research using NLP of pathology reports (Xu, Anderson et al. 2004) and identification of pneumonia from chest radiographs, which demonstrated that it had an accuracy comparable to physician interpretation (Hripcsak, Friedman et al. 1995).

For the detection of pneumonia in neonates, MedLEE recognises words and phrases in the report for example, 'CHF', 'lungs' maps them to standard terms ('congestive heart failure', 'lung') and classifies them into semantic categories ('findings', 'body-location'). MedLEE processes free-text reports and converts it to coded output consisting of clinical information (i.e., findings and procedures), along with corresponding modifiers (e.g., body locations, degree, certainty). The coded output of MedLEE is then accessed by rule-based algorithms derived from NNIS definitions for nosocomial pneumonia to classify reports as positive or not for pneumonia (Mendonca, Haas et al. 2005).

Complete data was available for only one NICU (Mendonca, Haas et al. 2005). At this site, 75% of 1277 neonates had chest radiographs in the 2-year study period. The electronic system identified 5 of the 7 nurse confirmed nosocomial pneumonias and flagged another 61 false positive reports. Sensitivity of the computerised surveillance was 71%, and specificity was 99.8% compared to

the infection preventionist. However, the positive predictive value was low (7.9%), whereas the negative predictive value was >99%. The low PPV was primarily due to a broad rule used to detect pneumonia, akin to casting a wide net, which generated many false positives. Manual chart review of these 61 false positives revealed that 54 (88%) of cases complied with the criteria specified by the rules but not to all the NNIS criteria, mainly due to the absence of positive microbiology—i.e., pneumonia was present, although not strictly health care associated. The developers cited the potential benefits of adjunctive data such as laboratory and pathology results in improving the precision or PPV of the classifier. The 2 cases of pneumonia that were missed by the system were due to one misspelling of the word 'increased' and one patient whose pneumonia was identified on autopsy but whose chest x-ray report focused on problems related to congenital heart disease (Mendonca, Haas et al. 2005).

5.6.5 Detection and Isolation of Patients with Suspected Tuberculosis

NLP has been partnered with clinical decision support. In one study NLP triggered a clinical protocol following detection of suspected tuberculosis from chest radiograph reports ensuring timely isolation of patients (Knirsch, Jain et al. 1998). Knirsch et al. (1998) used MedLEE in a New York City hospital from 1995 to 1996 to prospectively monitor radiology reports for evidence of abnormalities suggestive of tuberculosis in combination with adjunctive sources of data in the patient's clinical repository such as hospital location, laboratory and pharmacy data. The system detected patients who should be isolated who were not detected using standard manual methods. Of 43 patients

with tuberculosis in the prospective evaluation phase, 30 (70%) were isolated by clinicians adhering to the standard protocol while an additional 4 patients were isolated as a result of a clinical alert raised by the automated protocol. Importantly, the system was deemed valuable by hospital administration and became part of routine hospital operations in order to detect patients with suspected tuberculosis during an era when HIV/AIDS was highly prevalent (Knirsch, Jain et al. 1998).

5.7 Unresolved Issues of NLP and Automated Surveillance Systems

In spite of published evidence supporting the success of NLP in specific clinical domains, it has had a modest effect on patient care. The limited integration of NLP into clinical applications is likely due to multiple reasons with a failure to demonstrate value to end-users being central. Early engagement with end-users informing the software development process and addressing usability issues, including where NLP tools fit into user workflow is essential (Chapman 2010; Chapman, Nadkarni et al. 2011). Importantly, accuracy or predictive performance of an automated system is not in itself a guarantee that that the system will be useful in the clinical setting.

Currently the perceived cost of applying NLP in clinical domains outweighs the perceived benefit. Developers experienced in integration of NLP into hospital systems agree that implementation of an NLP-based monitoring system is not a trivial task (Mendonca, Haas et al. 2005). Deployment typically

requires a degree of local customisation because applications may not generalise with mapping to the specific task and therefore must be refined and re-evaluated. Reproducibility may be facilitated by the availability of source code under open release but despite this provision, a tool devised in the context of a research collaboration may not work well in practice as it may not meet the highest standards in software engineering, maintainability, scalability and usability (Chapman, Nadkarni et al. 2011). The dependence on deeply annotated data that requires the input of domain experts like senior clinicians is a barrier to scalability, which could be addressed through more efficient techniques for manual annotation. Improved collaboration with industry, engineers and end-users will assist towards the development of higher quality software that can be integrated into the workflow of real-world clinical applications (Chapman, Nadkarni et al. 2011).

A recent review examining the economic impact of computerised surveillance systems did not identify a single study from 2000 to 2007 that assessed cost or cost-effectiveness (Furuno, Schweizer et al. 2008). Only 2 studies used economic analyses to assess infection control interventions incorporating informatics components. One study used hand-held computers (personal assistant devices) (Farley, Srinivasan et al. 2005) while the other employed a relational database for identification of patients at high-risk of active colonisation or infection with antibiotic resistant organisms (Wernitz, Keck et al. 2005). Neither approaches were strictly representative of automated surveillance systems.

5.7.1 Are the Time Savings Achieved by Automating Surveillance Worthwhile?

The time savings realised by automated surveillance systems have been used as a persuasive argument for their adoption. Indeed, a reported benefit of automation is improved resource utilisation, saving about 10 weeks of infection prevention time annually and requiring only 1/6 to 1/3 of the time required for standard manual surveillance (Grota, Stone et al. 2010). However, these benefits may not always be evident in practice (Furuno, Schweizer et al. 2008). A recent survey of 207 of 305 acute care hospitals in California (59% respondent rate) found that the proportion of time spent on surveillance by infection preventionists did not vary between those hospitals with and without automated surveillance systems (Grota, Stone et al. 2010). Among the 192 infection prevention departments that responded only 44 (23%) had an automated surveillance system. Of those, 52% reported using either a customised system or did not specify the system used; the other 48% used one of 4 commercial products (AICE, 32%; Medmined, 20%; Safety Suveillor, 9%; Theradoc, 2%).

Hospitals with an automated surveillance system used it to create reports and data summaries from built-in templates (77%), to provide automatic alerts (57%), to integrate infection data with CDC definitions and/or reporting requirements (43%), for data mining (36%), and for sharing reports with committees and administration (61%). Not unexpectedly, data collection, analysis and interpretation absorbed the majority of respondents time in hospitals with and without automated surveillance systems being 41% and 36%

(p=0.13) respectively (Grota, Stone et al. 2010). These responses are consistent with surveillance being one of the most time consuming activities for infection preventionists taking on average of 45% of the total time of infection prevention (Stone, Dick et al. 2009).

In those 23% of hospitals with automated surveillance systems, organisational support rather than years of experience of the infection control director, daily usage of the automated surveillance system or years since the electronic surveillance system was implemented, was the strongest predictor of satisfaction with automated surveillance systems by infection preventionists (Grota, Stone et al. 2010). This suggests that in hospitals with strong leadership and a culture of patient safety, infection preventionists may feel better supported in using automated surveillance systems. It is clear from this qualitative study that automated surveillance systems are a long-term investment in alignment with organisational goals of patient safety and the cost-effective delivery of high quality health care. However, these systems once purchased require an ongoing commitment of human and informatics resources for implementation and maintenance (Grota, Stone et al. 2010). That commitment is not trivial when considering that an estimated 4000 hours is required for the development of an internal clinical data warehouse for infection control exclusive of ongoing maintenance costs (Wisniewski, Kieszkowski et al. 2003).

5.7.2 Do Automated Surveillance Systems Promote Best Practice?

A follow-up survey of Californian hospitals tested the hypothesis that hospitals that have adopted automated surveillance systems have improved infection prevention standards. Practices were evaluated for 5 important HAIs (MRSA, Clostridium difficile, catheter-associated urinary tract infections, VAP, CLABSI) and important infection control processes (hand hygiene, use of contact precautions, compliance with the surgical care improvement project) compared to hospitals reliant on manual surveillance (Halpin, Shortell et al. 2011). Of 303 eligible hospitals, 241 responded for a final response rate of 80%. Approximately 1/3rd (32%) of hospitals had adopted automated surveillance systems for HAIs with an additional 24% planning to acquire automated surveillance systems in the subsequent 12 months. The specific automated surveillance systems among 78 hospitals included: a customised system developed at the hospital, n=23; AICE n=20; CareFusion's MedMined, n=14; MIDAS1 Care Management-Infection Control, n=7; MEDITECH Healthcare Information System, n=6; Premier's SafetySurveillor-Infection Control, n=4; another commercial system (not specified), n=3 and Hospira's Theradoc at one site (Halpin, Shortell et al. 2011).

The depth and breadth of implementation of evidence-based infection control practices was assessed using global implementation scales for each of the 5 HAIs and 3 process measures (Halpin, Shortell et al. 2011). The survey instrument assessed the following characteristics in hospitals: the presence of formal evidence-based practices to prevent HAIs, implementation of these practices and whether hospitals assessed compliance with these practices. On

multivariate analysis, adoption of automated surveillance systems was significantly associated with global measures of implementation of evidence-based practices for MRSA, VAP, surgical care improvement project and contact precautions while breadth of implementation for all 5 HAIs was also positively associated with the use of automated surveillance systems (Halpin, Shortell et al. 2011).

Despite limited power in this study to detect differences between commercial compared to custom built systems, implementation scales were higher in hospitals using in-house systems, suggesting that they had made better progress compared to their counterparts (Halpin, Shortell et al. 2011). This survey does not prove causality but only a statistical association between better evidence-based infection control practices in those hospitals with automated surveillance systems. This may reflect the fact that hospitals that invest in automated surveillance systems are more committed or more advanced along the path towards implementation of evidence-based infection control practices.

5.8 Health Innovation and Adoption of Automated Surveillance in the US is Being Driven by Government Mandates

The majority of states in the US have made public reporting of specific HAIs a mandatory requirement (Bell, Benneyan et al. 2011). Hospitals are under increasing pressure to innovate with several states incentivising the adoption of automated surveillance systems by hospitals. Adding to the pressure to

improve health care delivery is the fact that government payers such as Medicare will no longer pay for the additional hospitalisation costs attributable to specific HAIs (Stone 2009). It is likely that the adoption of automated surveillance systems by hospitals will increase due to changes in mandatory public reporting requirements and hospital reimbursement (Halpin, Shortell et al. 2011). Indeed, the Association for Professionals in Infection Control and Epidemiology supports the use of automated surveillance technologies as an essential part of infection prevention and control activities (Greene, Cain et al. 2009). Such mandates have not yet arrived in Australia but with increasing pressure on health care budgets that situation may change.

5.9 Summary: Automated Infection Surveillance for Selected Conditions and Their Parallels with IMDs

Automated infection surveillance with or without the incorporation of NLP has in some settings realised time savings and demonstrated improved accuracy compared to manual reporting (Evans, Larsen et al. 1986; Hazlehurst, Naleway et al. 2009; Hota, Lin et al. 2009; Huang, Yokoe et al. 2010; Lin, Hota et al. 2010; Murff, FitzHenry et al. 2011; Elkin, Froehling et al. 2012). Improved accuracy has been partly due to better case ascertainment through the use of multiple sources of hospital data (Evans, Larsen et al. 1986; Klompas, Kleinman et al. 2008; Huang, Yokoe et al. 2010) and a more consistent application of case definitions for complex conditions like CLABSI or VAP (Klompas, Kleinman et al. 2008; Hota, Lin et al. 2009; Lin, Hota et al. 2010). When linked to clinical decision support automated systems turn outcome

measures such as HAIs or tuberculosis into actionable knowledge facilitating antimicrobial stewardship (Evans, Larsen et al. 1986) or the earlier isolation of infectious patients (Knirsch, Jain et al. 1998).

Electronic surrogates of clinical criteria have been successfully used for automated surveillance of VAP (Klompas, Kleinman et al. 2008) and CLABSI (Hota, Lin et al. 2009; Hota, Harting et al. 2010). Where electronic data has not been readily available then techniques such as NLP have been developed to extract patient-level data from free-text unstructured documents or EHRs as for surveillance of post-operative infections, influenza biosurveillance, VAEs, neonatal pneumonia and CLABSI. Rare but important events such as vaccine adverse reactions have become amenable to detection by NLP from large linked datasets (Hazlehurst, Naleway et al. 2009). Automated outbreak detection using software originally designed for public health surveillance but customised to local conditions identified more nosocomial outbreaks than manual methods with a wider coverage of pathogens, including fungal species (Huang, Yokoe et al. 2010) demonstrating the scope for these systems across entire networks.

It remains unresolved as to whether automated surveillance systems are cost-effective given the substantial investment required for their capital outlay, implementation and maintenance (Classen 1994; Wisniewski, Kieszkowski et al. 2003; Klompas and Yokoe 2009). Other issues such as clinical relevance, usability and value to end-users deserve further research. Publication bias is a concern because if studies only demonstrating cost-effectiveness are published

then economic reviews may lead to biased conclusions. Further, no studies address whether increased accuracy or efficiency of surveillance methods (which is the goal of automated detection systems) actually leads to improved patient or economic outcomes such as mortality or LOS.

Automated surveillance has been successfully applied to conditions that have parallels with IMDs. The study on VAP surveillance (Klompas, Kleinman et al. 2008), while small showed that it may be feasible to conduct automated surveillance of a an important condition with similar characteristics as IMDs—i.e., a lack of a gold standard for diagnosis, chest imaging being a key diagnostic modality, a condition lacking an easily identifiable laboratory prompt such as a positive blood culture. The authors of this study emphasised the importance of a good screening strategy (which in their case was ventilator change criteria) as an efficient means of reducing the work of case ascertainment (Klompas, Kleinman et al. 2008).

Discrepancies in surveillance practice are commonly due to variability in case ascertainment and classification. Traditional manual surveillance for complex conditions such as CLABSI is imperfect partly due to subjective interpretation of complicated case definitions (Trick, Chapman et al. 2003). For CLABSI not all positive blood cultures may represent infection and there is significant variability in the application of surveillance definitions where infection preventionists (and clinicians) may not always agree as to the origins of a positive culture (line versus an alternative site) resulting in classification errors (Trick, Chapman et al. 2003; Lin, Hota et al. 2010). Diagnosis of IMDs like

VAP relies on a constellation of clinical, laboratory and radiological features (De Pauw, Walsh et al. 2008). Thus, case finding is difficult as it requires multiple data sources and classification is dependent on expert adjudication using complicated case definitions.

In people lacking domain expertise, case definitions may be prone to misinterpretation resulting in classification errors. Neonatal bacterial pneumonia shares similar characteristics to IMDs. For example, microbiology as the primary data source for surveillance is inadequate because it is often not possible to distinguish between infection and colonisation and appropriate microbiologic specimens may not be feasible due to the risks associated with invasive procedures. Chest imaging being a key element of the clinical case definition makes it the most efficient means to screen patients, with subsequent clinical review used to confirm or reject the diagnosis. In this study, less than 2% of chest radiographs were flagged positive by the NLP system potentially reducing, by >95% the number of possible cases that would require screening (Mendonca, Haas et al. 2005). Automated surveillance of neonatal bacterial pneumonia and vaccine adverse reactions demonstrates that maximising existing hospital information systems (being radiology and EHRs in these respective studies) and extracting meaning from text documents using NLP is a powerful and efficient means of detecting uncommon but important events.

5.10 Addressing Surveillance of IMDs Based on Expert Recommendations and Experience in Other Domains

Manual surveillance of IMDs is an onerous task for hospitals requiring case ascertainment from multiple data sources and the application of complex case definitions by clinical experts in order to identify patients who may truly have the disease. An appropriate screening strategy, as demonstrated for the surveillance of nosocomial infections in immunocompromised haematology-oncology patients (Engelhart, Glasmacher et al. 2002; Dettenkofer, Ebner et al. 2003), VAP (Klompas, Kleinman et al. 2008; Klompas 2010) or hospital-acquired pneumonia in neonates (Mendonca, Haas et al. 2005) would minimise the burden of case ascertainment.

Given the presence of pulmonary involvement in the vast majority of patients with IMDs but especially IA (see Table 2.1), it is reasonable to use CT reporting as starting point for screening large numbers of patients for evidence of IMD. CT has the additional advantages of being a widely available diagnostic modality unlike the NCBTs such as GM or PCR, and non-invasive with results available within hours rather than days as is the case with send away tests. We hypothesise that NLP of CT reports may help identify patients with reports suggestive of IMD with the added advantage of real-time functionality.

The development of NLP of CT reports for IMD surveillance, as described in the following chapter, draws on several observations and recommendations

made by experts. It was a *clinician-led* endeavour driven by clinicians who informed every step of software development. It *maximised existing hospital information* systems—namely, radiology. It relied on the *exploitation of unstructured text* from CT reports, recognising that the majority of patient-level data in hospitals is hidden in free-text unstructured data. It underwent *local development* in response to an unmet clinical need. For this task, vendor systems were not considered and none to our knowledge address surveillance of IMDs.

While this work does not represent a complete solution we realise that it is an *incremental* but critical step towards the development of full scale automated surveillance of IMDs that may, in the future, be refined with inclusion of adjunctive data from other hospital information systems such as microbiology, pharmacy and patient census sources. NLP is an *emerging technology* in hospitals and this project aimed to use the best available technology to support surveillance of IMDs. In choosing CT reports we hope to *minimise the burden of case ascertainment* by focusing attention on a key diagnostic modality.

Chapter 6: Attributable Hospital Cost and Antifungal Treatment of IFDs in High-risk Haematology Patients: An Economic Modelling Approach

This section is based on a published paper (see Appendix 4).

Authorship

6.1 Introduction

Improvement in the short-term survival of patients with IA (Neofytos, Horn et al. 2009; Pagano, Caira et al. 2010) is encouraging, but crude mortality rates remain high at >30% in patients with AML (Pagano, Caira et al. 2010) and

57% in HSCT recipients (Baddley, Andes et al.). As a result, interest in prevention continues with efficacy demonstrated for posaconazole in patients receiving induction-remission chemotherapy for AML/ myelodysplastic syndromes (MDS) and high-risk allogeneic HSCT (allo-HSCT) recipients (Cornely, Maertens et al. 2007; Ullmann, Lipton et al. 2007). However, given incidence rates of IFDs of 10% to 15% among AML and HSCT recipients (Pagano, Caira et al. 2006; Caira, Girmenia et al. 2008; Kontoyiannis, Marr et al. 2010), non-selective prophylaxis has raised concerns regarding overtreatment and expenditure (De Pauw 2007; Pagano, Fianchi et al. 2008) because numbers of eligible patients are high and duration of prophylaxis potentially lengthy.

Increasingly, the economic impact of IFDs has been considered in the clinical debate. One centre, after determining the attributable mean IA-associated medical cost in AML/MDS patients to be €15,280 in association with a 30% institutional incidence, concluded that anti-mould prophylaxis was likely cost-beneficial from the patient and hospital perspective (Slobbe, Polinder et al. 2008). Cost determination methods for IFDs have included gross costs (Tong, Lau et al. 2009; Kim, Nicolau et al. 2010), expert opinion (Van Campenhout, Marbaix et al. 2008), clinical trial data (Wenzel, Del Favero et al. 2005; Wingard, Herbrecht et al. 2007) but studies reporting attributable cost, a key component of cost-effectiveness analyses, are few (Wilson, Reyes et al. 2002; Menzin, Lang et al. 2005; Morgan, Meltzer et al. 2005; Slobbe, Polinder et al. 2008; Menzin, Meyers et al. 2009) and those using patient-level data even rarer (Slobbe, Polinder et al. 2008).

Importantly, sound estimates of attributable cost are dependent on the appropriate selection of case and reference groups in order to disentangle the confounding effect of underlying illness. In addition, measures of resource use alternative to cost, which are independent of country and inflation, are needed if health economic studies are to have improved generalisability. Thus, our goal was to determine the median hospitalisation cost, LOS and consumption of costly antifungal treatment [C-AT: liposomal amphotericin (L-AmB), voriconazole, posaconazole, caspofungin] attributable to IFD from a hospital perspective in high-risk haematology patients using actual hospital costs, preliminary results of which were used for the listing of posaconazole on Australia's national formulary.

6.2 Methods

6.2.1 Study Design and Setting

We undertook a retrospective case-control study of patients with acute leukaemia or HSCT from 2002 to 2007 at Alfred Health, a 750 bed adult quaternary-university–affiliated hospital-network with heart/lung and HSCT units, the latter performing approximately 50 allo-HSCTs per year. Patients were identified from ICD-10AM (Australian modification) diagnostic codes and underwent manual chart review. Hospitalisation costs 12 weeks subsequent to index admission were also examined. Institutional ethics approval was obtained.

6.2.2 Matching Criteria

Control patients were matched 1:1 with case-patients using the following criteria: age within 10 years of a case-patient, same underlying haematological disease or year of transplantation; LOS at least as long as case-patients prior to IFD whose date of onset was determined by investigators (MA-R, MS) following manual chart review. The LOS criterion meant that selection of control patients began after chart review of case-patients. Exclusion criteria were: death $\leq$ 48 hours of admission, LOS <3 days, HIV infection or key data missing from the chart. If suitable controls were not found, the matching criteria were relaxed sequentially: the age criterion was dropped; alternative haematological conditions considered; for HSCT recipients, year of transplantation within 2 years of case was accepted. The LOS criterion was not relaxed as this was regarded as a key component of cost.

6.2.3 Clinical Data and Definitions

Collected information included demographics, antifungal drug indications and usage expressed as defined daily doses (DDDs) (WHO Collaborating Centre for Drug Statistics Methodology, http://www.whocc.no) with prescribed daily doses used for L-AmB of 250mg/day (de With, Steib-Bauert et al. 2005), type/ stage of chemotherapy, duration of neutropenia (absolute neutrophil count <500 cells/mm^3), status of underlying disease, HSCT type, GVHD, Charlson Co-morbidity Index (CCI), ICU admission, IFD classification according to accepted criteria (De Pauw, Walsh et al. 2008), in-hospital mortality and all-cause mortality 12 weeks after IFD diagnosis as recorded in the medical chart.

Date of IFD onset was defined as the first day of suspicious radiological abnormality or positive microbiology. All data was recorded on a standardised case report form (see Appendix 9). Although the galactomannan assay became available in 2005, it is not widely used and results were not used in this study.

6.2.4   Costing Data

Hospitalisation costs were obtained from an activity-based costing (ABC) system (Power Business Analytics) in use since 1994. It captures direct (i.e., patient-related) and indirect (e.g., overhead/capital outlay) medical costs reflecting fixed (e.g., salaries) and variable (e.g., investigations, medication costs), ascribing 130 categories per patient, which were collated into diagnostics, procedures, theatre, pharmacy, ICU and ward costs using mapping tables. Variable costs are patient-specific and itemised, with fixed costs apportioned across all inpatients. Collection of detailed resource utilisation data was restricted to antifungal treatment after preliminary analysis indicated that antifungal drugs were a major contributor to cost. Antifungal drug acquisition costs are primarily the list price or the Victorian Health Purchasing State Contract price (Health Purchasing Victoria Tender 2007 to 2009, http://www.hpv.org.au).

Costs of antifungal drugs available on imprest (only fluconazole) are apportioned across all ward-patients. Indirect non-medical (e.g., loss of productivity) and intangible costs were not evaluated. The short time-horizon obviated discounting of future costs or benefits. Costs are reported in Australian dollars inflated to 2009 using the health care component of the

Australian Consumer Price Index (Australian Institute of Health and Welfare, http://www.aihw.gov.au/publications/index.cfm/title/10954) and final costs were converted to 2009 US$/€using purchasing power parity (PPP) measures (OECD Stat Extracts, http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE4).

6.2.5   Statistical Analysis

The highly skewed nature of health outcomes (cost, LOS, antifungal treatment) motivated the choice of median (quantile) regression for data analysis. The median is a more reliable measure of central tendency than the mean or geometric mean as it is more resistant to outlier influence, and median regression models are less sensitive to assumptions that are made in generalised linear models (GLMs), particularly heteroscedasticity and error normality. In this technique, the coefficient represents the incremental median cost associated with a unit change in the explanatory variable; for dummy-coded categorical variables, this was the cost associated with the presence of the factor.

We considered dependent variables in a univariable analysis against each outcome variable; all explanatory variables associated with each outcome variable with $p < 0.1$ and eliminated by backwards stepwise selection were selected for 3 multivariable models. We forced inclusion of case-control status (as the primary dependent variable of interest) and ICU admission (a factor known to be strongly associated with increased cost) into all multivariable models. Model fit was assessed using the link test. Reported p-values were

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two-tailed and for each analysis p<0.05 was considered significant. All analyses used Stata 11.0 statistical package (Stata Corp, College Station, Texas).

6.3   Results

6.3.1   Patient Characteristics

A total of 110,744 admissions were screened from coding data and 43 matched-pairs identified after manual chart review. Study groups were similar with regard to pre-specified characteristics (see Table 6.1) and additional clinical features, including prolonged (≥10d) and baseline neutropenia (74% versus 70% and 35% versus 33%) and poor-risk haematological disease (86% versus 84%). More case-patients required ICU admission (21% versus 9.3%, p=0.23) occurring after IFD diagnosis in 8 of 9 case-patients.

Table 6.1: Characteristics of Patients with and without IFD

Variable	IFD Group n=43 (%)	Control Group n=43 (%)
Age: years; median, mean (range)	50, 44 (26–76)	54, 52 (20–83)
Male sex	23/43 (53)	22/43 (51)
LOS: days; Median, mean (range)	39, 44 (7–193)	31, 29 (3–54)
Haematological malignancy		
Leukaemia	35/43 (81)	36/43 (84)
Leukaemia newly diagnosed	16/43 (37)	21/43 (49)
Relapsed leukaemia	8/43 (19)	3/43 (7.0)
SCT	13/43 (30)	12/43 (28)
Allogeneic	11/43 (26)	11/43 (26)
Transformed MDS	2/43 (4.7)	2/43 (4.7)
Lymphoma	4/43 (9.3)	4/43 (9.3)
Other	2/43 (4.7)	1/43 (2.3)

Variable	IFD Group n=43 (%)	Control Group n=43 (%)
Poor-risk haematological disease[a]	37/43 (86)	36/43 (84)
Receipt of myelotoxic chemotherapy	32/43 (74)	33/43 (77)
ICU admission	9/43 (21)	4/43 (9.3)
Neutropenia (<500 cells/μL): days; median (range)	24 (5–53)	19 (1–47)
Neutropenia ≥10 days	32/43 (74)	30/43 (70)
Neutropenia at baseline	15/43 (35)	14/43 (33)
Date of index admission		
2003	0/43 (0)	3/43 (7.0)
2004	11/43 (26)	7/43 (16)
2005	13/43 (30)	12/43 (28)
2006	15/43 (35)	15/43 (35)
2007	4/43 (9.3)	6/43 (14)
CCI		
CCI <4	41/43 (95)	38/43 (88)
CCI≥4	2/43(4.7)	5/43 (12)
Inpatient Death	6/43 (14)	5/43 (12)
Inpatient Death≥14days	6/43 (14)	3/43 (7.0)
All-cause mortality at 12 weeks for evaluable patients	11/42 (26)	8/36 (22)
Site of infection[b]		N/A
Sino-pulmonary	30/43 (70)	
Fungaemia	8/43 (19)	
Hepatic	4/43 (9.3)	
Other[c]	2/43 (4.7)	
Disseminated	10/43 (23)	
Localised	33/43 (77)	
Antifungal drug consumption: (DDD)		
Total; median, mean (range)	52, 70 (1.5–287)	32, 33 (0–113)
Costly antifungal treatment[d] Median, mean (range)	19, 34 (0–122)	0, 5.5 (0–32)
Receipt of systemic antifungal prophylaxis	26/43 (60)	26/43 (60)
Number of courses[e] of antifungal prophylaxis		
Fluconazole	13/31 (42)	11/37 (30)
Itraconazole	14/31 (45)	19/37 (51)
Voriconazole	4/31 (13)	4/37 (11)
Posaconazole	0	1/37 (2.7)
Caspofungin	0	2/37 (5.4)

[a]Poor-risk disease includes relapse, progressive disease, partial remission, induction, failed induction; [b]Some patients had ≥1 site involved; [c]One each: CNS, hepatosplenic; [d]Denoted by liposomal amphotericin, voriconazole, posaconazole, caspofungin; [e]Course denotes antifungal drug administered for any duration.

IFD complicated chemotherapy-induced aplasia in 24/43 (56%) patients with induction (n=21) regimens predominating. Haematological disease progression or leukaemic relapse was a factor in 6/43 (14%). IFD onset from allo-HSCT was ≤30d (n=4), 30 -100d (n=2) and late (>100d) in 2 patients (GVHD and leukaemic relapse respectively); IFD preceded allo-HSCT in 2 patients.

Antifungal prophylaxis was administered to 60% (n=26) in each study group with fluconazole and itraconazole most common and voriconazole used off-label as prophylaxis after 2004 in small numbers. Antifungal prophylaxis was not administered to 11 case-patients with IFD complicating post-induction aplasia (n=2 in 2004, n=2 in 2005, n=4 in 2006, n=3 in 2007).

6.3.2   Characteristics of Case-patients and Clinical Outcomes

The most common site of infection was sino-pulmonary (70%) followed by fungaemia (19%). A total of 21 fungal isolates (13 moulds, 8 *Candida* species) were recovered from 20 patients with probable/proven IFDs. *Aspergillus* species were most frequently isolated (10/21, 48%) with *A. fumigatus* recovered in 9/13 patients. Opportunistic moulds (*Scedosporium, Rhizopus* species) were uncommon (n=3). Non-albicans *Candida* species. accounted for 6 of 8 *Candida* isolates.

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Overall mortality at 12 weeks for 42 evaluable case-patients was 26%. The high number of control patients (n=7) unevaluable at 12 weeks limited outcome comparisons.

6.3.3   Characteristics of Unmatched Case-patients

Our anticipated goal of 50 matched-pairs (based on feasibility considerations) was undermined by insufficient control patients complicated by the loss of 24 potential candidates due to previous (n=11) or possible (n=13) IFD. Thus, our case target was easily met but 13 case-patients (10 probable/proven IFD) lacked suitable controls. Unmatched case-patients had a mean age of 44 years (range 25 to 67 years), median LOS of 36d (range 10d-133d) and median (mean, range) hospitalisation costs of AU$76,456 (AU$160,854; AU$34,548–AU$820,452). There were 7 HSCT recipients (5 allo-HSCT) and all had poor-risk haematological disease.

6.3.4   Cost, LOS and Antifungal Drug Consumption Adjusted for Additional Clinical Characteristics

Differences between groups resulted in a crude median (mean) IFD-attributable cost of AU$28,309 (AU$79,129) (see Table 6.2) and LOS of 8d (15d). Median regression analyses adjusted for additional clinical characteristics not accounted for by matching criteria (see Table 6.3). Of several candidate variables (p<0.1), only receipt of chemotherapy and late (≥14d) in-hospital mortality (in addition to case-status and ICU admission) were included in the

final model based on their consistent association on univariable analyses with all outcome variables.

On multivariable analysis, IFD-status was associated with an excess median cost over the baseline patient of AU$30,957 (95% CI AU$2368 to AU$59,546; p=0.034) and 17 DDDs of C-AT. If ICU was also required then the excess median cost increased to AU$80,291 (95% CI AU$33,636 to AU$126,946; p=0.001) and an additional 19 DDDs of C-AT were required (p<0.001). Late in-hospital mortality was strongly associated with prolonged excess median LOS (33d, p<0.001) and 13 DDDs of C-AT (p<0.001) but not cost (p=0.39) unless ICU was omitted from the multivariable model (AU$105,115; 95% CI AU$60,437 to AU$149,792, p <0.001). Case-status was not associated with increased median LOS (p=0.83) but following inclusion of 22 unmatched patients (13 case-patients, 9 control patients) in a sensitivity analysis akin to Dubberke et al. (2008) a significant association (LOS 8d, 95% CI 1.8 to 14d, p=0.012) emerged while median cost (AU$29,441, 95% CI AU$5571 to AU$53,310, p=0.016) and C-AT (17 DDDs, 95% CI 16 to 18, p<0.001) remained largely unchanged.

Distribution of costs is shown in Table 6.2. Main determinants of the difference in mean cost were pharmacy (64%, p<0.001), of which antifungal drugs comprised 27% (p<0.001), followed by ward (27%, p=0.091) costs. Proportionate differences in mean hospitalisation cost were maintained 12 weeks from index hospitalisation for the 25 surviving matched-pairs (pharmacy 60%, ward costs 31%) but were not statistically significant.

Table 6.2: Hospitalisation Costs Inflated to 2009 AU$ Per Patient for Index Hospitalisation and Hospitalisations 12 Weeks After Index Admission. Outpatient Care Excluded

Cost category	Index hospitalisation				Hospitalisation costs up to 12 weeks from index hospitalisation[a]			
	IFD Group (n=43)	Control Group (n=43)	Difference between groups (%)	p[b]	IFD Group (n=25)	Control Group (n=25)	Difference between groups (%)	p[b]
Hospital stay								
Ward[c]	49,947	33,292	16,655 (21)		26,512	10,927	15,585 (30)	
ICU	7609	2655	4954 (6.3)		847	196	651 (1.2)	
Total	57,556	35,947	21,609 (27)	0.091	27,359	11,123	16,235 (31)	0.21
Pharmacy (total)[d]	72,529	22,130	50,399 (64)	<0.001	40,358	8,731	31,627 (60)	0.12
Antifungal drugs	26,219	4775	21,444 (27)	<0.001	*	*	*	*
Diagnostics								
Pathology	10,563	7066	3497 (4.4)		5307	2918	2389 (4.5)	
Radiology	4567	2322	2245 (2.8)		1820	982	838 (1.6)	
Total	15,130	9,388	5742 (7.3)	0.072	7127	3900	3227 (6.1)	0.15
Procedures[e]	2082	1179	903 (1.1)	0.32	1131	348	783 (1.5)	0.20
Theatre	1008	532	476 (0.6)	0.14	1020	201	819 (1.6)	0.043
Total costs								
Mean	148,305	69,176	79,129[f]		76,995	24,303	52,692	
Median	81,691	53,382	28,309[f]	0.0099	37,815	11,237	26,578	0.098
Range	(10,518–687,574)	(3468–233,020)			(0–425,631)	(0–148,886)		

*Data not available; Values are reported as means (unless otherwise stated); [a]For surviving matched-pairs at 12 weeks; [b]Test of difference between IFD and control groups used the Mann-Whitney U test; [c]Ward costs include emergency and inpatient care; [d]Pharmacy expenditure includes staff salaries as well as

medications; [e]Therapeutic or diagnostic procedures (e.g., bronchoscopy); [f]Cost

at PPP (2009): mean US$54,198 & €40,356; median US$19,390 & €14,438.

Table 6.3: Median Regression Model for Hospitalisation Costs (Inflated to

2009 AU$), LOS and Antifungal Treatment Per Patient

Variable	Outcome					
	Hospitalisation cost (AU$)		LOS (days)		Costly antifungal treatment[a] (DDD)	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	p
Univariable analysis						
IFD patient	28,309 (568 to 56,049)	0.046	8.0 (0.57 to 15)	0.035	19 (18 to 20)	<0.001
LOS	1961 (1518 to 2405)	<0.001	_	_	0.45 (0.33 to 0.56)	<0.001
ICU admission	65,470 (19,224 to 111,716)	0.006	13 (0.99 to 25)	0.034	25 (5.6 to 44)	0.012
HSCT	53,549 (24,576 to 82,521)	<0.001	-2.0 (-13 to 9)	0.71	11 (-2.6 to 25)	0.11
Allo-HSCT	57,681 (27,602 to 87,760)	<0.001	5.0 (-6 to 16)	0.37	12 (-1.4 to 25)	0.078
Receipt of chemotherapy	49,268 (13,047 to 85,489)	0.008	25 (15 to 35)	<0.001	12 (3.2 to 20)	0.008
Inpatient death ≥ 14 days[b]	104,164 (51,646 to 156,681)	<0.001	45 (31 to 59)	<0.001	41 (17 to 65)	0.001
Inpatient death	52,502 (5,555 to 99,449)	0.029	10 (-3.24 to 23)	0.14	25 (5.6 to 44)	0.012
Age (years)	-1392 (-2377 to -407)	0.006	-0.29 (-0.60 to 0.02)	0.066	-0.34 (-0.63 to -0.06)	0.018
Receipt of costly antifungal treatment[a]	426 (-162 to 1,014)	0.15	0.39 (0.23 to 0.54)	<0.001	_	_
Neutropenia ≥10 days	19,529 (-22,524 to 61,581)	0.36	19 (11 to 27)	<0.001	11 (2.5 to 20)	0.012
Neutropenia at baseline	-12,252 (-52,628 to 28,124)	0.55	-1.0 (-11 to 9.3)	0.85	-1.05 (-17 to 14)	0.89
Poor-risk haematological disease[c]	-40,267 (-85,936 to 5402)	0.083	1.0 (-11 to 13)	0.87	1.4 (-20 to 23)	0.90
Newly diagnosed	-10,048 (-44,615 to	0.57	7.0 (-1.81 to	0.12	-5.3 (-20 to	0.47

leukaemia	24,520)		16)		9.2)	
Multivariable analysis[d]						
Base-case[e]	23,964 (-8819 to 56,747)	0.15	12 (2.8 to 21)	0.011	0 (-1.5 to 1.5)	1.0
IFD patient[f]	30,957 (2368 to 59,546)	0.034	7.0 (-0.95 to 15)	0.083	17 (15 to 19)	<0.001
ICU admission[f]	80,291 (33,636 to 126,946)	0.001	6.0 (-7.23 to 19.23)	0.37	19 (16 to 22)	<0.001
Receipt of chemotherapy	29,418 (-4695 to 63,531)	0.09	20 (11 to 29)	<0.001	0 (-1.9 to 1.9)	1.0
Inpatient death ≥ 14 days[b]	24,824 (-32,713 to 82,360)	0.39	33 (17 to 49)	<0.001	13 (9.0 to 17)	<0.001

* DDD for liposomal amphotericin 250mg IV was regarded as equivalent to one DDD (de With, Steib-Bauert et al. 2005); haematological stem cell transplantation; Allo-, allogeneic; ICU, intensive care unit; Values are reported as medians. Dashes indicate variables not included in the model; [a]Denoted by liposomal amphotericin, voriconazole, posaconazole, caspofungin; [b] The reference group comprised surviving patients and 2 control patients who died early in their admission—i.e., within the first 7 days; [c]Poor-risk disease includes relapse, progressive disease, partial remission, induction, failed induction; [d]Multivariable analysis included forced inclusion of case-status and ICU admission and variables significant on univariable analysis (p<0.1); [e]The baseline patient who did not develop an IFD, receive chemotherapy and survived a minimum of 14 days in-hospital. All values for each variable in the multivariable analysis refer to the excess cost, LOS or antifungal drug consumption attributable to an IFD and added to the base-case; [f]Median excess cost for an IFD patient at PPP (2009): US$21,203 (95% CI US$1622 to US$40,784) /€15,788 (95% CI €1208 to €30,368) increasing to US$54,993 (95% CI US$23,038 to US$86,948) /€40,948 (95% CI €17,154 to €64,742) with intensive care admission.
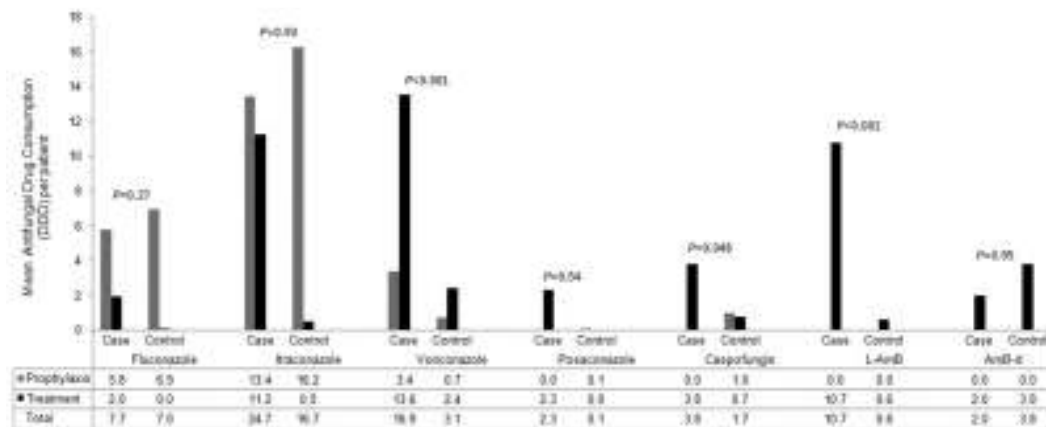
Figure 6.1: Mean antifungal drug consumption (in DDDs) for patients with and without IFDs. For liposomal amphotericin B, 250 mg intravenously was regarded equivalent to 1 DDD (11). Differences in total drug consumption between case and control patients were determined using the Mann-Whitney U test.

Antifungal drug consumption according to treatment indication is presented in Figure 6.1. Mean drug consumption was higher among case-patients with the exception of amphotericin-deoxycholate (AmB-d) but significant differences were observed for voriconazole (p<0.001), L-AmB (p<0.001) and caspofungin (p=0.048). Small numbers (n=3) using posaconazole (prior to its licensure) limited its interpretation. In case-patients median (mean) drug administration was: L-AmB 240 (266) mg/d for 7.5d (11d); voriconazole 400 (464) mg/d for 6d (10d) and caspofungin 50 (52) mg/d for 6d (10d).

6.4   Discussion

Determining disease attribution and broadening the generalizability of economic analyses are challenges we attempted to overcome in this study. A

comparative attribution approach using a case-control method followed by regression modelling to adjust for clinical characteristics not accounted for by matching criteria was used to separate the confounding effect of underlying illness from IFD-related outcomes. Informed by Graves et al.'s (2010) caution against overestimating the cost of HAIs, we therefore reported median outcomes to describe the typical value for most patients rather than the arithmetic mean, which while relevant to payers (e.g., the hospital), is highly sensitive to outliers, thus limiting its generalisability while potentially overstating cost. Commonly used approaches for adjustment of highly skewed data include linear regression models for log-transformed dependent variables and GLMs with a logarithmic link function (Polsky and Glick 2009). However, normalisation of data is not always successful (Graves, Birrell et al. 2005) and, for linear regression models, re-transformation of predicted results may be misleading (Polsky and Glick 2009).

Quantile regression models, in contrast, make no assumptions about distribution of errors or outcomes and can accommodate different quantiles depending on the focus of interest—i.e., median to describe the general population or higher quantiles for outliers (Bang and Tsiatis 2002). Predictably, the crude hospitalisation cost in our matched-pairs analysis was right-skewed with median and mean IFD-attributable cost of AU$28,309 and AU$79,129 per patient respectively. By median regression analysis adjusted for ICU requirement, receipt of chemotherapy and late (≥14d) in-hospital mortality, IFD-cost was AU$30,957 (95% CI AU$2368 to AU$59,546, p=0.034); approximating at PPP US$21,203/€15,788 over the baseline patient and

consistent with the crude estimate differing by <10%. Median excess cost increased to AU$80,291 (95% CI AU$33,636 to AU$126,946, p=0.001) if intensive care was also required as occurred in 21% of case-patients.

Antifungal drugs being a substantial component of our IFD attributable cost is contrary to previous studies (Rentz, Halpern et al. 1998; Dasbach, Davies et al. 2000), which have found LOS to be the main determinant of hospitalisation cost. This finding was not unexpected due to the high acquisition costs of drugs we commonly use for treatment—namely, L-AMB, voriconazole, caspofungin and to a lesser extent posaconazole.

Driving the difference in mean cost per patient was overwhelmingly pharmacy (64%, p<0.001), of which antifungal drugs accounted for 43% of pharmacy expenditure or 27% of the overall difference (p<0.001) with no significant difference in ward costs seen (27%, p=0.091). The robustness of these results was confirmed in the 12-week analysis of subsequent inpatient care (pharmacy 60%, ward costs 31%), which was not significant probably due to fewer surviving matched-pairs (n=25). Historically, antifungal drugs have accounted for 7% to 15% of total treatment costs (Rentz, Halpern et al. 1998; Cagnoni, Walsh et al. 2000; Wilson, Reyes et al. 2002) a finding supported by a recent US study where intravenous antifungal drugs accounted for 7.2% of IA-associated hospitalisation cost (Kim, Nicolau et al. 2010) but differences in case-mix and clinical care are likely responsible.

Slobbe et al. (2008) in a cohort similar to ours (2002 to 2007) used fluconazole prophylaxis and AmB-d (pre-2003) or voriconazole (typically the less costly oral form) for treatment of IA. In contrast, our practice is characterised by anti-mould prophylaxis (58% of case-patients, 70% of control patients), C-AT (i.e., costly antifungal therapy being voriconazole, posaconazole, caspofungin, L-AmB) with voriconazole (mean 16.9 DDDs/case versus 3.1 DDDs/control patient, p<0.001) and L-AmB (mean 10.7 DDDs/case versus 0.6 DDDs/control patient, p<0.001) predominating principally for empiric or definitive treatment of IFD with AmB-d rarely used due to its recognised toxicities. The high contribution of antifungal treatment to hospitalisation costs is recognised in ICU also, where it is regarded as a costly intervention along with haemodialysis and blood product administration (McLaughlin, Hardt et al. 2009).

Alternatives to cost as a descriptor of resource utilisation were sought in order to enhance generalizability. IFD-status was associated with an excess crude median (mean) LOS of 8d (15d, p=0.083), which reached significance after inclusion of 22 unmatched patients into the model (8d, 95% CI 1.7d to 14d, p=0.012), suggesting a sample size effect. Thus, a conservative estimate of opportunity costs per IFD episode includes the loss of 8 ward-bed days at AU$700/day and the crude mean difference in antifungal treatment of AU$21,444 approximating AU$27,044 in total notwithstanding other marginal costs (e.g., diagnostics and potential loss of ICU-bed days at AU$3200/day).

C-AT represented another measure not previously described in the economic literature but proved useful in comparing subgroups, including case-patients (17 DDDs, 95% CI 15 to 19 DDDs, p<0.001), ICU patients (19 DDDs, 95% CI 16 to 22 DDDs, p<0.001) and patients with late in-hospital mortality (13 DDDs (95% CI 9.0 to 17 DDDs, p<0.001). In case-patients, 17 DDDs approximates L-AmB 250mg/d for 7 to 10d followed by voriconazole 400mg/d for 7d and is consistent with documented prescribing, thus validating the model. Late in-hospital mortality—i.e., non-survivor care, was not more costly (compared to the reference group comprising survivors and 2 control patients who died early in-hospital) despite a strong association with C-AT and prolonged LOS (33d, p<0.001) perhaps due to the competing effect of intensive care, which was required by some non-survivors (6 of 10, data not shown) but by more patients overall (n=13). Indeed, with omission of ICU from the final model, non-survivor care was substantial (AU$105,115; p <0.001), suggesting that IFD could prolong hospitalisation and increase cost before death supervenes.

The economic burden of IFDs on hospitals is recognised (Menzin, Meyers et al. 2009; Kim, Nicolau et al. 2010) but methodological differences between our study and others limit comparisons. Kim et al. (2010) using actual costs reported median gross hospitalisation costs of US$72,029 for a subset of haematology patients with IA (2000 to 2006) while Tong et al. (2009) using cost-to-charge ratios (2003) reported a median gross cost of US$47,949 for non-HSCT haematology patients. Menzin et al. (2009) estimated the mean IFD-attributable cost in patients with haematological malignancies and HSCT recipients to be US$37,046 (p<0.001) and US$60,190 (p<0.001) respectively, a

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range that includes our crude mean estimate approximating at PPP US$54,198. These studies (Menzin, Meyers et al. 2009; Tong, Lau et al. 2009; Kim, Nicolau et al. 2010) like others now ≥10 years old (Rentz, Halpern et al. 1998; Dasbach, Davies et al. 2000; Wilson, Reyes et al. 2002; Slavin, Fastenau et al. 2004) used administrative datasets that have poor case-detection (Chang, Burwell et al. 2008)– in our case, an administrative IFD diagnosis was absent in 13 possible case-patients.

Study limitations include the small sample size reflecting the epidemiology of a disease with a low institutional incidence (Kontoyiannis, Marr et al. 2010) compounded by difficulties in finding suitable controls. Inpatient care underestimates the true burden of IFDs that have outpatient and societal costs but previous studies have suggested that >50% of costs are incurred in-hospital (Wilson, Reyes et al. 2002). Generalizability, a concern of single centre studies, was mitigated by median regression modelling and by using C-AT as a resource metric. Retrospective data in combination with ABC is a valid approach (Jegers, Edbrooke et al. 2002) with ABC a highly regarded cost capturing tool (Barnett 2009). However, studies utilising bottom-up methods are few (Slobbe, Polinder et al. 2008) with proxies such as cost-to-charge ratios popular in the US despite their recognised shortcomings as billing parameters rather than actual expenses (Jegers, Edbrooke et al. 2002).

Gross hospitalisation costs are of interest but attributable estimates are preferred for pharmaco-economic analyses. To this extent, our case and reference groups were well defined and chart review ensured only patients

truly with or without IFD were included. Time-dependent bias was addressed by controlling for LOS prior to IFD onset, thus separating pre-infection from post-infection costs (Graves, Harbarth et al. 2010). Inclusion of parameters (e.g., receipt of chemotherapy) predictive of treatment-related complications not controlled for (e.g., mucositis) minimised residual confounding. A sensitivity analysis addressed omitted variables and selection biases inherent in matched-cohort studies (Graves, Harbarth et al. 2010) by, including all unmatched patients and showed similar results. The CCI was poorly discriminatory in our cohort as in HSCT recipients (Sorror, Maris et al. 2005) because many co-morbidities are exclusion criteria for chemotherapy and therefore no adjustment for co-morbidities was made. Strategies such as prophylaxis as part of a stewardship program may reduce costs as highlighted by the few patients (2 to 3/year, 2004 to 2007) who failed to receive antifungal prophylaxis and developed IFD during post-induction aplasia.

Ameliorating the economic burden of IFDs while optimising the return from finite health care resources, is possible with better diagnostics, improved antifungal stewardship and individualised prophylaxis. In our setting the attributable cost of an IFD is driven by pharmacy expenditure, of which antifungal drugs are a major contributor with supportive care (i.e., ICU) also substantial. Our methods are applicable to other settings and results provided can inform future studies assessing the cost-effectiveness of IFD interventions.

Chapter 7: Optimising Outcomes: The Role of Antifungal Prophylaxis, Therapeutic Drug Monitoring and Antifungal Stewardship

7.1 Comparative Clinical Effectiveness of Prophylactic Voriconazole/Posaconazole to Fluconazole/Itraconazole in Patients with AML/Myelodysplastic Syndrome Undergoing Cytotoxic Chemotherapy Over a 12-year Period

This section is based on a published paper (see Appendix 3).

- Ananda-Rajah, M.R., Grigg, A., Downey, M.T., Bajel, A., Spelman, T., Cheng, A., Thursky, J.V. & Slavin, M.A. (2012). Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with AML/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period. *Haematologica, 97*(3), 459–463. doi: haematol.2011.051995

7.1.1 Introduction

Post-induction aplasia for AML/myelodysplastic syndromes (MDS) is a period at high-risk for IFD (Bow, Loewen et al. 1995; Pagano, Caira et al. 2010). IA remains the commonest cause of IFD and crude mortality remains considerable at 33% to 47% (Neofytos, Horn et al. 2009; Pagano, Caira et al. 2010; Perkhofer, Lass-Florl et al. 2010). For patients surviving IFDs, delays or modifications to curative chemotherapy may compromise long-term prognosis (Bow, Loewen et al. 1995; Even, Bastuji-Garin et al. 2010). Poor clinical outcomes coupled with diagnostic uncertainty underlies the rationale for antifungal prophylaxis, the efficacy of which in preventing IFD and improving short-term survival has best been demonstrated for posaconazole in AML/MDS patients receiving remission-induction chemotherapy (Cornely, Maertens et al. 2007).

Despite recognition of the high health and economic burden of IFD (Ananda-Rajah, Cheng et al. 2011), non-selective broad-spectrum prophylaxis has raised concerns about expenditure, overtreatment and emergent drug resistance (De Pauw 2007) as only a subset (Caira, Girmenia et al. 2008) of AML patients develop IFD. Currently, a more targeted use of prophylaxis is hampered by limited knowledge of local fungal epidemiology (Vehreschild, Ruping et al. 2010) and an evolving but incomplete understanding of patient-level risk. Antifungal prophylaxis in AML/MDS patients undergoing intensive chemotherapy has been our approach, characterised by use of fluconazole, itraconazole, voriconazole and posaconazole consecutively over 10 years. We retrospectively reviewed the relative effectiveness and safety of azole

antifungal prophylaxis with particular attention to the newer triazoles compared to fluconazole/itraconazole.

7.1.2 Design and Methods

7.1.2.1 Study Design and Setting

The Royal Melbourne Hospital is a 690-bed adult university-affiliated tertiary hospital that performs 45 allogeneic HSCT annually. Consecutive patients with AML/MDS undergoing remission-induction chemotherapy from December 1998-January 2010, who received ≥1day of azole prophylaxis, defining a course, were included. Prophylaxis consisting of fluconazole 400mg daily, itraconazole solution 2.5mg/kg bd, voriconazole 200mg bd and posaconazole 200mg tds co-administered with fatty food, was started at or 1 to 2 days prior to cytoreductive chemotherapy and continued until: neutrophil recovery to >0.5cells/L, occurrence of a confirmed or suspected IFD, drug-related toxicity/intolerance or the patient's condition becoming palliative. Oral administration was preferred with intravenous dosing of either fluconazole or voriconazole reserved when gastrointestinal absorption was deemed inadequate.

Suspicion of IFD lead to high resolution CT (HRCT) introduced routinely in 2003, and lung sampling (i.e., bronochoalveolar lavage/biopsy) as tolerated. Galactomannan (GM) or beta-D-glucan assays were not used. AML treatment protocols were predominantly anthracycline- and cytarabine-based. Neutropenic fever was treated with cefepime prior to 2005 and piperacillin-tazobactam thereafter. Empiric antifungal therapy (EAFT), usually liposomal

amphotericin, was typically initiated, once voriconazole and posaconazole prophylaxis became routine, in the presence of HRCT changes suspicious for IFD. G-CSF was used as part of trial protocols or at physician discretion when expected neutropenia duration was ≥18 days. The majority of patients received proton pump inhibitors for stress ulcer prophylaxis. TDM was not routine. HEPA filtration was extended from 5 to all rooms in April 2005. However, the vast majority of patients were nursed in HEPA filtered rooms from 1996 to 2005.

7.1.2.2 Clinical Data, Definitions and Imaging Review

Collected information included host and treatment-related characteristics; receipt of total parenteral nutrition (TPN) as a surrogate marker of severe mucositis and chest/sinus CT scans performed 3 days prior to, during prophylaxis or within 7 days from drug cessation. IFD classification adhered to consensus criteria (De Pauw, Walsh et al. 2008) whereby probable/proven cases required fungal pathogen isolation. IFD onset was defined as the first day of suspicious CT abnormality or positive microbiology or pathologic test. All data was recorded on a standardised case report form (see Appendix 10). CT scans were reviewed by a radiologist (JV) blinded to IFD classification, for the presence of accepted IFD-related lesions (De Pauw, Walsh et al. 2008) as distinct from non-specific pulmonary infiltrates.

Prophylactic effectiveness was assessed in patients receiving azoles at standard doses for ≥7 consecutive days (to approximate steady state). Breakthrough IFD was defined as occurrence of IFD in patients during azole prophylaxis or ≤7

days from drug cessation. Antifungal susceptibility testing of fungal isolates followed reference methods (CLSI 2008).

Plasma concentrations of itraconazole, voriconazole and posaconazole drawn ≥5 days after drug commencement (to approximate steady state) were defined as sub-therapeutic for: itraconazole ≤0.5μg/mL; voriconazole <0.7mg/L and posaconazole <500ng/L (Andes, Pascual et al. 2009). Institutional ethics approval was obtained.

7.1.2.3 Statistical Analysis

The primary objective of the study was to evaluate the incidence of breakthrough IFD. Secondary outcomes were requirement for EAFT and toxicity/tolerability. Prophylaxis courses in patients who either died or became palliative were excluded from safety analyses. Categorical variables were analysed using the χ^2 test or Fisher's exact test as appropriate. The Student's t-test or Wilcoxon rank-sum test was used to compare continuous variables depending on their distribution. Differences in continuous variables between the azole drugs were assessed using the Kruskal-Wallis test. Reported p-values were two-tailed and for each analysis $p \leq 0.05$ was considered significant. All analyses used Stata 11.0 (Stata Corp, College Station, Texas).

7.1.3 Results

7.1.3.1 Patient Characteristics According to Azole Antifungal Prophylaxis

A total of 216 patients (91% with AML) received 573 courses of azole prophylaxis (see Table 7.1). The majority of patients (213/216, 99%) underwent chemotherapy for remission-induction/re-induction or relapsed disease. Significant differences in clinical characteristics were noted between fluconazole/itraconazole and voriconazole/posaconazole recipients respectively: median duration of neutropenia per prophylaxis course [16 days versus 14 days, p=0.003]; median age (56 versus 51-years, p<0.001); male gender (47% versus 56%, p=0.035); TPN requirement (39% versus 26%, p=0.001) and median duration of prophylaxis (18 days versus 22 days, p<0.001). Changes in clinical practice may have accounted for some of these differences. For example, fluconazole early in the study period was started during chemotherapy or at its cessation accounting for its shorter duration of use, a practice that was later abandoned due to the high number of breakthrough IFDs.

Table 7.1: Clinical Characteristics According to Azole Antifungal

Prophylaxis

Characteristic	Fluconazole n (%)	Itraconazole n (%)	Voriconazole n (%)	Posaconazole n (%)
Characteristics of patients, n=216				
No. of patients[1]	57	59	82	68
Age at start of chemotherapy, years Median, range	57, 20–79	55, 20–79	51, 17–81	51, 19–78
Male gender	27 (47)	29 (49)	38 (46)	43 (71)
Dates of use	Dec 1998-Sept 2008	May 1999-Jan 2003	Nov 2002-Aug 2008	Sept 2006-Jan 2010
Characteristics per prophylaxis course, n=573				
No. of prophylaxis courses	95 (17)	119 (21)	206 (36)	153 (27)
Underlying diagnosis				
AML[2] (197 patients)	73 (77)	112 (94)	195 (95)	145 (95)
Transformed MDS (18 patients)	22 (23)	7 (5.9)	11 (5.3)	8 (5.2)
Phase of treatment				
Induction/re-induction	55 (58)	63 (53)	83 (43)	67 (44)
Relapse	10 (11)	16 (13)	26 (13)	15 (9.8)
Consolidation	30 (32)	40 (34)	97 (47)	71 (46)
Duration of neutropenia (≤0.5cells/L) per chemotherapy cycle, days				
Median, range	16, 0–54	16, 4–41	13, 0–54	15, 0–48
Receipt of TPN, n (%)	36/95 (38)	48/119 (40)	44/206 (21)	48/153 (31)
Duration of prophylaxis, days				
Median, range	15, 3–53	20, 1–71	21, 2–79	23, 1–69

[1]Some patients received >1 antifungal drug as prophylaxis; [2]Includes 1 patient with acute undifferentiated leukaemia who received 4 courses of posaconazole prophylaxis.

7.1.3.2 Breakthrough IFDs

Breakthrough IFDs occurred in 27 patients (27/216, 13%) comprising probable/proven (n=11) and possible (n=16) infections (see Table 7.2). Among the 210 patients who received ≥7days of azole prophylaxis, breakthrough probable/proven IFD incidence declined over time: fluconazole 6/36, 17%; itraconazole 4/49, 8.2%; voriconazole 1/58, 1.7%; posaconazole 0/67 with a similar trend following inclusion of possible IFDs: 9/36, 25%; 8/49, 16%; 8/58, 14% and 2/67, 3.0% respectively. The incidence of breakthrough possible/probable/proven IFDs associated with voriconazole/posaconazole was significantly lower than fluconazole/ itraconazole (17/85, 20% versus 10/125, 8.0%, p=0.011).

All probable/proven IFDs were moulds, most commonly aspergillosis. The single *A. fumigatius* isolate tested for susceptibility (2001) demonstrated reduced dose-dependent susceptibility to itraconazole in a patient who had consecutive courses of itraconazole prophylaxis lasting 23 and 15 days, 18 days apart and later died of *Aspergillus* pneumonia. IFD complicated remission-induction chemotherapy in 24/27 patients (9/24 had disease relapse) and consolidation chemotherapy in 3 patients. Breakthrough probable/proven IFD incidence among patients receiving ≥1day of prophylaxis (akin to an intention-to-treat group), with occurrence during or ≤30 days from drug cessation, was: fluconazole 8/57, 11%; itraconazole 6/59, 10%; voriconazole 2/82, 2.4% and posaconazole 0/68.

7.1.3.3 Plasma Levels of Itraconazole, Voriconazole and Posaconazole

A total of 55 patients had 141 plasma levels after ≥5 days of itraconazole, voriconazole or posaconazole. Sub-therapeutic plasma drug levels, regardless of timing (i.e., trough, peak, random), were common for itraconazole 15/36 (42%), voriconazole 35/92 (38%) and posaconazole 9/13 (69%). None of the 5 patients with breakthrough probable/proven IFDs during itraconazole or voriconazole prophylaxis had TDM performed. Median drug levels were not significantly different with or without TPN (administered in the 7 days prior to plasma level) (data not shown).

7.1.3.4 Discontinuations, Use of EAFT and CT Scan Demand

Table 7.3 describes secondary outcomes analysed by course of prophylaxis. Overall, premature discontinuations, for any reason were significantly higher among fluconazole/itraconazole compared to the voriconazole/posaconazole groups combined (46% versus 22%, p<0.001). Escalation to EAFT lasting ≥4days accounted for the majority of fluconazole and itraconazole discontinuations (74% and 62% respectively) and to a lesser extent voriconazole, 51%. Gastrointestinal-related discontinuation rates were similar for itraconazole and posaconazole (19% each) but accounted for the majority of premature discontinuations for posaconazole (71%) compared to 42% for itraconazole. This was not due to differences in severe mucositis reflected by TPN requirement (71% versus 76% respectively). Hepatotoxicity was low overall but significantly higher for voriconazole compared to the other drugs combined (5% versus 1.1%, p=0.007).

EAFT was higher in the combined fluconazole/itraconazole compared to the voriconazole/ posaconazole groups (31% versus 8.5%, p<0.001) as were pulmonary lesions on CT treated for suspected IFD but not meeting criteria for possible IFD (10% versus 4.0%, p=0.004). Itraconazole offered no advantage over voriconazole/posaconazole in preventing pulmonary lesions consistent with IFD (8.7% versus 4.0%, p=0.047). Demand for CT scans was not diminished with voriconazole/posaconazole compared to fluconazole/itraconazole (42% versus 37%, p=0.26) due to the high numbers of voriconazole courses necessitating CT scanning (45%)—only posaconazole was associated with a significant reduction compared to fluconazole/itraconazole/voriconazole courses combined (43% versus 26%, p<0.001).

7.1.4   Discussion

In our centre, adoption of voriconazole/posaconazole in comparison to fluconazole/itraconazole prophylaxis in a high-risk cohort of AML/MDS patients was associated with a significant decrease in the incidence of breakthrough possible/probable/proven IFD (20% versus 8.0%, p=0.011) in addition to reductions in less specific but not insignificant outcomes, including escalation to EAFT (31% versus 8.5%, p<0.001) and pulmonary lesions on CT treated for suspected IFD but not meeting consensus criteria for possible IFD (De Pauw, Walsh et al. 2008) (10% versus 4.0%, p=0.004).

A declining trend in breakthrough proven/probable IFDs (fluconazole 17%, itraconazole 8.2%, voriconazole 1.7%) persisted when more stringent criteria akin to an intention-to-treat analysis were applied (fluconazole, 11%; itraconazole, 10%, voriconazole, 2.4%). Notably, the breakthrough IFD incidence of 3% associated with posaconazole was due to possible IFDs and comparable to the 2% proven/probable IFD incidence in the randomised trial (Cornely, Maertens et al. 2007). Qualifying these findings is the fact that as a non-contemporaneous cohort, host or treatment-related factors (e.g., duration of azole prophylaxis or neutropenia), may have contributed to improvements in effectiveness but further analysis controlling for key variables was not possible due to low numbers of breakthrough IFDs overall.

Local epidemiology informs the choice and risk-benefit of prophylaxis. Prophylaxis seems warranted in our setting where baseline IFD incidence is likely higher than the 17% observed in our fluconazole cohort and above the 15% threshold identified in a meta-analysis of non-HSCT neutropenic patients (Kanda, Yamamoto et al. 2000). In our setting the number-needed-to-treat (NNT) with posaconazole prophylaxis to prevent one probable/proven IFD is 6, which is lower than the posaconazole registration trial (NNT=16) (Cornely and Ullmann 2008) but similar to other real-world experience comparing posaconazole to topical polyene prophylaxis (NNT=7) (Vehreschild, Ruping et al. 2010). Breakthrough IFDs were predominantly IA, in-keeping with the decline in invasive candidiasis seen in recent years (Pagano, Caira et al. 2006) but notable in our setting given the high requirement for TPN and its

association with mucositis, both of which are risk factors for invasive candidiasis (Leon, Ruiz-Santana et al. 2009).

Premature discontinuations were lower, with voriconazole/posaconazole compared to fluconazole/itraconazole (46% versus 22%, p<0.001). Clinical failure denoted by escalation to EAFT accounted for the majority of discontinuations among the standard azoles (fluconazole, 74%; itraconazole, 62%). Concern regarding potential incomplete gastrointestinal absorption or intolerance accounted for the majority of posaconazole discontinuations (71%) compared to 42% for itraconazole. This was likely due to a greater propensity for gastrointestinal intolerance with itraconazole and the lack of an IV formulation for posaconazole when mucositis supervened. The Cologne group (Vehreschild, Ruping et al. 2010) in contrast, reported no significant intolerance/toxicities associated with posaconazole, perhaps reflecting a higher degree of clinician confidence in the drug even in the presence of mucositis. Serious adverse events were consistent with the recognised toxicities of azoles (Cronin and Chandrasekar 2010) but for voriconazole, less frequent than post-marketing reports (Eiden, Peyriere et al. 2007; Riedel, Choe et al. 2007).

The emergence of resistant fungi is a potential drawback of broad-spectrum antifungal prophylaxis. Intrinsically resistant organisms, including *A. niger, Scedosporium prolificans,* and *Rhizopus spp.* were seen but in association with fluconazole, itraconazole, and both fluconazole/voriconazole respectively limiting conclusions about causation. Our single case of possible acquired itraconazole resistance echoes the low prevalence of azole resistance in

Aspergillus isolates (0.85%) reported from a haematology unit where periods of drug exposure were also short (Alanio, Sitterle et al. 2011).

TDM was performed when absorption was suspected to be inadequate, hence sub-therapeutic levels were common and further interpretation was limited by an absence of TDM among the 5 patients who developed probable/proven IFDs.

Our burden of IFD is likely underestimated due to a lack of routine GM testing and like other transplant centres, falling autopsy rates. Multiple prophylactic azole drugs were administered to 52 patients (data not shown) during their entire treatment schedule due to toxicities/intolerance, changes in unit policy or following long intervals between treatment (e.g., disease relapse). Therefore, we analysed courses rather than patients assuming that episodes of chemotherapy-induced neutropenia were discrete, temporally separate and therefore independent periods of risk. The choice of fluconazole/itraconazole as comparators to voriconazole/posaconazole was based on clinical trial experience (Cornely, Maertens et al. 2007). That consolidation chemotherapy is low risk for IFD (affecting 3/27 patients) compared to post-induction aplasia (Pagano, Caira et al. 2006; Lewis, Hall et al. 2010; Pagano, Caira et al. 2010), suggests a review of our universal policy of broad-spectrum prophylaxis may be warranted.

Concordance of real-world effectiveness of posaconazole prophylaxis with trial experience is reassuring but we welcome advances in risk stratification tools to better direct prophylaxis to those at highest risk. However, unless persuasive

evidence emerges that approaches alternative to broad-spectrum prophylaxis (Cordonnier, Pautas et al. 2009) do not threaten longer term outcomes—i.e., the completion and intensity of leukaemia treatment, due to the development of IFD (Even, Bastuji-Garin et al. 2010)—then it is not a strategy we are likely to abandon but would prefer to refine.

Table 7.2: Clinical Characteristics of Patients with Breakthrough IFD

Characteristic	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Probable or proven IFDs[1]	6	4	1	0
Female sex	4	1	1	NA
Age, years Median (range)	50 (40–60)	59.5 (50–70)	71	NA
Year of IFD diagnosis	1999, 2000, 2003/04	2001/02	2003	NA
Underlying disease	AML	AML	AML	NA
Phase of treatment				NA
Induction/Re-induction	5	3	0	
Induction for relapse	1	0	1	
Consolidation	0	1	0	
Site of infection				NA
Lung	5	3	1	
Sinus	1	0	0	
Blood	0	1	0	
Organism				NA
A. fumigatus	2	1	0	
A. niger	1	0	0	
Fungal hyphae resembling *Aspergillus spp.*	2	1	0	
Fungal hyphae not specified	0	1	0	
Rhizopus spp.	1	0	1	
Scedosporium prolificans	0	1	0	
Receipt of TPN[2]	4/6	3/4	0/1	NA
Outcome at 12 weeks				NA
Cure	3	0	0	
Unfavourable response[3]	3	4	1	
Death	3	2	0	
Possible IFD[4]	3	4	7	2
Lung resection performed	0	2	1	2
Lung biopsy or lavage	2	4	1	2
Any positive PCR	0/1	1/2	0/1	0/2
Probable or proven IFDs by intention-to-treat[5]	8	6	2	0

[1]IFD occurrence in patients receiving ≥7 days of antifungal prophylaxis, during

or ≤7 days from cessation of azole prophylaxis; [2]Receipt of TPN a surrogate

marker for the presence of mucositis; [3]Unfavourable response defined as partial response, progressive infection or death; [4]Evidence of either halo, nodule(s) or cavitation on CT of the chest. Non-specific pulmonary infiltrates or infiltrates not suggestive of fungal infection were excluded; [5]IFD occurrence during or ≤30 days of drug cessation in patients receiving ≥1 days of prophylaxis.

Table 7.3: Reasons for Discontinuation of Azole Prophylaxis Courses[1]

Clinical outcome	Fluconazole, n (%)	Itraconazole, n (%)	Voriconazole, n (%)	Posaconazole, n (%)	P[2]
Premature discontinuation, no. of courses (%)[1]	42/93 (45)	53/115 (46)	37/202 (18)	41/149 (28)	<0.001[3]
Reason for discontinuation					
EAFT (≥4days) for suspected IFD	31/93 (33)	33/115 (29)	19/202 (9.4)	11/149 (7.4)	<0.001[3]
EAFT & pulmonary lesions suggestive of IFD[4]	11/93 (12)	10/115 (8.7)	9/202 (4.5)	5/149 (3.4)	<0.001[3]
Gastrointestinal intolerance/absorption concerns	2/93 (2.2)	22/115 (19)	7/202 (3.5)	29/149 (19)	0.012[5]
Receipt of TPN in subset with GIT absorption/intolerance concerns	0/2	16/22 (73)	4/7 (57)	22/29 (76)	*
Abnormal LFTs[6]	1/93 (1.1)	2/115 (1.7)	10/202 (5)	1/149 (0.7)	0.009[7]
Other[8]	4/93 (4.3)	3/115 (2.6)	4/202 (2.0)	1/149 (0.7)	*
Courses discontinued due to death or palliation of patient	2	4	4	4	*

Abbreviations: LFTs (liver function tests); [1]In some cases patients discontinued drugs for more than one reason. Premature discontinuation excludes courses where patients subsequently died or were palliated; [2]Test of difference used the χ^2 test or Fisher's exact test as appropriate; [3]Comparing discontinuation in the standard azole (fluconazole, itraconazole) versus voriconazole & posaconazole

groups combined; [4]Pulmonary lesions treated for suspected IFI but not meeting consensus criteria (De Pauw, Walsh et al. 2008); [5]Comparing discontinuation in the itraconazole versus voriconazole & posaconazole groups combined; [6]Abnormal LFTs according to clinician judgement as documented in medical chart; [7]Comparing discontinuation in voriconazole versus fluconazole/itraconazole/posaconazole groups combined; [8]Includes discontinuations due to photopsia and rash (voriconazole, n=2); avoidance of drug-drug interactions with voriconazole (all-trans retinoic acid and arsenic in one patient and amiodarone in another patient); ventricular fibrillation associated with a prolonged QT interval with posaconazole (n=1); reasons for discontinuation were unclear for fluconazole and itraconzole; *No test of comparison performed.

7.2 Intermittent Liposomal Amphotericin Prophylaxis in Patients with Haematological Malignancies at High-Risk for IFD: Effectiveness and Safety

- Ananda-Rajah, M.R., Grigg, A., Bajel, A., Thursky, J.V. & Slavin, M.A. ICAAC ASM 2011, San Francisco.

Authorship

Study conception and design: AG, MS, MA-R; Data collection: MA-R, AG, MS; Data analysis and interpretation: MA-R, KT, AG, MS; Drafting of abstract and poster presentation: MA-R; Critical revision of abstract and poster

7.2.1 Introduction

As in several centres worldwide (Vehreschild, Ruping et al. 2010; Auberger, Lass-Florl et al. 2012; Girmenia, Frustaci et al. 2012), posaconazole is now our prophylactic agent of choice in patients at high-risk of IFD (Ananda-Rajah, Grigg et al. 2012). However, it has recognisable limitations given its oral formulation, inconsistent bioavailability and potential for drug-drug interactions. Thus, not all patients can either be commenced on posaconazole (e.g., patients undergoing vincristine-based chemotherapy) or maintained on it due to gastrointestinal absorption concerns. For patients who are either intolerant or unable to take azole prophylaxis no standard approach exists. At our centre, liposomal amphotericin (L-AmB) has been used as prophylaxis at a non-weight based dose of 100 mg 3 times weekly.

Following our azole antifungal prophylaxis study (Ananda-Rajah, Grigg, Downey et al. 2012) we decided to perform a similar audit of intermittent liposomal amphotericin prophylaxis. It encompassed a wider population than AML patients and in doing so provided epidemiological surveillance information on the burden of IFDs in patients with other haematological malignancies and HSCT recipients. Data collection for this study is now complete (as of March 2013) and the preliminary findings from one (i.e., Royal Melbourne Hospital) of 3 centres (the other centres being Alfred Health and

Austin Health) has been reported in abstract form (see Appendix 6). A synopsis of this study is provided below.

This was a retrospective study of the effectiveness of L-AmB prophylaxis (50 to 100mg 3 times/week or alternate days) in consecutive haematology-oncology and HSCT patients over 7 years from January 2003 to December 2010 at the Royal Melbourne Hospital.

7.2.2 Methods

Manual reviews of medical charts, pathology and radiology were conducted using a standardised case report form (see Appendix 11). Collected information included: demographic details, breakthrough fungal infections, toxicities related to L-AmB prophylaxis, indications for prophylaxis, serial measurements in creatinine clearance, receipt of nephrotoxic medications (aminoglycoside antibiotics, diuretics, ACE inhibitors, cyclosporine, tacrolimus, cyclophosphamide, cisplatin, non-steroidal anti-inflammatory drugs), status of underlying leukaemia, phase of chemotherapy (induction versus consolidation), duration of neutropenia (defined as days with absolute neutrophil count less than $0.5cells/mm^3$).

L-AmB prophylaxis was administered with each chemotherapy cycle typically starting a few days before or at the commencement of chemotherapy. Prophylaxis was continued until resolution of neutrpenia, occurrence of a suspected IFD or until resolution of gastrointestinal symptoms and resumption of oral prophylaxis. Escalation to EAFT for suspicion of IFD was based on

persistent unexplained fever associated with typical radiological findings on CT. NCBTs, including galactomannan or beta-glucan assays are not routinely used in our setting. All patients who received L-AmB prophylaxis either 50 mg or 100 mg 3 times per week or alternate daily were included in the analysis.

7.2.3 Definitions

Clinical effectiveness was defined as the incidence of possible/probable or proven IFDs occurring during the prophylaxis course or up to 7 days after its cessation in patients who received at least 5 consecutive days of therapy. The definitions of possible, probable, and definite breakthrough fungal infections were based on EORTC/MSG criteria (De Pauw, Walsh et al. 2008). Day of IFD diagnosis was defined as the first day of suspicious radiological abnormality or positive microbiological or histopathological test.

Nephrotoxicity was defined as (1) a sustained reduction in creatinine clearance—i.e., $\geq 25\%$ or $\geq 50\%$ reduction from baseline over at least 2 consecutive measurements; (2) a clinically significant reduction in renal function—i.e., a decrease in creatinine clearance to <50mls/min if the baseline was $\geq$50mls/min or a decrease in creatinine clearance of $\geq$10mls/min if the baseline was <50mls/min.

7.2.4 Results

From 2003 to 2010, 139 consecutive patients received 202 courses of L-AmB prophylaxis. Results are presented in tables 7.4 to 7.8 and in Figure 7.1.

Underlying conditions per prophylaxis course were: AML, 81/202, 40%), ALL (50/202, 25%), lymphoma (28/202, 14%) and other lymphoproliferative diseases inclusive of aplastic anaemia, multiple myeloma, refractory anaemia with excess blasts, biphenotypic leukaemia, acute promyelocytic leukaemia, mixed lineage leukaemia and Burkitt leukaemia (30/202, 15%). Of 202 courses of L-AmB prophylaxis, 50% were administered to patients undergoing allogeneic HSCT. The median age of patients was 47 years, median weight 77 kg (range 42 to 125 kg) and median duration of prophylaxis was 15 days (interquartile range 10 to 24 days). Neutropenia was present in 83% of 202 courses of prophylaxis administered.

Indications for L-AmB prophylaxis were: gastrointestinal absorption concerns (62/202, 31%); an anticipated prolonged neutropenia (e.g., for cord blood HSCT, aplastic anaemia or in the context of allo-HSCT pre-engraftment) lasting at least 14 days (50/202, 25%); vincristine-based chemotherapy (51/202, 25%); avoidance of azole drug-drug interactions in HSCT patients (24/202, 12%) or contraindication/intolerance to azole drugs in non-ALL patients (e.g., abnormal LFTs, rash) in 15/202 (7.4%).

Breakthrough possible/probable/proven IFDs using pre-defined criteria (i.e., diagnosed after at least 5 consecutive days of prophylaxis with onset up to 7 days from cessation of prophylaxis) in 9/132 patients (6.8%) with 6 proven/probable IFD comprising IA (n=4) inclusive of *Scedosporium apiospermum* co-infection (n=1) and one each of, *Rhizopus spp.* and *C. krusei* fungaemia. Premature discontinuations were 34/202 (17%) and reasons were:

suspected IFD (23/202, 11%), infusional reactions 2/202 (1.0%) and hepatoxicity 2/202 (1.0%). A sustained decrease in creatinine clearance complicated 45/202 (22%) but resultant discontinuation was uncommon (2/202, 1.0%).

Table 7.4: Patient Characteristics

Characteristic, n=139 patients	
Age, median (range), years	47 (18–68)
Male gender (%)	79 (57)
Weight, median (range), kg	77 (42–125)
Underlying condition per course, n=202 courses	**n (%)**
AML	81 (40)
ALL	50 (25)
Lymphoma	28 (14)
Chronic leukaemia	13 (6.4)
Lymphoproliferative disease	30 (15)
Treatment administered	
Chemotheraphy for AML	53 (26)
Chemotherapy for ALL/aggressive lymphoma	49 (24)
SCT	100 (50)
Peri-SCT	65/100 (65)
Allo-SCT	99/100 (99)
Duration of prophylaxis, median (IQR), days	157 (10–24)
Neutropenia present during course	167 (83)
Duration of neutropenia, median (IQR) days	16 (11–22)
LAMB dose/kg/week	4mg/kg/wk

Table 7.5: Reason for Prophylaxis with Intermittent L-AmB, n=202

Courses

Reason for prophylaxis	n (%)
Decreased oral intake/incomplete GIT absorption	62 (31)
—AML	33 (16)
—SCT	29 (14)
Vincristine-based chemotherapy	51 (25)
Prolonged neutropenia expected (e.g., cord blood SCT, aplastic anaemia)	50 (25)
—SCT	35/50 (70)
—periSCT	27/35
—AML	11/50 (22)
—ALL	4/50 (8)
Avoidance of drug-drug interaction in SCT recipients	24 (12)
Contraindication/intolerance to azole drug in non-ALL pts (e.g., abnormal LFTs, rash)	15 (7.4)

Table 7.6: Breakthrough IFDs in Patients

Characteristic	By pre-defined criteria,[1] n=132, (%)	By intention to treat,[2] n=139, (%)
Probable/proven IFDs	6 (4.5)	7 (5.0)
Possible IFDs	3 (2.3)	7 (5.0)
All IFDs	9 (6.8)	14 (10)

[1]At least 3 doses LAMB, up to 7 days from cessation; [2] Single dose, up to 60d from cessation.
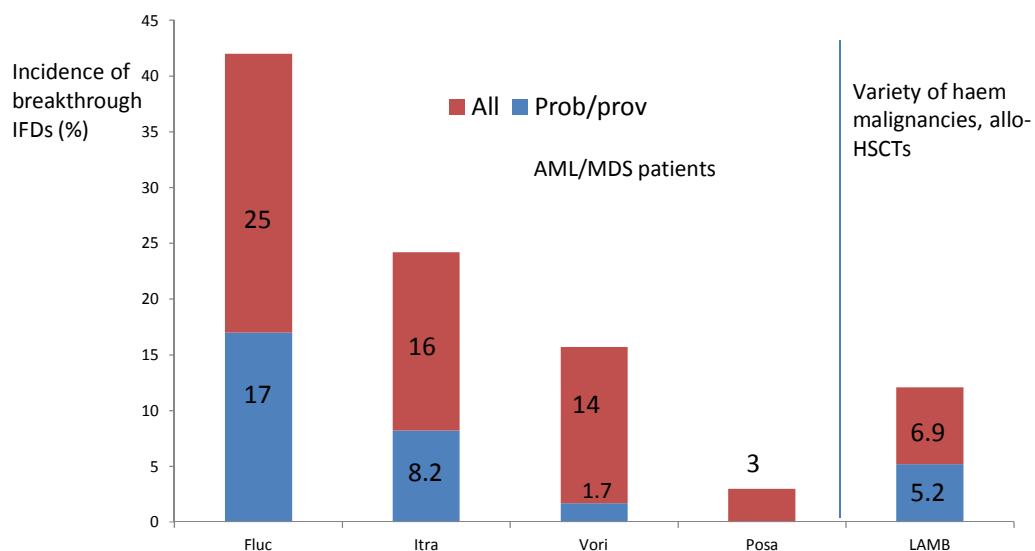
Characteristic	Fluc	Itra	Vori	Posa	LAMB
Probable/proven IFDs	6	4	1	0	6
Possible IFDs	3	4	7	2	2
Probably/proven IFDs by ITT	8	6	2	0	7

Figure 7.1: Comparison of breakthrough IFD rates between diverse patient groups: AML/MDS patients (to the left of the vertical line) undergoing remission-induction chemotherapy from (Ananda-Rajah, Grigg, Downey et al. 2012) and a patients with a variety of haematological conditions, including HSCT recipients (to the right of the vertical line).

Table 7.7: Characteristics of Patients in Receipt of at Least 3 Doses of L-AmB Who Developed Breakthrough IFDs Occurring up to 7 Days from Cessation of Intermittent L-AmB, n=9

Age/sex/wt	Condition/reason for LAMB	Phase of Rx	IFD onset from al-loSCT, days	Duration LAMB, days	Prophylaxis prior to LAMB	EORTC/MSG/IFD year of diagnosis	Pathogen	Site
55F, 64kg	AML/GIT issues	New dx	NA	8	Posa200tds, 22d	Proven, 2008	*Hyphae cw Asp, Scedo apio-spermum*	Lung, liver, spleen, renal
52M, 78kg	AML/GIT issues	New dx	NA	10	Posa200tds, 10d	Proven, 2007	*Hyphae cw Asp, Asp PCR pos*	Lung
58F, 68kg	AML/GIT issues	Other	NA	7	Posa200tds, 11d	Proven, 2008	Nil	Lung
36F, 53kg	Burkitt lymph/vinc	CR	NA	11	Nil	Proven, 2009	Nil	Lung
28M, 89kg	Hodgkins lymph/periB MT prol neu	Relapse/failed induction	10	7	Nil	Proven, 2007	Nil	Lung
66M, 90kg	RAEB/BMT post eng intol azoles—non-GIT issues	Relapsed/failed induction	367	5	Posa200tds, 77d	Proven, 2007	*Rhizopus*	Lung
36M, 85kg	AML, early periBMT, avoid drug interac-tions	Relapsed/failed induction	28	27	Nil	Proven, 2008	*C. krusei*	Blood
57M, 76kg	MDS, as above	CR	29	22	Caspo 50/d, 4d	Proven, 2009	*A. fusispora*	Lung

Table 7.8: Toxicity and Tolerability of Intermittent L-AmB Prophylaxis

Premature discontinuations (n=202 courses)		
Persistent fever	23	11%
Infusional reactions	2	1%
Abnormal LFTs	2	1%
Renal impairment	2	1%
Death or palliation of pt	4/202	2.0%
Nephrotoxic meds	175	87%
(diuretics, ACE inhibitors, cyclosporine, tacrolimus, cyclophosphamide, cisplatin, NSAIDS, aminoglycosides		
Nephrotoxicity		
Significant renal function (clinically significant reduction—i.e., a decrease in creatinine clearance to <50mls/min if the baseline was ≥50mls/min or a decrease in creatinine clearance of ≥10mls/min if the baseline was <50mls/min)		
No	190	94%
Yes	12	5.9%
Sustained CrCL	45	22%
(i.e., ≥25% or ≥50% reduction from baseline over at least 2 consecutive measurements		
≥25%	36	18%
One discontinuation		
≥50%	9	4.5%

7.2.5 Conclusions

Intermittent L-AmB prophylaxis is a reasonable alternative to azole prophylaxis in certain patient groups: it was well tolerated with clinically significant nephrotoxicity necessitating premature discontinuation rare. Microbiologically confirmed IFDs were predominantly mould infections and consistent with our previous audit of azole antifungal prophylaxis in patients undergoing intensive chemotherapy for AML (Ananda-Rajah, Grigg, Downey et al. 2012). IFD incidence in AML/MDS patients on posaconazole prophylaxis, our current choice, is 3% (Ananda-Rajah, Grigg, Downey et al.

2012), which contrasts to the 6.8% from this audit. Patient groups were not directly comparable but it may be argued that patients with AML undergoing high-dose remission-induction chemotherapy with a cytarabine-based regimen are at higher risk for IFD raising questions as to how our program using intermittent L-AmB prophylaxis may be optimised. Of the 9 patients with breakthrough IFDs, 4 had received posaconazole prophylaxis administered for 10, 11, 22 and 77 days respectively before switch to liposomal amphotericin prophylaxis (in 3 patients with AML this was due to mucositis; in one patient post allogeneic HSCT intolerance to azole drugs was the reason for switch). Notably, intermittent L-AmB appeared to be effective in patients with ALL with none developing breakthrough IFDs- although this observation may be a result of small numbers of patients with ALL evaluated.

It is likely that for some patients at high-risk for IFD (such as AML patients undergoing cytarabine-based chemotherapy) the dose of L-AmB (overwhelmingly being 100 mg 3 times weekly) administered in our setting is suboptimal. Dosage adjusted for body weight may improve prophylactic effectiveness bearing in mind that in one study a weekly dose of 10mg/kg was associated with a high rate of adverse events in predominantly HSCT recipients resulting in premature study termination (Cordonnier, Pautas et al. 2009). Thus, an unresolved issue lies in finding the dose of L-AMB which optimises efficacy, convenience, cost-effectiveness while minimising toxicity particularly as it will be administered to many patients in order to protect the few.

Alternative explanations to the higher than expected breakthrough IFD rate on intermittent L-AmB prophylaxis are: that patients with breakthrough IFDs had incipient fungal infections that were being suppressed on prophylactic doses of posaconazole only to develop clinically overt infection when switched to a less efficacious regimen in low dose L-AmB or fungal acquisition and invasive disease occurred following switch to L-AmB.

This audit of intermittent L-AmB prophylaxis prompted an evidence-based review of the use of posaconazole. We intended to ensure that we were adhering to up-to-date practice, focusing on methods designed to safeguard its efficacy, reasons for switch therapy to L-AmB and the role of TDM. The following published paper is a synthesis of current literature on the topic resulting in practice recommendations to guide clinicians on optimising the use of posaconazole for either prophylaxis or treatment of established IFDs.

7.3   Making Sense of Posaconazole TDM: A Practical Approach

This section is based on a published paper (see Appendix 1).

- Ananda-Rajah, M.R., Grigg, A. & Slavin, M.A. (2012). Making sense of posaconazole therapeutic drug monitoring: A practical approach. *Curr Opin Infect Dis, 25*(6), 605–611. doi: 10.1097/QCO.0b013e328359a56e

Authorship

7.3.1 Introduction

The increasing uptake of posaconazole as antifungal prophylaxis has been driven by trial evidence demonstrating its efficacy in high-risk haematology-oncology patients (Cornely, Maertens et al. 2007; Ullmann, Lipton et al. 2007), its favourable toxicity profile over the long term (Raad, Graybill et al. 2006) and a recognition of the high health and economic burden of IFDs (Kontoyiannis, Marr et al. 2010; Pagano, Caira et al. 2010; Ananda-Rajah, Cheng et al. 2011) with a predominance of mould pathogens in the current era (Pagano, Caira et al. 2006; Kontoyiannis, Marr et al. 2010; Pagano, Caira et al. 2010; Park, Pappas et al. 2011).

The clinical effectiveness of posaconazole appears to be similar to trial experience with several centres reporting low IFD breakthrough rates ranging from 3 to 7.5% (Vehreschild, Ruping et al. 2010; Winston, Bartoni et al. 2010; Nicolle, Benet et al. 2011; Ananda-Rajah, Grigg, Downey et al. 2012). However, there have been isolated reports of higher than expected breakthrough rates of 13% (Auberger, Lass-Florl et al. 2012; Girmenia, Frustaci et al. 2012), which may be a consequence of enhanced detection effort

employing intensive diagnostic strategies employing galactomannan (GM) (Girmenia, Frustaci et al. 2012) and/or the absence of adjuvant TDM at these centres.

The influence of posaconazole on fungal epidemiology should be corroborated by large-scale surveillance studies but unconfirmed reports from single centres document a reduction in the incidence of IA from 4.9% to 3.3% (p=0.04) (Nicolle, Benet et al. 2011) and a shift to non-*Aspergillus* moulds with the *Mucormycetes* prominent (Auberger, Lass-Florl et al. 2012) since its introduction as prophylaxis in patients with acute leukaemia undergoing intensive chemotherapy or in allogeneic-haematological stem cell transplant recipients.

Unpredictable bioavailability associated with high inter- (up to 68% in adult patients) and intra-patient variability (Gubbins, Krishna et al. 2006; Krishna, Martinho et al. 2007; Krishna, AbuTarif et al. 2008) means that TDM is increasingly being used to guide prescribing, although its effect on patient outcomes is less well studied. Rather than an appraisal of pharmacokinetic/pharmacodynamic (PK/PD) aspects of posaconazole that can be found elsewhere (Li, Theuretzbacher et al. 2010; Lewis 2011a,c; Dolton, Ray et al. 2012), we will outline the controversies surrounding its use and make recommendations on the role of TDM in IFD treatment and prevention, cognisant that this is an evolving area of research.

7.3.2   How Should Posaconazole Levels Be Interpreted?

Limited clinical studies suggest that an exposure-response relationship for posaconazole exists (Krishna, Martinho et al. 2007; Walsh, Raad et al. 2007; Jang, Colangelo et al. 2010). Improved outcomes with progressively higher plasma concentrations in patients with established disease (Walsh, Raad et al. 2007) have been observed but therapeutic targets for either treatment or prophylaxis are undefined and hampered by the variability of parameters (e.g., AUC: MIC, average, trough, Cmax) reported in the literature with no clear PK/PD index predictive of efficacy in moulds (Li, Theuretzbacher et al. 2010). An early expert recommendation proposed a trough TDM target of 0.5ng/L for prophylaxis (Andes, Pascual et al. 2009), which corresponded to the concentration required to suppress growth in 90% of most *Aspergillus* isolates in vitro (i.e., the MIC_{90} being 500ug/mL for *A. fumigatus* and *A. flavus* but 1.0 ug/ml for *A. niger*) (Pfaller, Messer et al. 2002; Sabatelli, Patel et al. 2006).

Given the wide therapeutic index of posaconazole, a threshold of 500ng/ml may be regarded as conservative and 700ng/ml has been proposed based on a post-hoc analysis (Jang, Colangelo et al. 2010) of a subset of patients (i.e., 252/600, 42% from (Ullmann, Lipton et al. 2007) and 215/602, 36% from (Cornely, Maertens et al. 2007)) with PK data from the posaconazole registration trials. In this analysis, patients were stratified according to quartile posaconazole average (Cavg) steady state concentrations. Higher quartiles were associated with lower clinical failure defined as a composite of receipt of EAFT, premature discontinuation, survival and proven/probable IFDs. Logistic regression revealed that clinical failure was substantially higher at greater than

25% to 25% when Cavg concentrations were less than 700ng/ml (Jang, Colangelo et al. 2010).

Importantly, in this analysis the major factor driving clinical failure was receipt of EAFT rather than IFD or death (Cornely and Ullmann 2011) and in 3 patients who developed IFDs Cavg concentrations were >1500ng/ml (Jang, Colangelo et al. 2010). It seems likely, although it is not stated, that a composite definition of clinical failure was chosen because the number of treatment emergent (i.e., during prophylaxis) IFDs was too low for meaningful analysis (11 of 14 IFDs were treatment emergent in the intention-to-treat cohort excluding 1 patient who developed *Pneumocystis carinii* pneumonia where azoles would be ineffective prophylactically) (Cornely and Ullmann 2011). Further, for 3 patients plasma posaconazole concentrations were not coincident with the emergence of IFD being sampled 3 to 7 weeks prior to IFD onset (Cornely and Ullmann 2011). In light of these shortcomings a cautious interpretation of this TDM target is warranted.

An exposure-response relationship for IFD prophylaxis is difficult to establish when studies are underpowered for this endpoint. Again, separate post-hoc analyses of the PK dataset from the registration trials are conflicting. In patients with GVHD, median Cavg concentrations at steady state were lower among 5 patients who developed proven or probable IFDs compared to 241 without IFD (611ng/ml versus 922ng/ml) (Krishna, Martinho et al. 2007). However, among the higher risk AML/MDS patients receiving intensive chemotherapy no difference in mean Cavg levels at steady state was seen

between the 6 patients who developed IFDs compared to the 188 uninfected patients (457 versus 586 ng/mL respectively) (Krishna, AbuTarif et al. 2008). Importantly, a survival benefit in the posaconazole arm of the latter study was observed despite 75% of patients having Cavg levels of only 319 ng/ml or more (Krishna, AbuTarif et al. 2008).

In routine practice sub-therapeutic posaconazole levels are common (ranging from 44% to 76%) (Lebeaux, Lanternier et al. 2009; Thompson, Rinaldi et al. 2009; Bryant, Slain et al. 2011; Eiden, Meniane et al. 2012; Hoenigl, Raggam et al. 2012) but because numbers of breakthrough IFDs are few, observational real-world studies like the original trials, do not unequivocally validate the putative threshold concentrations described for prophylaxis. In a retrospective study of 54 patients with mostly haematological malignancies, 44% (16/36) of patients in the prophylaxis group had low levels (<500ng/ml) after 5 days therapy while the 2 patients who subsequently developed IFDs had levels of 310 and 190ng/ml (Lebeaux, Lanternier et al. 2009). In a prospective study of 63 haematology patients, 74% had low levels (<0.70 mg/L, median 0.44mg/L) at steady state but the single patient with treatment emergent IFD had a level of 0.11mg/L (Eiden, Meniane et al. 2012). Similarly, a prospective study of 34 haematology patients in whom 31 received posaconazole prophylactically, found that 71% of patients had sub-therapeutic levels (<0.5ug/ml) with steady state levels among the 3 patients developing breakthrough IFDs of 0.28, <0.20 and 0.31ug/ml prior to prophylaxis failure (Hoenigl, Raggam et al. 2012).

A retrospective evaluation of posaconazole steady state concentrations in patients with chemotherapy-induced neutropenia for AML/MDS showed that 3 of 21 patients who developed breakthrough IFDs had levels <0.5ug/ml but overall most patients were sub-therapeutic with 76.2% and 90.5% failing to reach targets of 0.5 ug/ml and 0.7ug/ml respectively (Bryant, Slain et al. 2011). It is noteworthy that in a small prospective study 2 patients developed breakthrough IFDs, although they attained posaconazole levels of 900ug/L at IFD onset (Neubauer, Engelhardt et al. 2010). It is unclear if TDM can further improve the prophylactic efficacy of posaconazole given the fact that even outside the controlled conditions of clinical trials among unselected patients, breakthrough IFDs remain uncommon despite sub-therapeutic levels being commonplace.

7.3.3   Cell Associated Fraction of Posaconazole and Efficacy

The prophylactic efficacy of posaconazole may be explained by differential penetration into cells important in the front-line defence against *Aspergillus* species. Concentrations in alveolar cells and monocytes are 22 to 67 times plasma concentrations (Conte, Golden et al. 2009; Conte, DeVoe et al. 2010; Farowski, Cornely et al. 2010), which is above the MIC$_{90}$ of *Aspergillus* for the entire 12 hour dosing interval. In addition a recent in vitro study (Campoli, Al Abdallah et al. 2011) demonstrated inhibition of fungal growth in pulmonary epithelial cells and macrophages on exposure of drug exposed cells to *Aspergillus* conidia, which occurred after a relatively brief exposure (4 hours) to posaconazole and persisted for up to 48 hours. Resistance to infection occurred at cellular concentrations above 80 to 100 ug/ml, which is the steady

state level in alveolar cells isolated from healthy volunteers (Conte, Golden et al. 2009), suggesting that 400mg bd of posaconazole may be effective in treating or preventing IA.

It is possible that these high cellular concentrations are responsible for the curative potential of posaconazole despite recent experimental data questioning the likelihood of attaining adequate systemic exposure with the approved treatment regimen (Howard, Lestner et al. 2011). Using a murine model of inhalational aspergillosis, Howard et al. (2011) showed that attainment of a 24-hour serum AUC:MIC target associated with a 90% maximal antifungal effect (as measured by GM kinetics) was 440, which is unfeasible in practice because 800mg/day is estimated to deliver an AUC:MIC of only 100 to 150 in patients. However, in vitro studies suggest that cellular levels may be several fold higher than serum and still within the effective range (Conte, DeVoe et al. 2010; Campoli, Al Abdallah et al. 2011). Indeed, observed clinical success raises questions as to whether the AUC:MIC is the appropriate PK/PD parameter for *Aspergillus* and *Candida* species as underlined by a proof-of-principle study showing higher than expected antifungal activity against *Candida* species of unbound drug at concentrations far below the MIC, suggesting flux from the protein bound fraction to the fungal target (Lignell, Lowdin et al. 2011).

7.3.4   Targets in Curative Treatment

In patients with established infection, TDM is advisable based on the PK dataset of 67 patients from a salvage study of 107 patients with IA, which showed improved outcomes with progressively higher maximum or average

steady state plasma concentrations of posaconazole (Walsh, Raad et al. 2007). Response rates were 24%, 53%, 53% and 75% corresponding to mean plasma levels of 134, 411, 719 and 1250 mg/ml but the timing of TDM was not recorded. Based on this study it seems reasonable for curative intent to aim for an average concentration at steady state of at least 1mg/ml, although in practice this may be difficult to achieve.

7.3.5 When Should Posaconazole Levels Be Performed?

Patients with established infection should have TDM while for prophylaxis, our recommendation includes those patients at highest risk for either IFD or if concerns regarding bioavailability prevail as summarised in Table 7.9.

Table 7.9: Indications for Posaconazole TDM

Recommended
Treatment of established fungal infection
Impaired gastrointestinal absorption (e.g., presence of diarrhoea, mucositis, poor oral intake, vomiting)
Compliance concerns
On drugs known to either impair absorption or increase clearance (e.g., proton pump inhibitors)
Patients at highest risk for development of fungal infection (e.g., relapsed or refractory disease, anticipated duration of neutropenia >14days)

7.3.6 Can Posaconazole TDM Be Performed Prior to Steady State?

TDM should ideally be performed at steady state. However, this entails a delay of at least 7 days in addition to the turn-around time of results. Of interest, recent clinical studies (Cornely, Helfgott et al. 2012; Green and Woolery 2012) corroborate a PK computer simulation, suggesting that day 2 levels may be

predictive of steady state concentrations (satfda_docs/nda/2006/022003s000_Noxafil_ClinPharmR.pdf.). Cornely et al. (2012) in a study of 49 AML patients many of whom had chemotherapy related gastrointestinal disease, demonstrated that levels at day 3 were predictive of levels at day 8 (R^2 0.64) with 22 of the 30 patients (73%) who achieved a mean level of 250ng/ml at day 3 reaching a threshold of 500ng/ml by day 8.

Similarly, a small retrospective study of 16 patients on 200 mg tds, undergoing intensive chemotherapy for acute leukaemia showed that the majority (14/16) experienced a doubling or near doubling ($\geq$150%) of serum levels when levels taken 3 to 5 hours after the fourth consecutive dose on day 2 were compared to trough levels on day 7 (Green and Woolery 2012) when posaconazole was administered with a series of adjuvant interventions described elsewhere (Green and Woolery 2011). These findings suggest that for a proportion of patients, day 3 measurements may be predictive of steady state levels thereby potentially allowing earlier dose modification or interventions to optimise drug exposure.

7.3.7   Are Posaconazole Trough Levels Necessary?

Posaconazole has a prolonged half-life of 35 hours (Conte, DeVoe et al. 2010; Li, Theuretzbacher et al. 2010), and its frequent dosing results in a relatively flat concentration-time profile at steady state (Cornely, Helfgott et al. 2012), which may be exploited for TDM purposes. Heinz et al. (2011) in a PK study of 25 haematology patients showed a less than 20% variation in levels between a trough and 4 hours post-dose in 60% of patients despite intentionally

selecting a dosing regimen (400mg bd) associated with the highest daily PK variability; corresponding mean levels at trough, 4 hours and 8 hours post-dose were 645, 687 and 616 ng/ml respectively. These findings indicate that at steady state, untimed levels may be a reliable alternative to the trough level, which is typically collected prior to the morning dose, thus enhancing the practicalities of TDM especially when there is a pressing need to optimise drug exposure in light of either breakthrough IFD or absorption concerns.

7.3.8 What to Do When Posaconazole Levels are 'Sub-therapeutic'
7.3.8.1 Optimising Posaconazole Drug Exposure

Addressing modifiable patient factors and optimising drug delivery (summarised in Table 7.10) are the initial steps in safeguarding the effectiveness of posaconazole. Posaconazole should be co-administered with either a high fat meal, nutritional supplement or non-fat meal but if that is not possible then at the minimum with an acidic beverage. Avoidance of proton pump inhibitors and histamine antagonists in addition to drugs that increase posaconazole drug clearance is advisable. Dose fractionation (e.g., 200mg qid rather than 400mg bd) is of greatest benefit in fasting patients but in fed patients, 400mg bd with food is associated with a higher exposure (AUC) and lower variability than 200 qid (Krishna, Moton et al. 2009; Pea, Furlanut et al. 2009) with associated compliance benefits. One centre reported successful attainment of therapeutic levels at steady state in 5 haematology-oncology patients following introduction of a 'posaconazole bundle' aimed at maximising absorption with a series of strictly enforced interventions (Green and Woolery 2011).

Table 7.10: Safeguarding Posaconazole with Attention to Modifiable

Patient Factors and Drug Delivery

Recommendation	Comment	References
Co-administer posaconazole during or within 10–20 minutes of either:		
High fat meal if tolerated	4 fold increase in exposure relative to relative to fasting state with a meal containing 841 calories comprising 52% fat	Courtney, Wexler et al. 2004
Nutritional supplement (e.g., Boost Plus-14g fat) if solids poorly tolerated	2.6 fold increase in exposure relative to fasting state	Sansone-Parsons, Krishna et al. 2006
Non-fat meal	Approx. 2.6 fold increase in exposure relative to fasting state	Courtney, Wexler et al. 2004
Acidic beverage (e.g., ginger ale 12 oz) if solids poorly tolerated	70% increase in exposure relative to fasting state	Krishna, Moton et al. 2009
If daily dose is 800mg/day choice of regimen (400mg bd or 200 qid) is largely dependent on prandial status:	Effect of food most marked only with 400mg bd rather than 200mg qid dosing	Krishna, Moton et al. 2009, Pea, Furlanut et al. 2009, Ezzet, Wexler et al. 2005
In fed state, 400mg bd with high fat meal If fasting conditions, then 200mg qid preferred	Higher exposure and lower variability than 200mg qid in fasting state; Better compliance than qid dosing but dose fractionation preferred in fasting state	
Avoidance of proton pump inhibitors in all patients in the absence of a specific indication	Decreases exposure by 32%; Antacids potential alternatives	Krishna, Moton et al. 2009, Alffenaar, van Assen et al. 2009, Neubauer, Engelhardt et al. 2010
Avoidance of drugs known to increase posaconazole clearance or impair absorption (e.g., cimetidine, phenytoin, rifamycin derivatives)	_	Li, Theuretzbacher et al. 2010

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7.3.8.2 Is Increasing the Daily Dose of Posaconazole Effective?

Available data would suggest that dose escalation in an attempt to increase posaconazole drug exposure is unlikely to be effective. Jang et al. (2010) recommended dose escalation beyond the saturable limit of 800mg/day (Courtney, Pai et al. 2003) proposing 1200mg/day if levels were <350ng/ml on day 2 or <700ng/ml on day 7. Cornely et al. (2012) recently tested this hypothesis in a cohort of AML patients with gastrointestinal compromise randomised to 3 regimens (200mg tds, 400mg bd, 400mg tds) after receiving standard prophylactic doses (200mg tds) for 8 days.

They identified a subset of patients with persistently low levels who were resistant to dose escalation. Among the 12 patients who did not achieve a mean plasma concentration of 250ng/ml on day 8, 75% (9/12) did not attain the target of 500ng/ml at day 15 following dose escalation to 800mg and 1200mg per day. Consistent with these findings is the observation that no increase in plasma concentrations was seen in healthy volunteers or neutropenic patients administered 1200mg/d compared to 800mg/day (Courtney, Pai et al. 2003; Ullmann, Cornely et al. 2006). Shields et al. (2010) describe dose escalation in 7 of 17 heart or lung transplant recipients from 800mg to 1200mg daily as being largely ineffective with only 2 of 7 patients achieving trough levels >0.5ug/ml, the exception being 3 patients subsequently given 1600mg/day who achieved levels of ≥1ug/ml but at the cost of dose limiting gastrointestinal and hepatic toxicity.

In clinical trials, posaconazole at prophylactic doses and without TDM, was associated with significant reductions in proven/probable IA making the need for TDM for this indication questionable. Further, efficacy was demonstrated despite the presence of incipient IA at trial recruitment in a subset of patients as evidenced by a positive serum GM which was returned in 4% each of posaconazole (12/304) and comparator groups (13/298) with AML/MDS (Cornely, Maertens et al. 2007) and in 7% (21/301) and 10% (10/299) of posaconazole and fluconazole patients respectively (Merck Sharp Dohme data on file) with severe GVHD (Ullmann, Lipton et al. 2007).

A recent observational study from France reported the presence of IA at admission in 11% of hospitalised haematology-oncology patients of whom 76% had AML, but this is likely an underestimate of the true incidence as investigation was clinician initiated rather than protocol-driven (Nicolle, Benet et al. 2011). Replicating or improving trial outcomes in routine practice is dependent on several measures, among them, attention to drug delivery and perhaps, although unproven at this stage, consideration towards screening for IA at initial presentation in order to identify those patients requiring treatment rather than prophylaxis.

There is no standard approach for selection of an alternative prophylactic agent when discontinuation of posaconazole is contemplated. As an effective prophylactic agent, ceasing posaconazole is not a trivial issue and we believe that criteria for switch should be explicit and endorsed in unit protocols. TDM,

rather than bedside assessment alone (e.g., frequency of diarrhoea/vomiting or oral intake), provides an objective measure of absorption, which may inform the decision to switch provided it is available in a timely manner. Difficulties arise for the subset of asymptomatic patients at highest risk for IFD with persistently low levels despite optimisation of drug delivery. In this group, options include: (i) performing enhanced surveillance for IFD using regular biomarkers (e.g., GM, *Aspergillus* PCR, beta-D-glucan and HRCT screening), (ii) switching to alternative antifungal prophylaxis, which in our setting is typically, intermittent liposomal amphotericin (Ananda-Rajah 2011) or intravenous voriconazole, or (iii) posaconazole dose escalation with or without fractionation to 800mg/day accepting that this may not be effective in increasing serum levels.

7.3.9   Conclusion

Posaconazole TDM does not unequivocally stratify patients into high and low risk for prophylactic or therapeutic failure but it does provide an objective measure of drug exposure and the subsequent opportunity to individualise therapy while also augmenting clinician confidence in using the drug. The solid tablet and capsule formulations will address some of the shortcomings of the oral suspension given their higher bioavailability and less variability (Krishna, Ma et al. 2012) but until they become available safeguarding the prophylactic efficacy of posaconazole entails attention to drug delivery and modifiable patient factors but as important is adherence to infection control standards (Weber, Peppercorn et al. 2009) and prospective surveillance for IFD in order

to evaluate the effectiveness of preventative interventions such as antifungal prophylaxis.

7.3.9.1 Key points

- Posaconazole TDM provides an objective measure of drug exposure and may guide prescribing.

- Higher plasma posaconazole levels are associated with improved clinical response in patients with established IFDs on salvage therapy.

- Predictors of low plasma posaconazole levels are well established but identifying patients at high-risk of prophylactic failure is more difficult and not necessarily contingent on plasma levels.

- The prophylactic efficacy of posaconazole appears to be mediated by high concentrations in host cell membranes, thus explaining the observed discrepancy between low serum levels that are commonplace and prophylactic efficacy.

- Levels performed at day 3 may be predictive of steady state concentrations.

- Untimed serum levels at steady state are a reliable alternative to the traditional pre-morning dose trough level, thus expanding the practicalities of TDM.

7.4 Promoting Best Practice in Antifungal Prescribing, Antifungal Stewardship and Processes of Care that Affect IFD Rates

Process of care measures are interventions with known efficacy in decreasing the burden of IMDs. Process measures are less well defined for IMD prevention (Slavin, Heath et al. 2008; Worth, Blyth et al. 2008) than for other conditions such as antibiotic prophylaxis for preventing surgical site infections. For IMDs, TDM of antifungal drugs may be regarded as a process measure because it aims to optimise clinical outcomes and minimise drug toxicity by guiding the administration and dosage of antifungal therapy (Pascual, Calandra et al. 2008; Lewis 2011a; Lewis 2011b; Lewis 2011c; Ananda-Rajah, Grigg et al. 2012). Monitoring process measures may enhance interpretation of IMD incidence rates. For example, the introduction of posaconazole prophylaxis at one centre was associated with higher than expected IFD incidence rates (Girmenia, Micozzi et al. 2010), which prompted enhanced surveillance efforts and consideration of TDM (Girmenia, Micozzi et al. 2010; Girmenia, Frustaci et al. 2012). Process measures may be more easily monitored than IMD incidence, with significant deviations in practice easier to detect than changes in infection rates. Lapses in infection prevention practices or antifungal stewardship may therefore be recognised and addressed, before an increase in the infection rate has occurred. Concordance of antifungal drug prescribing with published guidelines (Pagano, Caira et al. 2010) is another potential process measure aimed at optimising treatment outcomes while minimising drug toxicities.

Haematology services are the highest prescribers of antifungal drugs, with empiric antifungal therapy (EAFT) the most common indication closely followed by prophylaxis (de With, Steib-Bauert et al. 2005; des Champs-Bro, Leroy-Cotteau et al. 2011). EAFT is usually administered to neutropenic patients with persistent fever unresponsive to 5 to 7 days of broad-spectrum antibiotics before definitive evidence of IFD has emerged. EAFT accounts for 62% (Pagano, Caira et al. 2010) to 72% (des Champs-Bro, Leroy-Cotteau et al. 2011) of antifungal prescribing in haematology-oncology patients noting that only a minority (10% to 15%) will truly have an IFD (Walsh, Finberg et al. 1999; Walsh, Teppler et al. 2004). Therefore, establishing or excluding the diagnosis of IFD in a timely fashion is important to avoid overtreatment of patients, excessive drug expenditure and unnecessary exposure of patients to potential drug toxicity.

The completeness and timeliness (i.e., intensity) of the diagnostic work-up once patients are commenced on EAFT is a potential process measure that could facilitate descalation of antifungal drugs while improving clinical outcomes through earlier diagnosis. Variations in diagnostic intensity such as the frequency and timing of investigations (e.g., CT imaging, lung sampling with or without GM or PCR, GM serum monitoring); or their use as surveillance tools during periods of risk compared to when there is clinical suspicion of fungal disease, will affect the detection and subsequent reported incidence of mould diseases (see Chapter 3).

The diagnostic sensitivity of GM and PCR depends to a large extent on the number of samples taken, with testing at least twice weekly during periods of risk being associated with a higher sensitivity (Arendrup 2009; Arendrup, Bille et al. 2012). Thus, the frequency of diagnostic testing may have an enormous effect on reported rates among centres (Kontoyiannis, Marr et al. 2010) but are, with the occasional exception (Nicolle, Benet et al. 2011; Ananda-Rajah, Grigg, Downey et al. 2012), infrequently reported in epidemiological studies. Other factors that affect rates include supportive care strategies and variations in prophylactic, pre-emptive or treatment algorithms across sites, but collecting this information is not feasible in large multicentre studies (Marr 2010; Azie, Neofytos et al. 2012; Steinbach, Marr et al. 2012).

Given the high contribution of antifungal drugs to the cost of managing IFDs (Ananda-Rajah, Cheng et al. 2011), antifungal drug stewardship targetting adherence to process measures (such as the completeness and timeliness of diagnostic investigations or the use of TDM), are an alternative to outcome measures such as IFD incidence rates. These themes will be elaborated on in the following published paper (see Appendix 2).

- Ananda-Rajah, M.R., Slavin, M.A. & Thursky, K.T. (2012). The case for antifungal stewardship. *Curr Opin Infect Dis, 25*(1), 107–115. doi: 10.1097/QCO.0b013e32834e0680

Authorship

7.4.1 Introduction

Antimicrobial stewardship (AMS) has largely focused on the judicious use of antibiotics while antifungal agents have received less attention. However, it is likely that the practice of antifungal stewardship (AFS) has been commonplace at many institutions for years principally because of the high cost of antifungal drugs and the specialised patients to which they apply. Antifungal agents are usually on restricted formularies in hospitals requiring the input of experts such as infectious diseases (ID) physicians and pharmacists who are knowledgeable of local fungal epidemiology, susceptibility patterns and current clinical literature to guide prescribing. AMS has been defined as the ongoing effort by a health care institution to optimise antimicrobial use in order to improve patient outcomes, ensure cost-effective therapy and reduce adverse sequelae (MacDougall and Polk 2005).

Inappropriate antibiotic use is associated with collateral damage—namely, the emergence of bacterial resistance adding to the burden of HAI, patient morbidity, mortality and cost (Cosgrove and Carmeli 2003; Roberts, Hota et al. 2009). As a result there has been a call to arms in recent years promoting the institution and strengthening of hospital AMS programs (Dellit, Owens et al. 2007). However, while these programs broadly include antifungal agents, data on optimising rather than auditing their use in clinical settings is scarce (Apisarnthanarak, Yatrasert et al. 2010).

Similar to the diminishing pipeline of new antibiotic choices in the face of escalating global resistance, novel antifungal agents are few (Denning and

Hope 2010) and the range of fungal pathogens along with the population at risk continues to expand. However, while bacterial resistance has been the impetus behind the initiation and strengthening antibiotic stewardship programs in hospitals, fungal resistance is less of a problem being confined to certain contexts. Triazole resistance in *Aspergillus fumigatus* has been described in both azole naive (Bueid, Howard et al. 2010; Alanio, Sitterle et al. 2011; Denning, Park et al. 2011) and azole exposed patients (Howard, Cerar et al. 2009; Bueid, Howard et al. 2010; Denning, Park et al. 2011) mostly in patients with cavitatory disease (Howard, Cerar et al. 2009) but also in patients with allergic aspergillosis and cancer patients with IA (Denning, Park et al. 2011).

Alarmingly high rates have been reported in the Netherlands, with 6% to 12.8% of clinical isolates harbouring resistance, which has been associated with clinical failure of azole therapy (Howard, Cerar et al. 2009; van der Linden, Jansen et al. 2009; Verweij, Snelders et al. 2009; Thors, Bierings et al. 2010). Resistance appears be geographically restricted to some settings within Europe but not others (Alanio, Sitterle et al. 2011). Extensive use of azoles in agriculture is responsible (Verweij, Snelders et al. 2009) but the problem is likely under-recognised due to a paucity of field studies (Verweij, Camps et al. 2011). Among *Candida* species, the issue of resistance largely applies to fluconazole and to a lesser extent the echinocandins (Sun and Singh 2009). Longitudinal data from laboratory surveillance shows that fluconazole resistance among *C. albicans* and *C. parasilopsis* is uncommon, but *C. glabrata* resistance may exceed 15% (Pfaller, Diekema et al. 2010). Breakthrough candidiaemia on caspofungin therapy has been documented in

2.4% of patients and was typically associated with prolonged therapy when source control of sepsis was not achieved (Sun and Singh 2009).

7.4.2 Principles of Stewardship

Optimising the use of currently available antifungal agents is principally driven by their high cost and attendant toxicities. We will focus on haematology-oncology patients because they are high-users of antifungal agents (de With, Steib-Bauert et al. 2005) and have an established record of practice guidelines. However, the principles discussed are applicable to other high-users, including ICU and SOT recipients. We will highlight some of the shared tenets with antibiotic stewardship and features peculiar to antifungal agents while providing practical examples from our own experience in over 10 years of guideline development (Slavin 2008; Australian Commission on Safety and Quality in Healthcare 2011), implementation and computerised decision support systems (CDSS) (Thursky and Mahemoff 2007; Buising, Thursky et al. 2008), along with engagement with end-users and institutional stakeholders.

7.4.3 Health and Economic Burden of IFDs

Patients with AML are at high-risk for IFD particularly following remission-induction chemotherapy or treatment for refractory or relapsed disease (Pagano, Caira et al. 2010), with historical rates of IFD complicating high-dose cytarabine-based chemotherapy reaching 36% (Bow, Loewen et al. 1995). In recent clinical trials, IFD incidence rates in patients with AML/MDS were higher than in allo-HSCT recipients (Ullmann, Lipton et al. 2007; Wingard,

Carter et al. 2010; Marks, Pagliuca et al. 2011), a finding consistent with earlier (1999 to 2003) Italian registry data showing IFD incidences of 16.9% and 8.2% among AML and allo-HSCT patients respectively (Caira, Girmenia et al. 2008).

The low incidence of IFD (3.2%) recently reported by the TRANSNET consortium among HSCT recipients 12 months from transplantation is due to 60% of the denominator comprising autologous recipients who had the lowest incidence (1.2%) of IFDs overall (Kontoyiannis, Marr et al. 2010). In fact, among HLA-mismatched-related and unrelated allo-HSCT recipients, IFD incidence rates were 8.1% and 7.7% respectively with wide inter-institutional variation noted ranging from 3.1 to 20.6% among 6 sites with a high case-load (Kontoyiannis, Marr et al. 2010). Marked institutional variation in IFD incidence is likely due to differences in case-mix, treatment practices, infection control and possibly geoclimatic factors (Panackal, Li et al. 2010). Mould infections predominated with IA and zygomycoses accounting for 46% and 8% respectively followed by invasive candidiasis (28%) (Kontoyiannis, Marr et al. 2010).

Although improvements in the short-term survival of IA are encouraging, crude mortality remains considerable at 33% to 47% (Neofytos, Horn et al. 2009; Nucci, Nouer et al. 2010; Pagano, Caira et al. 2010; Perkhofer, Lass-Florl et al. 2010) and for patients surviving IFD the prospect of delays or modifications to curative chemotherapy may compromise long-term prognosis (Bow, Loewen et al. 1995; Even, Bastuji-Garin et al. 2010). For HSCT

recipients, invasive candidiasis is not a benign disease with a 12-month mortality similar to IA of 67% and 75% respectively (Kontoyiannis, Marr et al. 2010).

Studies using large administrative datasets have reported that antifungal agents contribute 7% to 15% of total treatment costs of patients with IFDs (Rentz, Halpern et al. 1998; Wilson, Reyes et al. 2002; Kim, Nicolau et al. 2010) but this may be an underestimate. A recent single centre study of haematology-oncology patients, using patient-level data and ABC methods (a highly regarded costing tool (Barnett 2009)) showed that pharmacy costs accounted for 64% of the difference in mean hospital cost per patient (Ananda-Rajah, Cheng et al. 2011). Antifungal agents accounted for 27% of the overall difference (p<0.001) with no significant differences in ward costs between infected and uninfected controls seen (27%, p=0.091) (Ananda-Rajah, Cheng et al. 2011). The proportion of pharmacy (60%) to ward (31%) costs persisted at 12 weeks follow-up, suggesting that the finding was robust (Ananda-Rajah, Cheng et al. 2011).

Pharmaco-economic analyses are best informed by estimates of attributable cost. However, disentangling the effect of underlying illness in complex patients with cancer is challenging. Cost determination methods for IFDs have included gross costs (Tong, Lau et al. 2009; Kim, Nicolau et al. 2010), expert opinion (Van Campenhout, Marbaix et al. 2008) and clinical trial data (Wenzel, Del Favero et al. 2005; Wingard, Herbrecht et al. 2007). However, studies reporting attributable cost are few (Wilson, Reyes et al. 2002; Morgan, Meltzer et al. 2005; Slobbe, Polinder et al. 2008; Menzin, Meyers et al. 2009; Ananda-

Rajah, Cheng et al. 2011), and those using patient-level data are even rarer (Slobbe, Polinder et al. 2008; Ananda-Rajah, Cheng et al. 2011).

Attributable mean IA-associated medical cost in patients with AML/MDS has been estimated to be €15,280 (Slobbe, Polinder et al. 2008) but given the skewed nature of health outcomes, reporting the mean may potentially overstate costs due to the effect of outlier patients. Median costs, in contrast, represent a conservative estimate that in one study resulted in an IFD-attributable hospital cost of AU\$30,957 (95% CI AU\$2368 to AU\$59,546; p=0.034), approximating at PPP US\$21,203 (95% CI US\$1622 to US\$40,784) and €15,788 (95% CI €1208 to €30,368) (Ananda-Rajah, Cheng et al. 2011). Costly antifungal treatment (C-AT, defined as liposomal amphotericin B, voriconazole, posaconazole, caspofungin expressed as DDDs per IFD hospitalisation) was described as an alternative resource metric, which may be more generalisable than cost alone, being independent of country and inflation. IFD was associated with an excess of 17 DDDs of C-AT (95% CI 15 to 19 DDDs; $p<0.001$) per case-patient (Ananda-Rajah, Cheng et al. 2011).

It is the high mortality and morbidity of IFDs coupled with diagnostic uncertainty where culture positive rates are 30% to 50% in patients with confirmed IA (Hope, Walsh et al. 2005) that drives the overuse of antifungal agents.

7.4.4   Essential Elements of an Antifungal Stewardship Program

These are well described for AMS (Dellit, Owens et al. 2007; Australian Commission on Safety and Quality in Healthcare 2011) but are applicable to AFS also.

7.4.4.1 Implementation of Antifungal Guidelines

Practice guidelines are the starting point on the roadmap of AFS. Ideally, guidelines should be available at the point of care, whether embedded in CDSS or hospital intranet and linked to access to expert prescribers such as ID physicians or clinical pharmacists. Integration into the decision making process and workflow of prescribers who are typically busy junior staff is likely to enhance their uptake. Clinical care pathways for the management of IFDs have recently been proposed as a means of integrating clinical guidelines with diagnostic protocols in a feasible way for multidisciplinary teams to deliver (Donnelly 2011).

7.4.4.2 Guidelines Adapted to the Local Context

The many national and international guidelines for the management of patients with IFDs (Writing Group of the British Committee on Standards in Haematology 2008; Slavin 2008; Walsh, Anaissie et al. 2008; Maschmeyer, Beinert et al. 2009; Pappas, Kauffman et al. 2009; Maertens, Marchetti et al. 2011) are designed to assist clinicians in providing appropriate evidence-based care. Although little is known about their effect on provider behaviour, it is

clear that adaptation to local circumstances with input from senior clinicians is likely to increase acceptance rates (Mol, Rutten et al. 2004). We accommodated deviations from national guidelines (Slavin 2008) with, for example, the use of intermittent liposomal amphotericin prophylaxis in patients intolerant of azole drugs (Ananda-Rajah 2011) thereby increasing the acceptance of guidelines by our haematologists, their sense of ownership of the document and satisfaction with process.

Few studies have evaluated the translation of guidelines into practice. An evaluation of 136 cases of IA from an Italian registry (2004 to 2007) found poor compliance with IDSA and ECIL recommendations for first-line therapy being 55 and 28% respectively (Pagano, Caira et al. 2010). Non-compliance with guidelines did not affect mortality but guideline concordance was associated with improved short-term clinical outcome. The authors concluded that guidelines are often inapplicable to daily practice perhaps because patients with multiple co-morbidities and organ dysfunction are excluded from the clinical trials that ultimately inform practice guidelines. A cautious interpretation of this study is warranted as this was a post-hoc evaluation, used guidelines that were either outdated (IDSA 2000) or just published (ECIL 2007), examined appropriateness, which is one of several components of prescribing quality and used a controversial endpoint—namely, attributable rather than overall mortality assessed at 120 days rather than 6 weeks, which may be regarded as a more accurate time point for IFD-related outcomes (Wingard, Ribaud et al. 2008).

Given that EAFT accounts for the majority of inpatient antifungal prescription ranging from 62% to 72% (Pagano, Caira et al. 2010; des Champs-Bro, Leroy-Cotteau et al. 2011) and recent recommendations advocating either voriconazole (Maertens, Marchetti et al. 2011) or posaconazole prophylaxis (Walsh, Anaissie et al. 2008; Maertens, Marchetti et al. 2011) in high-risk haematology patients, these are the areas that at a minimum should be addressed by institutional guidelines.

7.4.5 Pre-prescription Approval with Post-prescription Review and Feedback

Restrictive interventions such as formulary restriction and pre-prescription approval are more than 3 times more influential than persuasive interventions such as education, on prescribing behaviour (Davey, Brown et al. 2005). Our web-based approval system allows doctors to obtain approval for standard (e.g., guideline concordant) and non-standard or guideline discordant indications (Buising, Thursky et al. 2008). All approvals are reviewed by the ID service within 24 to 48 hours but dispensing is not withheld pending ID review because it is impractical in a busy clinical service and risks unintended patient harm such as delaying the initiation of potentially life-saving therapy. Post-prescription review and feedback is a core activity of AMS (Dellit, Owens et al. 2007; Australian Commission on Safety and Quality in Healthcare 2011), whereby deficiencies in prescribing practice are identified by the AFS team and prescribers educated. In our setting, both methods are employed in a multifaceted approach using high visibility of AFS teams on regular rounds to build trust and encourage discussion with prescribers.

7.4.6 Antifungal Therapy: Opportunities for Improvement

Drug de-escalation and limiting EAFT are particular areas that require active guidance from AFS teams.

7.4.6.1 Challenges of De-escalation

Therapeutic streamlining is recommended by the IDSA in the management of candidiasis and IA (Walsh, Anaissie et al. 2008; Pappas, Kauffman et al. 2009) but current guidelines underappreciate the challenges of de-escalation in the empiric context (Freifeld, Bow et al. 2011). Even when susceptibility, results are available to guide therapy clinicians are often reluctant to de-escalate therapy when a seriously ill patient is improving on broad-spectrum treatment. A recent study of patients with Candidaemia reported that <40% of echinocandin treated patients with fluconazole susceptible isolates were de-escalated to fluconazole and only 50% of patients with less severe disease or *Candida albicans* underwent de-escalation (Shah, Yau et al. 2011). The solution, therefore, lies in building clinical confidence around de-escalation but this is hampered by the suboptimal diagnosis of IFDs using current tests.

7.4.6.2 Restraining Empiric Antifungal Use Relies on Improved Diagnostics

A diagnostic driven strategy or pre-emptive approach incorporating NCBTs such as GM and *Aspergillus* PCR along with CT aims to curtail unnecessary antifungal drug use and has best been studied in neutropenic patients. Most

studies to date have shown a reduction in antifungal use (Maertens, Theunissen et al. 2005; Barnes, White et al. 2009; Cordonnier, Pautas et al. 2009; Morrissey, Chen et al. 2013). However, the practice has attracted an experimental grading in the recent ECIL-3 guidelines (Maertens, Marchetti et al. 2011) because non-inferiority of the pre-emptive approach in a subgroup of leukaemic patients at very high-risk of IFD (i.e., undergoing remission-induction chemotherapy) could not be demonstrated with certainty in one open-label randomised study, although no overall difference in mortality was seen between groups (Cordonnier, Pautas et al. 2009). Indeed, similar concerns were raised by Girmenia et al. (2010) who, after comparing an intensive diagnostic approach to standard care, instituted posaconazole prophylaxis for patients with AML due to their high incidence of IFD. A lack of a consensus definition, target population, utility in patients on mould-active prophylaxis and cost-effectiveness need to be resolved before the pre-emptive approach is widely accepted.

Harnessing the excellent negative predicative value of NCBTs may be the most appropriate means of using them by excluding IA with confidence (Maertens, Groll et al. 2011). A meta-analysis of mainly haematological patients concluded that the serum GM assay for probable/proven IA had a low PPV 31% (95% CI 26% to 53%) but a high NPV 98% (95% CI 97% to 99%) (Pfeiffer, Fine et al. 2006). Similarly, studies have used the NPV of PCR as a screening tool in allo-HSCT and high-risk haematology patients to demonstrate no excess in mortality among patients in whom EAFT was withheld (Barnes,

White et al. 2009; Hebart, Klingspor et al. 2009) and in one setting realised savings in antifungal drug expenditure (Barnes, White et al. 2009).

Advances in molecular tests (Chen and Kontoyiannis 2010; Bretagne 2011) may enhance AFS through rapid identification of antifungal resistance. Differentiation between *C. albicans*, *C. glabrata* and other yeast species using PNA FISH probes ≤3 hours after cultures become positive has allowed earlier de-escalation from echinocandin therapy thereby saving US$1800 per patient (Alexander, Ashley et al. 2006; Shepard, Addison et al. 2008). Similarly, rapid identification of azole resistance in culture-negative samples in patients with pulmonary aspergillosis using ultrasensitive real-time *Aspergillus* PCR has recently been reported (Denning and Hope 2010) but the clinical relevance of this finding needs assessment.

7.4.7 Measuring the Performance of an AFS Program: Quality and Quantity of Prescribing

Demonstrating the continued benefit of an AFS program to hospital administrators, drug committees and senior clinicians relies on the cyclical monitoring of process, outcome and structural measures (see Table 7.11) relevant to the prevention and management of IFDs. Initial goals should be modest and achievable in order to demonstrate success of the program in the short-term (i.e., 'quick wins'). For example, targeting a few high cost antifungal drugs that may have suboptimal use such as liposomal amphotericin, the echinocandins or intravenous voriconazole may be preferable to demonstrating a reduction in all antifungal drugs.

In addition to clinical audit, population-level surveys are a useful means of identifying areas requiring attention. Schelenz et al. (2009) reported several deficiencies in clinical and laboratory standards among UK hospitals, including delayed initiation of antifungal therapy and central catheter-line line removal in patients with candidiaemia, low provision of on-site GM testing and suboptimal morphological fungal description. In a recent survey, lung transplant clinicians flagged the need for structural measures—namely, consensus guidelines on antifungal prophylaxis (Neoh, Snell et al. 2011).

7.4.8 Process and Outcome Measures

Measurement of antifungal consumption and the use of this data to benchmark institutions is problematic due to differences in case-mix (e.g., transplant centres, ICU workload) or institutional practices (e.g., local guidelines, transplant practices) (Meyer, Schwab et al. 2007). Unit- or ward-specific usage data should at a minimum include high-users such as haematology-oncology and ICU patients (de With, Steib-Bauert et al. 2005; Meyer, Schwab et al. 2007; Ramirez, Garcia-Rodriguez et al. 2011). Antifungal drug consumption in DDDs (WHO Collaborating Centre for Drug Statistics Methodology, http://www.whocc.no) has several limitations (Polk, Fox et al. 2007; Berrington 2010) and tends to overestimate use for fluconazole, itraconazole and amphotericin B (de With, Steib-Bauert et al. 2005). Usage data is commonly reported as a mean (de With, Steib-Bauert et al. 2005; Meyer, Schwab et al. 2007) but a distribution (median, IQR) should be considered because it is more resistant to outlier patients who skew all resource metrics,

including LOS, C-AT and hospital cost (Ananda-Rajah, Cheng et al. 2011). However, quantitative data, although relatively simple to obtain, is inherently limited by a lack of information on the appropriateness of prescribing (de With, Steib-Bauert et al. 2005; Pakyz, Gurgle et al. 2011).

The minimum standards of prescribing antimicrobials are well documented (Dellit, Owens et al. 2007; Australian Commission on Safety and Quality in Healthcare 2011). Cooke and Holmes (2007) proposed a care bundle, denoting adherence to its individual elements, as a means of gauging the health of an institution's AMS program, a proposition that has been recently tested (Toth, Chambers et al. 2010). From an AFS perspective, maintaining high prescribing standards could be regarded as a surrogate for patient safety and improved clinical outcomes as it ensures that the most effective antifungal agent is being given and that drug-related adverse events are being minimised.

A clear association between appropriateness and timeliness of antimicrobial administration and clinical outcomes in sepsis/ID has been demonstrated (Morrell, Fraser et al. 2005; Kumar, Ellis et al. 2009) and IFDs are no exception. For patients with invasive candidiasis the association between inadequate dosing or delayed initiation of antifungal therapy and increased LOS, health care costs, morbidity and mortality is well established (Morrell, Fraser et al. 2005; Garey, Rege et al. 2006; Zilberberg, Kollef et al. 2010). Inadequate dosing of fluconazole is an independent predictor of mortality (Labelle, Micek et al. 2008) and is common (Garey, Pai et al. 2007; Labelle,

Micek et al. 2008) seen in approximately half of critically ill patients and two-thirds of non-ICU patients in one single centre (Labelle, Micek et al. 2008).

Improved diagnosis of IFD is central to guiding antifungal therapy but dependent on the timeliness and completeness of the diagnostic work-up. Characteristic radiological features of IA such as the halo sign are associated with improved clinical response but being transient, present in 88% to 96% of patients at day 0 to 1 but only 22% to 37% by day 7 (Marom and Kontoyiannis 2011), underscores the importance of early CT scanning when IFD is suspected. Similarly, the diagnostic yield from bronchoscopy in HSCT recipients 100 days post-transplant declines after clinical presentation (75% at day1, 40% at day 5, 14% at day 10) (Shannon, Andersson et al. 2010) indicating that referral should be prompt. Indeed, a single centre specialising in the management of patients with multiple myeloma endeavours to confirm the diagnosis of IA using host, clinical and radiologic criteria within 24 to 48 hours (Nucci, Nouer et al. 2010). Another modality, BAL-based PCR diagnosis, in one study was associated with improved inpatient mortality compared to probable IA (80% versus 35.6%, p<0.003), because the latter represents a more advanced stage of disease (Hardak, Yigla et al. 2009).

Clinical audit as a core AFS activity should evaluate the effect of formulary changes on IFD incidence. At our institution consecutive use of fluconazole, itraconazole, voriconazole and posaconazole prophylaxis in 216 patients with AML/MDS undergoing high-dose cytarabine-based chemotherapy was associated an incremental reduction in breakthrough IFD incidence of 25%,

16%, 14% and 3% respectively (Ananda-Rajah, Grigg, Downey et al. 2012). In contrast, intermittent liposomal amphotericin prophylaxis appears to be less effective with a breakthrough IFD incidence of 6.9% prompting a review of our dosing regimen (Ananda-Rajah 2011).

7.4.9 Conclusion

Relative to infections caused by multi-resistant bacteria, IFDs have a lower institutional incidence but a high health and economic burden, which is likely to increase over time as the population of at-risk individuals expands (Juliusson, Antunovic et al. 2009). Institutional variation in incidence rates (Kontoyiannis, Marr et al. 2010), emerging but under-recognised antifungal resistance (Howard and Arendrup 2011) and evolving treatment practices underscores the importance of centres knowing their local epidemiology, which can only be achieved with surveillance. The cornerstone of AFS is the implementation of institutional guidelines that should largely accord with international or national standards augmented by provider audit and feedback, the quality use of medicine indicators and performance measures (Cooke and Holmes 2007; Australian Commission on Safety and Quality in Healthcare 2011). An orchestrated effort requiring a multidisciplinary team engaging and consensus building with end-users is vital for mission success. It is incumbent on AFS programs to demonstrate value to hospital administrators and while a reduction in health care costs is regarded as a secondary goal of AMS (Dellit, Owens et al. 2007), it is a common justification for stewardship programs (Drew, White et al. 2009), which should be exploited by AFS programs also,

given the high costs and high contribution of antifungal agents to the management and prevention of IFDs.

Table 7.11: Performance measures for an antifungal stewardship program

Process measures	Comments
Antifungal drug consumption	No information on appropriateness of therapy
	Measured in DDDs, prescribed daily doses or days of therapy adjusted for bed occupancy
	Large fluctuations in small populations (e.g., the ward level), due to effect of outlier patients
Minimum standards of prescribing	
Documentation of treatment rationale	The reason(s) for prescription should be recorded in the medical record
Dose optimisation using TDM	Resources should be available to ensure that the pharmacokinetic/pharmacodynamic endpoints proposed for voriconazole that optimise clinical efficacy and minimise toxicity are rapidly attained [75].
	The utility of TDM for posoconazole is unclear.
	TDM for itraconazole is well established
Therapeutic streamlining	
De-escalation of EAFT	Aided by the high negative predictive value of NCBTs such as galactomannan and *Aspergillus* PCR in the appropriate clinical context
	Best studied in neutropenic patients
De-escalation from broad to narrower spectrum drugs	Guided by susceptibility results and clinical response
Intravenous to oral switch therapy	Can decrease health care costs/adverse events without compromising outcomes
	Suitable for agents with high oral bioavailability (e.g., voriconazole)
Timeliness and completeness of diagnostic investigations when IFD suspected	Improved diagnosis to guide therapy—i.e., cease or modify antifungal therapy
Concordance of prescribing with institutional guidelines using an indication driven approach	Clinical audit can be a labour intensive process requiring chart review, on-line tools (e.g., computerised decision support system or point prevalence surveys)
	May be best performed targeting areas where there is reasonable quality evidence and/or institutional guidelines (e.g., antifungal prophylaxis in patients with AML undergoing intensive chemotherapy or use of EAFT)
	Includes timeliness, appropriateness and

	adequacy of initial antifungal therapy
Outcome measures	
IFD incidence in targeted groups	Targeted surveillance of patients at highest risk for IFDs—i.e., allogeneic HSCT recipients and patients with AML undergoing chemotherapy for initial remission; refractory or relapsed disease.
	Requires prospective surveillance
	Evolves in response to changing practices (e.g., formulary changes)
Antifungal drug expenditure	Patient quality and safety initiatives encompass AFS programs and should not be driven by cost
	Subject to fluctuations in purchase contracts, formulary changes, variations in ordering
	Targeting specific high cost drugs (e.g., liposomal amphotericin, IV voriconazole, echinocandins) is an efficient means of demonstrating value of an AFS program
Structural measures	At a minimum includes an antifungal drug policy or locally adapted practice guidelines

Chapter 8: Screening for IMDs Using Natural Language Processing of CT Reports: Towards Continuous Prospective Surveillance

This section is based on a manuscript that is under review.

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Authorship

Study conception and design: MA-R, MS, KT, LC; Data collection: MA-R, KT; Data analysis and interpretation: all authors; Drafting of manuscript: MA-R; Critical revision of manuscript: all authors

8.1 Introduction

Given the poor clinical outcomes (Neofytos, Horn et al. 2009; Kontoyiannis, Marr et al. 2010; Pagano, Caira et al. 2010; Azie, Neofytos et al. 2012), high cost (Ananda-Rajah, Cheng et al. 2011; Menzin, Meyers et al. 2011) and evolving epidemiology of IFDs in haematology-oncology patients, continuous prospective surveillance should be the standard of care. IFDs have substantial health and economic consequences and surveillance is a necessary step towards defining their burden, evaluating preventative interventions such as antifungal prophylaxis (Vehreschild, Ruping et al. 2010; Ananda-Rajah, Grigg, Downey et al. 2012; Girmenia, Frustaci et al. 2012), recognising sporadic but catastrophic outbreaks (Kainer, Reagan et al. 2012), monitoring epidemiological trends in response to changing therapeutic advances (Nucci and Anaissie 2009; Winthrop and Chiller 2009; Santini 2012) and making intra- and inter-facility comparisons.

Professional societies advocate surveillance of IFDs (Writing Group of the British Committee on Standards in Haematology 2008; Tomblyn, Chiller et al. 2009; Yokoe, Casper et al. 2009), but it is not routinely performed in most jurisdictions, the exception being France where nosocomial IA is a notifiable disease (Fourneret-Vivier, Lebeau et al. 2006). Surveillance of IMDs is difficult outside clinical studies because it is a resource-intensive activity (Fourneret-Vivier, Lebeau et al. 2006), necessitating multiple data sources for case ascertainment by multidisciplinary teams (Fourneret-Vivier, Lebeau et al. 2006; Kontoyiannis, Marr et al. 2010; Nicolle, Benet et al. 2011) (due to the

absence of an easily identifiable electronic trigger), followed by application of standardised but complicated case definitions by experts (De Pauw, Walsh et al. 2008; Nucci, Nouer et al. 2010).

Unlike Candidaemia, microbiology for IMDs such as *Aspergillus* and hyaline moulds is positive in <50% of cases (Denning, Marinus et al. 1998) and patients are often poor candidates for invasive diagnostic procedures making laboratory-based surveillance subject to significant underreporting (de Pauw and Viscoli 2011; Ostrosky-Zeichner 2012). Coding data is unreliable (Nguyen and Reid 2005; Chang, Burwell et al. 2008) and neither timely nor informative enough to uncover an environmental point source to be of benefit to hospitals. The most comprehensive surveillance study of IFDs to date, performed by the TRANSNET consortium (Kontoyiannis, Marr et al. 2010; Pappas, Alexander et al. 2010) provided meaningful insights but also highlighted key challenges and barriers to active surveillance: high operational costs requiring considerable government and industry support; missed numerator cases (comprising <5% in total) (Kontoyiannis, Marr et al. 2010) and denominator patients subsequently identified from coding data (Chang, Burwell et al. 2008); reporting delay, with dissemination several years after its closure (2007) and questionable sustainability as evidenced by its finite lifespan.

We hypothesised that prospective surveillance as advocated in practice guidelines (Writing Group of the British Committee on Standards in Haematology 2008; Tomblyn, Chiller et al. 2009; Yokoe, Casper et al. 2009) could be facilitated by the use of technology to make it sustainable and cost-

effective. Indeed, in response to the current US multistate fungal outbreak public health systems have been urged to modernise through the adoption of best available technology (Bell and Khabbaz 2013). In hospitals, clinical narratives are a rich source of information but their use is limited by their free-text, unstructured form. NLP is a computational method of analysing human language and a high-throughput technology that has been applied to automate detection of several medical conditions (Elkin, Froehling et al. 2008; Hazlehurst, Naleway et al. 2009; Hota, Lin et al. 2009; Lin, Hota et al. 2010; Murff, FitzHenry et al. 2011; Elkin, Froehling et al. 2012) from structured (e.g., electronic health records, EHRs) (Hazlehurst, Naleway et al. 2009; Murff, FitzHenry et al. 2011; Elkin, Froehling et al. 2012) and unstructured documents (Hripcsak, Friedman et al. 1995; Haas, Mendonca et al. 2005; Hota, Lin et al. 2009) with an accuracy comparable to human interpretation (Hripcsak, Friedman et al. 1995; Elkins, Friedman et al. 2000; Murff, FitzHenry et al. 2011).

As many hospitals lack comprehensive EHRs (Jha, DesRoches et al. 2009) we selected a readily available and timely resource, which is a key diagnostic modality for IMDs (Arendrup, Bille et al. 2012)—namely, CT reports. We aimed to develop a NLP classifier using machine-learning techniques, as a means of enabling real-time biosurveillance of IMDs in patients with haematological malignancies.

8.2 Methods

8.2.1 Study Design and Setting

This was a retrospective case-control cohort study of patients from 3 tertiary adult university-affiliated teaching hospitals (Alfred Health, AH; Peter MacCallum Cancer Institute, PM; Royal Melbourne Hospital, RMH). AH and RMH operate state-wide haematological stem cell transplant services, which collectively perform approximately 100 allogeneic transplants/year. Ethics permission was granted from each study site.

8.2.2 Inclusion and Exclusion Criteria

IMD and uninfected control patients from 2003 to 2011 inclusive were identified from previously completed clinical mycology studies (Cooley, Spelman et al. 2007; Ananda-Rajah 2011; Ananda-Rajah, Cheng et al. 2011; Ananda-Rajah, Grigg, Downey et al. 2012; Morrissey, Chen et al. 2013), pharmacy antifungal dispensing records (AH), antimicrobial stewardship (PM), HSCT (RMH), infectious diseases (PM) databases and microbiology records (AH, RMH). Patients lacking CT scan reports were excluded. Because the focus of the study was detection of IMDs, patients with isolated Candidaemia were excluded as laboratory-based surveillance is suitable for this infection. Brain reports were collected but later excluded from analysis due to few case numbers, unless performed in combination with another site (e.g., chest and/or sinus), in order to concentrate efforts on detection of sino-pulmonary disease.

8.2.3   Clinical Data and Definitions

CT scan reports were manually downloaded from each hospital information system as text files and de-identified. CT scans of any site, performed during the clinical encounter, defined from admission to separation (i.e., discharge, death or transfer) or for those few outpatients, from performance of the diagnostic scan and for 12 weeks thereafter (in order to evaluate radiological response) were included. Clinical information was extracted from aforementioned study datasets and hospital records. Subjects were case and control patients with and without IMDs respectively. IMDs were classified according to consensus definitions (De Pauw, Walsh et al. 2008). Date of IMD diagnosis determined by expert adjudication, was defined as the first day of suspicious radiological abnormality for possible cases or for probable/proven cases, a positive microbiological or histopathological test as detailed in consensus definitions (De Pauw, Walsh et al. 2008).

8.2.4   Development of the Reference Standard

A randomly selected convenience subset of reports from case and control patients was annotated at sentence and scan-level by 3 infectious diseases physicians (MA-R, KT, MS). The primary reviewer (MA-R) annotated all reports with concurrent secondary review of case reports only, undertaken by 2 physicians (KT, MS). The secondary reviewers served to validate the primary reviewer's analysis through measures of agreement. Pre-specified annotation guidelines were refined with differences in opinion resolved by discussion at face-to-face meetings. An iterative process of annotation ensued with reports

from case-patients annotated twice or 3 times over while those from control patients (from the outset regarded as less challenging to interpret) annotated once by the primary reviewer (MA-R).

For annotation, each sentence within a report and each report was treated as an independent observation, meaning that for sentence-level annotation, sentences rather than specific words were coded according to the following contextual features: specificity for IMD (specific versus non-specific features—e.g., macronodules, halo versus infiltrates, ground-glass, consolidation); certainty (suggestive, equivocal or not supportive of IMD), directionality/change (negation, stable, resolution, progression); temporality (recent, past); alternative processes (e.g., pulmonary emboli, edema) and clinical alerts (i.e., urgent follow-up required). Scan-level annotation referred to classification of the entire report as being either supportive or not for IMD with equivocal scans subsequently merged with those supportive of IMD. Supportive reports had either specific or non-specific features of IMD including halo, nodule, cavity, focal mass, wedge shaped lesions, bony sinus erosions, infiltrate, consolidation, ground glass change or effusions. Negative reports had none of the above features while equivocal reports included uncertainty by the reporting radiologist.

Importantly, the reference standard was informed by the opinion of clinician experts rather than radiologists given that the guiding principle behind this biosurveillance system is to flag reports of concern to end-users irrespective of the final diagnostic outcome.

8.2.5 Development of the Classifier

Reports were classified in a binary fashion as being supportive or not supportive of IMD (i.e., IMD positive/negative). A multi-class classification approach at sentence-level was used; each sentence allocated one of a number of classes, with all sentence-level classifications subsequently informing the report level decision. Each sentence within a report and each report were processed as independent observations.

Two main types of features were used—namely, bag and structural— and respectively applied to both sentence and scan-level predictions in the former and only scan-level predictions in the latter.

8.2.5.1 Bag Features

First, the documents were segmented into sentences using the JulieLab automatic sentence segmentor (Tomanek, Wermter et al. 2007). Semantic information was obtained by applying the MetaMap parser, which maps phrases in text to medical concepts from the UMLS Metathesaurus from the National Library of Medicine (Aronson 2001).

For bag features, 3 subtypes were tested as groups of words ('bag-of-words'), phrases ('bag-of-phrases') and concepts ('bag-of-concepts') (Aronson 2001) using lexical and semantic information derived from the annotated reports. Bag-of–words is the base model with the other types constructed by adding

semantic features to the base model. The bag-of-words framework collates unordered sets of words, mapping dates and numbers to date and number features respectively. Text was tokenised using the Genia Tagger (Kang, van Mulligen et al. 2011). With regards to punctuation, the position of question marks at either the beginning, within or at the end of the sentence was determined. All dates and numbers were normalised into date and number features respectively. The bag-of-phrases framework uses phrases mapped to medical concepts by MetaMap (Aronson 2001). These were added to the bag-of-words feature set. The version of MetaMap employed leverages the Negex (Chapman, Bridewell et al. 2001) tool to determine negation of a concept (e.g., 'is not consistent with …') and automatic disambiguation of concepts using a specific module within MetaMap. The output of Negex determined whether the identified phrases are marked as positive or negative indicators.

The bag-of-concepts framework was also added the bag-of-words feature set. Phrases identified by MetaMap were linked to concepts from the Metathesaurus enabling generalisation by linking multiple phrases with shared meaning to the same concept (e.g., phrases with common meaning such as 'mycosis' or 'fungal infection' are linked to the same concept 'C0026946'). The negation tool (Negex) marked whether concepts were found in the positive or negative context.

8.2.5.2 Structural Features

In contrast to bag features that use text in the target documents, structural features rely on sentence-level labels assigned by sentence-level classification

and on the anatomic site(s) of the report (e.g., chest, sinus, abdomen etc.). Two types of structural features were integrated into a single vector. These were the scan type (e.g., chest) and its status as a current or previous scan (e.g., number of scans preceding the target chest scan); sentence-level predictions in current and/or previous scans thereby indicating the number of sentences labelled positive or negative in target and previous scans.

8.2.5.3 Sentence-level Classification

Sentences in reports were classified according to 3 labels: positive, negative and neutral for evidence of IMD. This task was modelled as 2 separate binary classification tasks involving discrimination between positive sentences versus others and between negative sentences versus others. Two tools were used for this task: keyword-matching classifiers, machine-learning algorithms and a hybrid of these approaches.

For the keyword-matching approach, a list of manually curated terms associated with IFD positive sentences were compiled from medical experts and published literature (Greene, Schlamm et al. 2007) and a positive label was assigned to sentences containing these terms. A rule-based approach was used to identify when a keyword of interest was negated or if followed by a question mark to denote a clinical query-in this circumstance the sentence was labelled neutral. All positive terms were mapped to UMLS concepts. In addition to manually curated terms, automated extraction of terms from annotated reports in the reference standard was performed leveraging the feature set used in the bag framework, with the most commonly featured terms (according to their

log-likelihood of appearance in the dataset) listed as follows: 'nodular', 'glass', 'opacity', 'ground'.

8.2.5.4 Scan-level Classification

A binary classification at scan-level (i.e., positive or suspicious versus negative) was performed using heuristic rules and machine-learning approaches. For the heuristic rules approach simple rules were applied over sentence-level classifiers using 2 heuristics: conservative denoting that if a sentence in a report is labelled positive then the report is also labelled positive and balanced denoting that if a report contains more positive than negative sentences then the entire report is labelled positive for IMD.

We adopted a supervised machine-learning approach experimenting with several machine-learning algorithms, including Support Vector Machines, Naïve Bayes, Random Forests, and Bayesian Nets, as implemented in the Weka 3.6.0 (Frank, Hall et al. 2004) and LibSVM 3.11 (2012) toolkits. Briefly, supervised machine-learning is a group of computational methods that use machine-learning algorithms to automatically construct a model from labelled/annotated training data, which is then used to predict classification in unseen/unlabelled examples (Cohen and Hunter 2008). Of the hundreds of algorithms, we selected a few that have previously been used in similar classification tasks. Among these, SVM performed best and was selected for the final classifier. Further details relating to classifier development and performance can be found in Appendix 7.

Physician annotated reports were divided into training (n=366) and held-out sets (n=83), the latter annotated at scan-level only. We used 10-fold cross-validation on the training set with the optimal classifier identified from experiments, tested against the held-out set, which served as an additional validation step. Cross-validation is a method that maximises limited gold standard data while minimising the risk of overfitting associated with training on the test set (Stone 1974). Briefly, gold standard data is randomly partitioned into n subsamples (in our case n=10) and n runs (i.e., experiments) are performed. A model is trained using data from n-1 partitions with the single subsample used to evaluate or test the model; the process is repeated n times, with a different combination of partitions used for training until all combinations have been tested, and each subsample has been used once as the testing data. The final performance score is the mean over all n runs (Stone 1974).

8.3   Statistical Analysis

The results of each manually annotated report was compared to the binary and probabilistic predictions of the classifier allowing calculation of sensitivity, specificity and ROC, the latter accounting for the trade-off between sensitivity and specificity.

Given the absence of contemporary surveillance data, PPV, NPV were based on hypothetical IFD prevalence rates of 5%, 10% and 15%. Inter-annotator agreement was assessed using Cohen's kappa coefficient, a chance corrected

index of agreement (Goldman 1992). All analyses used Stata 11.0 software (Stata Corp, College Station, Texas, USA).

8.4 Results

8.4.1 Patient Characteristics

A total of 147 patients were included in the annotated subset; 79 (54%) had IMDs and 68 (46%) were control patients (see Table 8.1). Neutropenia ($\leq$0.5X10^9 cells/L) was present in 82% and 75% of clinical encounters among case and control patients respectively and was prolonged (median 18 and 19 days respectively). A history of transplantation was present in 46% and 52% of case and control patients being allogeneic in 86% and 77% of patients respectively.

IMDs were probable/proven in 33/79 (42%) and possible infections in 46/79 (58%). Sinus and/or pulmonary disease occurred in 91% of IMD patients. IA comprised 20/33 (61%) of microbiologically confirmed cases with rare moulds, including *Scedosporium* and *Rhizopus* species identified in 10/33 (30%).

Table 8.1: Characteristics of Patients with and without IMDs

Characteristic	IMD group n (%)	Control group n (%)
No. of patients	79	68
No. of clinical encounters[1]	79 (51)	75 (49)
Male gender	48 (61)	35 (51)
Age, mean (range) years	53 (20–89)	51 (18–89)
Underlying disease		
AML	32 (41)	35 (51)
ALL	14 (18)	14 (19)
Lymphoma	15 (19)	12 (16)
Chronic leukaemia	7 (8.9)	1 (1.3)
MDS/transformed MDS	6 (7.6)	2 (2.7)
Multiple myeloma	3 (3.8)	3 (4)
Other	2 (2.5)	5 (6.7)
Neutropenia (≤ 0.5 cells/L) present	65 (82)	56 (75)
Median duration of neutropenia (IQR), days	18 (8–45)	19 (5–39)
HSCT	36 (46)	39 (52)
Allogeneic	31/36 (86)	30/39 (77)
Autologous	5/36 (14)	9/39 (23)
Characteristics of IMDs, n=79		NA
Probable/proven IMDs	33 (42)	
Possible IMDs	46 (58)	
Site of infection		
Lung	67 (85)	
Sino-pulmonary	3 (3.8)	
Sinus	2 (2.5)	
Hepatosplenic	2 (2.5)	
Disseminated	4 (5.1)	

Organism	
Aspergillus fumigatus	13
Non-fumigatus *Aspergillus* species (*A. niger, A. flavus*)	4
Fungal hyphae resembling *Aspergillus* species	3
Scedosporium species	4
Any positive PCR	2
Rhizopus species	4
Other moulds (*Acrophialophora fusispora, Paecilomyces lilacinus*)	2
Candida glabrata (co-infection with *S. prolificans* fungaemia)	1

Abbreviations: ALL (acute lymphoblastic leukaemia); MDS (myelodysplastic syndrome); IQR (interquartile range; haematological stem cell transplant); [1]Clinical encounter defined from admission to separation (i.e., discharge, death or transfer) or for the few outpatients from performance of the diagnostic CT scan and for up to 12 weeks after.

8.4.2 Characteristics of the Dataset of Clinical Reports

Overall, 1880 reports were retrieved from 527 patients (51% with IMDs), of which 449 reports from 79 IMD patients underwent annotation (see Table 8.2). A total of 7083 sentences were annotated at sentence-level according to pre-defined contextual features. Mean report length per hospital was 314, 211 and 126 words reflecting inter-institutional variations in reporting styles. Hospital A supplied 50% of annotated reports. The annotated dataset predominantly comprised chest 375/449 (84%) and sinus scans (alone or in combination with other sites) 28/449 (8.5%).

Inter-annotator agreement between primary reviewer and the 2 secondary reviewers combined, was fair at sentence-level (K=0.64) and better at scan-level (0.83) given that K levels ≥0.75 represent excellent agreement (Goldman 1992).

Table 8.2: Characteristics of the Expert Annotated Reports in the Reference Standard and Unannotated Reports

Characteristic	Annotated reports n (%)	Unannotated reports n (%)
No. of reports	449	1431
Held-out reports[1]	83 (18)	NA
No. of patients total	147	380
No. of IMD patients	79	191
No. reports from IMD patients	294 (65)	905 (63)
No. reports from control patients	155 (35)	526
Chest (alone or in combination with sinus, abdo/pelvis, brain etc.)	375 (84)	865 (60)
Sinus (alone or brain-sinus, orbits, abdo/pelvis)	38 (8.5)	44
Other (abdo, abdo pelvis, liver, aorta, neck)	36 (8.0)	408
No. of reports according to study site		
Hospital A	226 (50)	713
Hospital B	131 (29)	422
Hospital C	92 (20)	296
No. of words per report according to study site		
Hospital A	211	229
Hospital B	126	128
Hospital C	314	348

[1]Held out reports were annotated at scan-level only as being supportive, unequivocal or negative for IMD.

8.4.3   Performance of the Classifier

Classifier performance among training and held-out sets was as follows (see Table 8.3): sensitivity (i.e., concordance between classifier and physician annotation for reports supportive of IMD) was 91% (95% CI 86% to 94%)/ 88% (95% CI 74% to 95%); specificity was 79% (95% CI 71% to 84%)/70% (95% CI 55% to 81%); false negative rates were 20/366 (9.2%) and 5/83 (12.5%) respectively. Using a sensitivity of 90% (95% CI 86% to 93%) and specificity of 77% (95% CI 70% to 82%) from the entire dataset of 449 reports, estimated PPVs and NPVs at IFD prevalence of 5%, 10%, 20% were 17%, 30%, 49% and 99%, 99%, 97% respectively. The area under the ROC curve for all reports was 0.87 (95% CI 0.84 to 0.91) and 0.90 (95% CI 0.86 to 0.93) for the inpatient subset (n=321) only (see Figure 8.1). For the inpatient subset performance of the classifier was: sensitivity 85% (95% CI 79% to 90%) and specificity 86% (95% CI 81% to 93%).

Table 8.3: Performance Characteristics of the Classifier

Characteristic	TP	FP	TN	FN	Sn, % (95% CI)	Sp,% (95% CI)
Training reports, n=366	197	32	117	20	91 (86 to 94)	79 (71 to 84)
1Held-out reports, n=83	35	13	30	5	88 (74 to 95)	70 (55 to 81)
All reports, n=449	232	45	147	25	90 (86 to 93)	77 (70 to 82)

[1]Held out reports were annotated at scan-level only; Abbreviations: TP (true positives); FP (false positives); TN (true negatives); FN (false negatives); Sn (sensitivity); Sp (specificity).
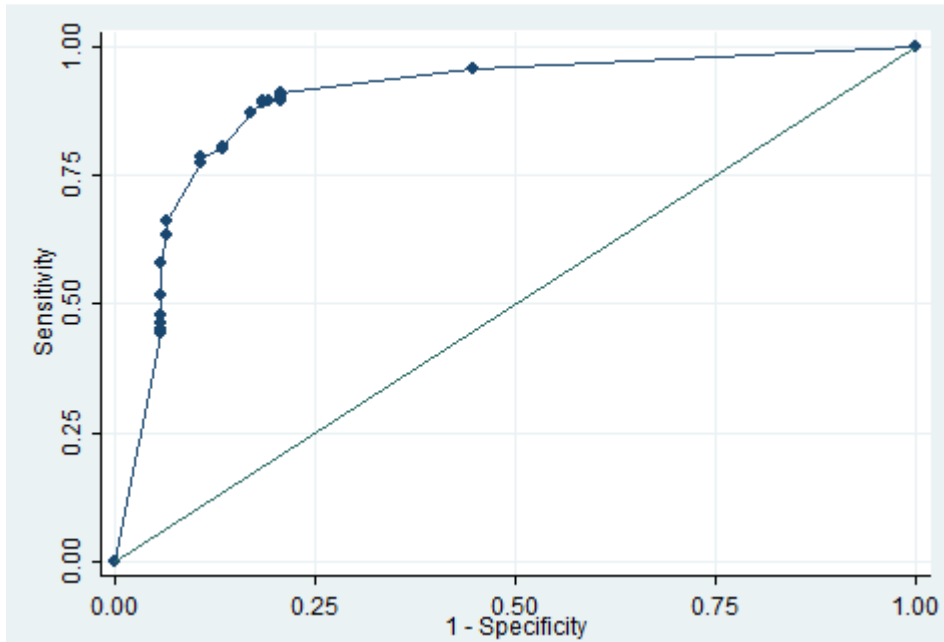
Figure 8.1: ROC curve for 321 inpatient reports comparing the probabilistic output of the classifier to expert opinion. Area under the ROC curve=0.90 (95% CI 0.86 to 0.93).

8.4.4 Error Analysis

Error analysis revealed that of the 25 missed cases (false negatives), 4 (4/449, 0.9%) were significant as shown in Figure 8.2. Reports from patients subsequently not diagnosed with IMD were discounted (n=10). The remaining 15 reports from IMD patients comprised 10 inpatient reports, including 6 progress reports whose antecedents were appropriately flagged. Among the 4 significant missed notifications, one was a sinus scan in combination with a chest scan, the latter was flagged appropriately.

Review of 45 false positive reports revealed several sources of systematic error described in Table 8.4. Unsystematic errors were the result of 3 reports inappropriately annotated negative; 2 with sinus mucosal thickening and one

describing ground-glass pulmonary changes with a fungal aetiology entertained by the radiologist.

Table 8.4: Major Systematic Errors Among False Notifications (False Positives) of CT Reports by the Classifier

Reason for misinterpretation	No. of reports	Characteristics
Inconsequential nodules	10	<1cm nodules, granulomas
Abdominal scans	9	Non-specific hepatic or splenic lesions
Progress scans	9	Change in lesions rather than diagnosis the focus, therefore reports annotated negative by experts
Non-specific pulmonary/ thoracic lesion	8	Atelectasis, scarring, mediastinal neoplastic mass
Misclassification	3	Pulmonary oedema, septic emboli, pulmonary lesions consistent with GVHD

```
                    ┌─────────────────────────┐
                    │  False negative reports, │
                    │  n=25 of 449 (5.6%)      │
                    └─────────────────────────┘
                       ↙                    ↘
        ┌──────────────────────┐   ┌──────────────────────┐
        │ Reports from IMD      │   │ Reports from control │
        │ patients, n=15        │   │ patients, n=10       │
        └──────────────────────┘   └──────────────────────┘
           ↙              ↘
┌──────────────────────┐   ┌──────────────────────┐
│ Reports from IMD      │   │ Reports from IMD      │
│ patients performed    │   │ patients performed    │
│ during inpatient      │   │ outside admission,    │
│ admission, n=10       │   │ n=5                   │
└──────────────────────┘   └──────────────────────┘
      ↙              ↘
```

Progress report with previous report(s) appropriately flagged positive by classifier, n=6

Site of CT scan	Comment	IMD classification[1], site, organism
Sinus, n=1	Sinus performed in combination with chest scan which was appropriately flagged positive by classifier	Possible, lung
Chest, n=2	IFD diagnosis on same date as scan, missed by classifier	-Possible, lung -Probable, lung, *A. fumigatus*
Chest, n=1	Subsequent scan performed closer to IFD diagnosis date appropriately flagged positive	Proven, lung *Acrophialophora fusispora*

Significant missed notifications, n=4 of 449 (0.89%); [1]Classification according to consensus guidelines (19); Abbreviations: CT, computed tomography

Figure 8.2: Error analysis of reports annotated supportive for IMD but missed by the classifier.

8.4.5 Timeliness of Detection in IMD Patients

Among 79 IMD patients, 72 of 76 (95%) reports first identified positive by annotator and the classifier were flagged either prior to (33%) or within 8 days (62%) of IMD diagnosis according to consensus criteria (see Figure 8.3). Late notifications flagged by the classifier >5 days after the IFD diagnosis date, were IMDs diagnosed at previous clinical encounters.
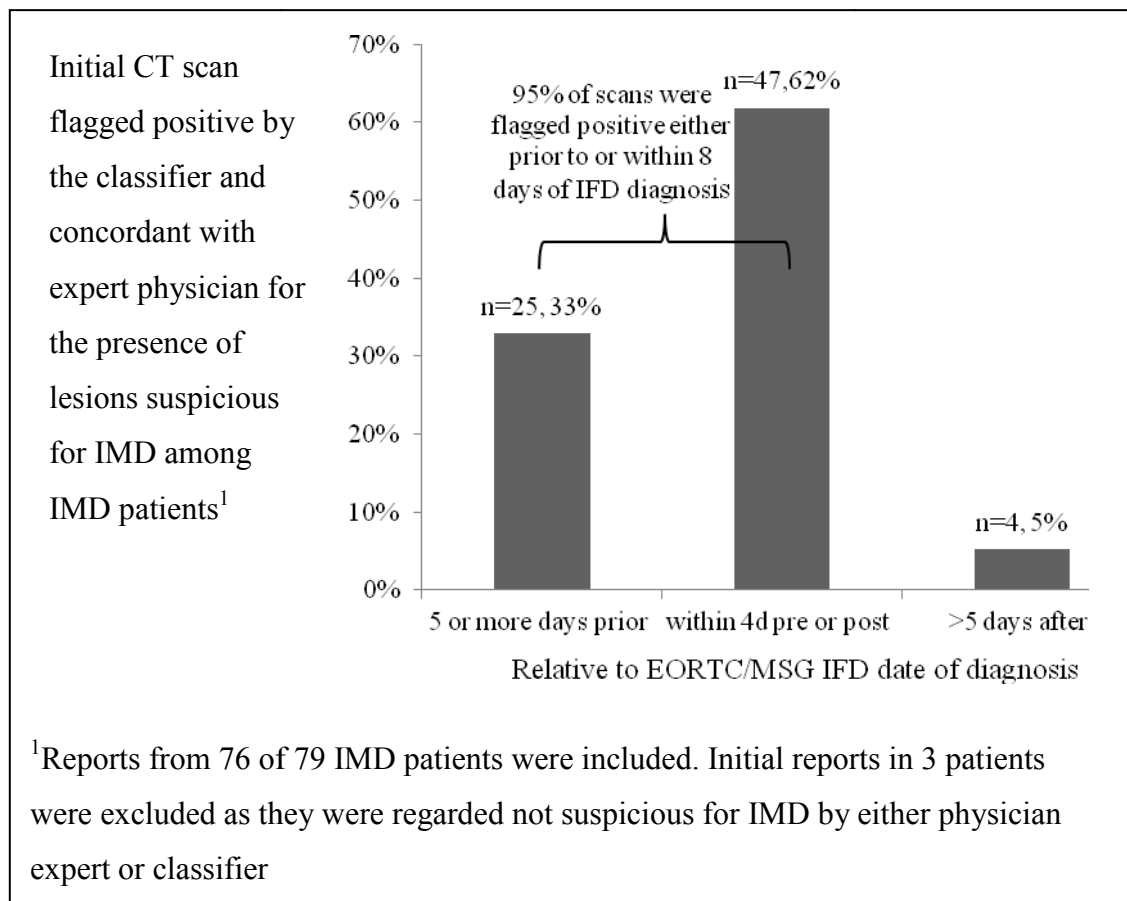

Initial CT scan flagged positive by the classifier and concordant with expert physician for the presence of lesions suspicious for IMD among IMD patients[1]

[1]Reports from 76 of 79 IMD patients were included. Initial reports in 3 patients were excluded as they were regarded not suspicious for IMD by either physician expert or classifier

Figure 8.3: Timeliness of IMD detection by classifier relative to date of diagnosis according to EORTC/MSG (2008) consensus criteria.

8.5 Discussion

Mould infections are not well suited to prospective detection using traditional methods of surveillance due to the absence of an easily identifiable electronic trigger but may be rendered amenable to real-time detection using NLP of free-text CT reports. The classifier flagged reports suggestive of IMD from a variety of anatomic sites but overwhelmingly the sino-pulmonary tract (92%, 413/449), the site most commonly involved by IA (Pagano, Caira et al. 2010; Lortholary, Gangneux et al. 2011), achieving a performance similar to physician interpretation with an overall sensitivity of 90% (95% CI 86% to 93%) and specificity of 77% (95% CI 70% to 82%). Performance was validated two-fold, by cross-validation of training data (n=366) in addition to held-out reports (n=83), importantly both methods using unseen data, and produced similar findings (see Table 8.3) lending robustness to the results. For inpatient reports representing higher acuity patients, area under the ROC, a global measure of diagnostic accuracy (Altman and Bland 1994), was excellent at 0.90 (95% CI 0.86 to 0.93). With regards to timeliness of detection, 95% (72 of 76) of reports initially suggestive of IMD in the clinical encounter among case-patients were flagged either prior to (33%) or within 8 days (62%) of IMD date of diagnosis using consensus definitions (De Pauw, Walsh et al. 2008) as the reference, illustrating the potential of NLP for real-time surveillance.

With regards to interpretation of CT reports, the opinion of expert physicians rather than radiologists informed development of the classifier as these are the end-users whose clinical acumen we sought to emulate. For similar syndromes

such as pneumonia, albeit in chest radiograph reports, clinicians have shown comparable performance to radiologists (Hripcsak, Friedman et al. 1995). CT scans present a greater challenge to interpret compounded by the varied, subtle and often transitory (e.g., halo) manifestations of IMDs, none of which are pathognomonic. The radiographic features promulgated in diagnostic guidelines (e.g., pulmonary nodules with or without halo, air-crescent, cavitation, sinusitis with or without bony involvement) (De Pauw, Walsh et al. 2008) we believe like others (Nucci, Nouer et al. 2010; Tsitsikas, Morin et al. 2012), are too restrictive, notwithstanding that IA may infrequently present as wedge-shaped infiltrates or lobar consolidation (Greene, Schlamm et al. 2007; De Pauw, Walsh et al. 2008).

Indeed, Nucci et al. (2010) recently challenged conventional radiological criteria by arguing that in a cohort of mostly myeloma patients, consolidation, pleural effusions or ground-glass infiltrates were also consistent with IA as confirmed by galactomannan kinetics, culture recovery and clinical response. Thus, consensus definitions (De Pauw, Walsh et al. 2008) while originally designed for clinical research to ensure recruitment of patients with likely IFD, may be suboptimal as surveillance tools on account of their poor test (i.e., radiologic) attributes.

For biosurveillance, sensitivity is favoured over specificity because missed cases especially for uncommon events like IMDs, are less tolerable than the resources spent following up false notifications (Elkin, Froehling et al. 2012). The 25/449 (5.6%) missed notifications occurred at the expense of a modest

number of false positive reports (45/449, 10%). Inpatient reports attracted greater attention than outpatient reports given the higher acuity of inpatients and remote but real risk of nosocomial acquisition accounting for the few missed notifications from case-patients regarded as clinically significant (0.9%). False notifications were expected as the classifier was tuned for sensitivity with inclusion of reports annotated equivocal in the positive training bucket. Accordingly the classifier, like the physician annotators, was not designed to be conservative, assigning a positive label if there was any possibility of IMD.

In the absence of a gold standard for IMD reporting we relied on peer review. However, sentence-level, in contrast to scan-level agreement, between the primary and secondary annotator pair was fair (K=0.64) rather than excellent despite the institution of measures mitigating unreliability, including pre-specified guidelines, multiple experts and repeated consultation to resolve differences (Goldman 1992). Our inter-annotator agreement is consistent with other cognitively challenging tasks such ascribing pneumonia (Hripcsak, Kuperman et al. 1999; Fiszman, Chapman et al. 2000; Haas, Mendonca et al. 2005) or CLABSI (Hota, Lin et al. 2009) because deciding if clinical narratives are compatible with these complex conditions is sometimes difficult.

In a multi-attribute utility model of biosurveillance, relevant data arriving with minimal delay is more highly valued over the cost of data acquisition (e.g., false notifications) (Doctor, Baseman et al. 2008). Our classifier satisfies these attributes but qualifying these strengths is its poor predictive value (17%, 30%,

49%) corresponding to hypothetical IFD prevalence rates of 5%, 10% and 15%. However, this is not unexpected as PPV is highly conditional on disease prevalence and for uncommon events like IMDs, will be low despite a high sensitivity, as we observed (McKnight, Wilcox et al. 2002). High NPVs (97%, 99%) meant that a negative result could exclude IMD with some confidence. False notifications could potentially undermine confidence in an alert system and may be minimised (i.e., improving specificity) by, including adjunctive sources of data (e.g., antifungal drug dispensing, microbiology, histopathology) in a predictive model or by raising pre-test probability by filtering reports (McKnight, Wilcox et al. 2002) based on clinical context (a clinical query of fever for example).

Further improvements in specificity may be achieved by omitting progress reports given their overrepresentation among false notifications because they were often annotated negative by experts (in many instances because the language features suggestive of IMD were not re-iterated in the follow-up scan report). Abdominal scans were flagged positive in order to capture the rare condition of hepatosplenic candidiasis but their removal would be expected to reduce false positive notifications. Non-specific pulmonary lesions such as atelectasis or scarring could be disregarded with the creation of hand-crafted rules. Pulmonary nodules of questionable significance are more challenging to address as size of lesions was not taken into account by the classifier. Training data did not exclusively comprise proven/probable IMDs (despite these representing a higher degree of certainty) for several reasons: they represent more advanced disease (Nucci, Nouer et al. 2010); possible IMDs constitute a sub-

stantial burden in clinical practice requiring similar health care resources (e.g., diagnostics, antifungal drugs) and their exclusion would underestimate true prevalence. Notably, all cases in our reference standard, including possible IMDs underwent expert adjudication. Although we used a sample of reports from the entire dataset, the narrow confidence intervals around overall performance measures suggests that additional reports would not have made an appreciable difference. Finally, a dataset enriched with positive cases was used for classifier development yielding results acceptable for subsequent human validation but verification in the field, where uncommon events prevail (Cohen, Hilario et al. 2006) is required.

Our work is a promising solution to IMD biosurveillance informed by the tenets of completeness, continuity, cost-effectiveness and accuracy. The classifier is not a diagnostic adjunct; but rather a screening tool designed to reduce the onerous work of fungal case ascertainment and data collection (Fourneret-Vivier, Lebeau et al. 2006; Kontoyiannis, Marr et al. 2010; Nicolle, Benet et al. 2011). It aims to support health care quality, safety and research initiatives by facilitating IMD surveillance (Chaudhry, Wang et al. 2006), which many centres have not invested in, leaving populations vulnerable to system failures (Bell and Khabbaz 2013). Indeed, the multistate US outbreak of fungal infections related to compounded steroid injections was detected following an alarm raised by an astute clinician but by then an unprecedented 14,000 patients had been exposed (Kainer, Reagan et al. 2012; Thompson, Kontoyiannis et al. 2013).

The classifier's strengths include transferability originating from its multi-site derivation; scalability, an inherent feature of machine-learning algorithms that unlike rule or knowledge-based systems do not require manual programming of specific language features (D'Avolio, Nguyen et al. 2009; Wang, Shah et al. 2012); consistency, by avoiding subjective interpretations of complicated case definitions and its potential for network-wide surveillance. As a multipurpose enabler the secondary uses of data from NLP include: clinical registry development (Evans, Scott et al. 2011); comparative effectiveness research (Conway and Clancy 2009) or clinical decision support (e.g., triggering of guidelines) (Fiszman, Chapman et al. 2000). At the minimum, by exploiting routinely available clinical data, this technology offers the potential to transform the business of surveillance of these important infections.

Chapter 9: Key Findings and Future Perspectives

9.1   Introduction

IFDs pose a significant economic burden to hospitals and are associated with increased hospitalisation costs and LOS (see Chapters 4 and 6). Robust costing estimates of IFDs inform cost-effectiveness assessments and business case proposals that support a raft of interventions such as IFD preventative strategies, the introduction of new antifungal agents on hospital or national formularies or the construction of better facilities for patients. Attributable hospitalisation cost is more informative than studies reporting gross cost estimates because it attempts to disentangle the effect of underlying disease and/or illness severity (see Chapters 4 and 6).

It is the high mortality and morbidity of IMDs coupled with their diagnostic uncertainty which drives the overuse of antifungal drugs as either empiric therapy or prophylaxis. The decision to initiate prophylaxis is in turn informed by local institutional epidemiology. Choices include either universal mould-active prophylaxis in high-risk patients (Ananda-Rajah, Grigg, Downey et al. 2012) or in centres with a low institutional prevalence, a diagnostically driven approach with or without NCBTs. Because the outcome of clinical trials that assess the efficacy of antifungal prophylaxis depends in part on the baseline incidence of IMD, differences in incidence between centres serve as a reminder that prophylaxis practices should not be based on trial data alone but should

take into account institutional prevalence. However, many centres are unaware of their baseline incidence because prospective surveillance of IMDs is not routinely performed.

Surveillance of IMDs is necessary for evaluating the effectiveness of specific measures such as mould-active prophylaxis (Ananda-Rajah 2011; Ananda-Rajah, Cheng et al. 2011) or general interventions such as antifungal stewardship programs (Ananda-Rajah, Slavin et al. 2012) (see Chapter 6). Guidelines advocate *routine* surveillance for IFDs but underappreciate the onerous task this poses for hospitals. The effort required to perform prospective surveillance particularly for the more diagnostically challenging mould infections is evident from jurisdictions where IA surveillance is a mandatory requirement as well as several epidemiological studies (see Chapter 3). These experiences consistently demonstrate that case ascertainment requires multidisciplinary teams using multiple data sources, including microbiology, radiology and clinical review with subsequent classification by experts using complicated case definitions which were chiefly intended for clinical trial recruitment rather than surveillance (see Chapter 3).

Choice of screening method for IMD surveillance is important for minimising the cost and effort associated with case ascertainment. However, the optimal screening method for IMDs is not well defined. Administrative and laboratory-based methods have several shortcomings with poor sensitivity being their major drawback (see Chapter 3). Laboratory based surveillance is unsuitable for IMDs because they lack an easily identifiable laboratory prompt.

Laboratory results when available are best regarded as an adjunctive source of data for IMD surveillance whose value lies in raising diagnostic certainty above clinical and radiological features (i.e., from possible to either probable or proven categories). Passive models of surveillance reliant on clinical review such as clinical registries suffer from inconsistencies in reporting across sites (see Chapter 3).

NLP of CT reports may be a useful screening method for identifying reports suggestive of IMD requiring subsequent human verification. CT has several attributes that lends itself to screening for IMDs. IA, the most common mould infection, overwhelmingly affects the lungs, with pulmonary involvement present in 90% to 100% of patients (see Table 2.1). CT is widely available, non-invasive with results available in hours rather than days. Although the radiological features of IMDs are non-specific, CT remains a key diagnostic modality the given difficulties in establishing a microbiological diagnosis (see Chapter 3).

9.2   Key Findings and Recommendations from the Thesis

- At a major Victorian transplant centre, IFDs complicating the admission of patients with haematological malignancies were associated with an adjusted median attributable hospitalisation cost of $30,957 (95% CI $2368 to $59,546, p=0.034); approximating at purchasing power parity US$21,203/€15,788 over the baseline patient. Median cost increased to

$80,291 among the 1 in 5 patients who required intensive care admission (Ananda-Rajah, Cheng et al. 2011) (see Chapter 6).

- This study used detailed patient-level data from a highly regarded costing tool known as activity-based costing rather than administrative, *per diem* costs or clinical assumptions.

- This study reported median costs (a conservative measure) to describe the typical value for most patients rather than the arithmetic mean, which while more fiscally relevant to hospitals, is highly sensitive to oulier patients thus limiting its generalisability while potentially overstating cost. At this centre, crude mean attributable hospitalisation cost was $79,129. Excess LOS was 8 days with inclusion of unmatched patients in the analysis (see Chapter 6).

- Pharmacy was the dominant cost driver, accounting for 64% of total mean excess costs (Ananda-Rajah, Cheng et al. 2011) in contrast to several US studies demonstrating that room charges account for the majority of the difference (see Chapter 4 and 6). High pharmacy costs may reflect differences in case-mix and preference for particular antifungal agents at this centre (Ananda-Rajah, Cheng et al. 2011).

- Costly antifungal drugs (defined as L-AmB, voriconazole, posaconazole or caspofungin) measured in DDDs is a novel resource metric alternative to cost that is independent of inflation or currency fluctuations (Ananda-Rajah, Cheng et al. 2011) (see Chapter 6).

- Mould pathogens are the predominant species in our setting (see Chapter 6), in line with worldwide reports (Pagano, Caira et al. 2006; Kontoyiannis, Marr et al. 2010).

- A declining incidence of IFDs following the adoption of mould-active antifungal prophylaxis in patients undergoing remission-induction cytotoxic chemotherapy for AML/MDS was observed in a single Victorian transplant centre (see Chapter 7) (Ananda-Rajah, Grigg, Downey et al. 2012).

- Incidence of breakthrough possible/probable/proven IFDs in 216 patients receiving antifungal prophylaxis was for: fluconazole 25%, itraconazole 16%, voriconazole 14% and posaconazole 3%. Our incidence rates likely underestimate the true burden of IFDs due to the absence of GM testing at this centre during the study period, 1998 to 2010. Our breakthrough rate of IFD on posaconazole is consistent with the original registration trial (Cornely, Maertens et al. 2007) (see Chapter 7).

- Our current choice of antifungal prophylaxis, posaconazole, is not suitable for all patients due to drug-drug interactions or concerns regarding GIT absorption (Ananda-Rajah, Grigg et al. 2011) (see Chapter 6). Intermittent L-AmB typically at a dosage of 100 mg thrice weekly is an alternative to azole prophylaxis. However, as we discovered, intermittent L-AmB prophylaxis is associated with a higher breakthrough rate of possible/probable/proven IFDs (7.2%) compared to posaconazole prophylaxis albeit among a more diverse group of patients. Notably, breakthrough IFDs were not seen in patients with

ALL although numbers of evaluable patients were small (see Chapter 7).

- The higher than expected breakthrough rate of IFDs among patients administered intermittent L-AmB prophylaxis prompted specific recommendations safeguarding the effectiveness of posaconazole for either targeted treatment or prophylaxis and guidelines for switching from posaconazole to alternative mould-active prophylactic agents (Ananda-Rajah, Grigg et al. 2012) (see Chapter 7).

- Performance of an antifungal stewardship program needs to include outcome measures beyond drug expenditure and should include track-ing local epidemiology in response to clinical practices such as changes to antifungal prophylaxis (Ananda-Rajah, Grigg, Downey et al. 2012) or environmental factors like agricultural fungicide use but this de-mands a commitment to ongoing surveillance (see Chapter 7).

- The essential elements of an antifungal stewardship program are con-sistent with the tenets of antimicrobial stewardship (Ananda-Rajah, Slavin et al. 2012). Briefly, practice guidelines based on best available evidence but adapted to the local context with input from local clinical leaders are the starting point. Guidelines should pay special attention to empiric therapy as it accounts for the majority of inpatient prescribing. Restrictive interventions such as formulary restriction and pre-prescription approval are valuable and superior to academic detailing or targeted educational activities. Unintended patient harm can be avoided through the dispensing of antifungal drugs pending timely expert re-view. Post-prescription review and feedback is a core activity which

provides the opportunity to identify deficiencies in prescribing practice, educate prescribers, build trust and promote the antifungal stewardship service (Ananda-Rajah, Slavin et al. 2012) (see Chapter 7).

- Demonstrating the continued benefit of an antifungal stewardship program to hospital administrators, drug committees and senior clinicians relies on the cyclical monitoring of process, outcome and structural measures relevant to the prevention and management of IFDs (see Chapter 6). Initial goals should be modest and achievable in order to demonstrate success of the program in the short term (i.e. 'quick wins') (Ananda-Rajah, Slavin et al. 2012) (see Chapter 7).

- Measurement of antifungal consumption at the unit or ward level should at a minimum include high users such as haematology–oncology and ICU patients. Quantitative data, although relatively simple to obtain, is inherently limited by a lack of information on the appropriateness of prescribing (Ananda-Rajah, Slavin et al. 2012) (see Chapter 7).

- This thesis demonstrates that a readily available and timely clinical resource may be exploited by NLP to facilitate continuous prospective IMD surveillance with the potential for multiple translational benefits beyond surveillance alone (see Chapter 8).

- Our classifier based on machine learning techniques was developed from CT reports derived from 3 tertiary adult referral centres that operate statewide HSCT services (see Chapter 8).

- CT reports including but not exclusively of the respiratory tract, from the clinical encounter and up to 12-weeks thereafter, from 79 case and

68 uninfected-control patients (from a total of 270 and 257 haematology-oncology patients respectively), were identified from research and hospital databases from 2003 to 2010. All case patients underwent expert adjudication for the presence of IMD according to published criteria (see Chapter 8).

- The classifier was trained and tested on a reference standard of 449 physician annotated reports from a total of 1880, using 10-fold cross validation, comparing binary and probabilistic predictions to the expert annotated reference standard (see Chapter 8).

- Overall, sensitivity was 90% (95%CI 86% to 93%), specificity was 77% (95%CI 70% to 82%) and the ROC area for the inpatient subset representative of high acuity patients was 0.90 (95%CI 0.86 to 0.93) (see Chapter 8).

- Of reports initially supportive of IMD in case-patients, 72 of 76 (95%) were flagged either prior to or within 8-days of EORTC/MSG date of IMD diagnosis illustrating the possibilities of this model for real-time surveillance. Of 25 (5.6%) missed notifications, only 4 (0.9%) reports were clinically significant (see Chapter 8).

- In summary, our classifier identified the majority of CT reports suggestive of IMD (sensitivity 90%) at the expense of a modest number of false negative reports also known as missed notifications (5.6%, n=25 reports), of which 0.9% (n=4 reports) were regarded as clinically significant (see Chapter 8).

- Further testing in field studies will be required to validate and refine classifier performance. It is only with a prospective multi-centre clinical trial that the true generalisability of the classifier will be determined.

9.3   Taking Surveillance to the Next Level

9.3.1   National E-Health Strategy

The Australian government has set in motion delivery of e-health for all Australians. The National E-Health Strategy outlines a vision of a more connected health care system underpinned by development of the EHR in order to improve the safety and quality of health care while making it more accessible, efficient, sustainable and affordable (NEHTA 2009). E-health is defined as 'the electronic collection, management, use, storage and sharing of health care information' (NEHTA 2009).

Much of the work in Australia has focused on primary health care where rates of EHR uptake exceed 90% (Jha, Doolan et al. 2008). However, for various reasons, including budgetary issues, Australian hospitals have not progressed to integrated systems (Jha, Doolan et al. 2008; Georgiou, Ampt et al. 2009) despite having the requisite building-blocks, including radiology, laboratory, patient census and pharmacy dispensing systems. Unlocking data from these clinical 'silos' requires novel technologies that can interpret and extract data from unstructured free-text clinical reports, which are subsequently stored in clinical data warehouses (STRIDE; Wisniewski, Kieszkowski et al. 2003) to be used for multiple quality, safety and research initiatives.

Adoption of health information technology is poor in the US (but higher than Australia), with <2% of hospitals having comprehensive EHR systems (Jha, DesRoches et al. 2009). However, this seems to be improving in the US with the recent doubling in the use of EHRs (Murdoch and Detsky 2013) largely driven by government mandates designed to encourage the improved and affordable delivery of health care (Iglehart 2009; Maro, Platt et al. 2009).

9.3.2 Comparative Effectiveness Research Requires an Investment in Data Infrastructure and Technology

Comparative effectiveness research (CER) also known as 'patient-centred outcomes research' addresses the need for health outcome data from real-world settings (Conway and Clancy 2009; Iglehart 2009). It is hoped that CER will address the need for practical information on the individual patient who may not be well represented by controlled clinical trials thereby exposing the factors that drive regional variations in clinical practice (Conway and Clancy 2009). CER activities have been grouped into 4 major categories, including: research; human and scientific capital such as training for new researchers; data infrastructure, including distributed data networks, registries or data linkage of administrative datasets and, finally but most importantly, the dissemination and translation into practice (Murdoch and Detsky 2013).

A major early investment in data infrastructure is planned with the Institute of Medicine concluding that 'the most important priority of all should be the building of a broad and supportive infrastructure to carry out a sustainable

national CER strategy' (Iglehart 2009). Thus, data infrastructure projects such as the linking of data sources, the development of distributed electronic data networks, patient registries, linked longitudinal administrative data and partnerships with the private sector (Conway and Clancy 2009) have received the majority of funding recommendations under the priority area of health care delivery (Iglehart 2009).

9.3.3 Successful Data Linkages Hospital-based but Australia-wide

National data networks with the potential to encompass millions of people are available in Australia (Hibbert, Gibbs et al. 2007) and planned for the US. A distributed data network currently in use within Australia under the auspices of BioGrid utilises a federated database integration platform. BioGrid established a dynamic data linkage platform in 2005 and has since facilitated research by connecting multiple databases between 34 major Australian hospitals and research institutions with coverage of >170,000 patients comprising 13.4 million records. This has included linkage of clinical and genomic data for audit and review, co-morbidity analysis, incidence and survival analysis. The BioGrid model is a 'live' system with data refreshed nightly allowing contemporaneous surveillance of a variety of conditions. The federated database integration model has been earmarked by the US Military Health (incorporating the Veteran Affairs system, a recognised e-health leader (Chaudhry, Wang et al. 2006) for the development of longitudinal health records (Weng, Levine et al. 2009) and by the CDC as a platform for public heath surveillance (Lober, Trigg et al. 2004). A similar platform could be used

in the future to collate contemporaneous data on the epidemiology of IMDs from multiple hospitals in Australia.

9.3.4   Developing an Expert System: Building on NLP

Here we provide an overview of the open (or interfaced) architecture proposed for an automated surveillance system incorporating information systems internal and external to hospital environments (see Figure 9.1). An expert system would comprise the following modules:

1. **Clinical interface** incorporating an information extraction tool.

2. **Clinical data repository** containing: (1) a medical logic module incorporating NLP of clinical narratives and algorithms, (2) a knowledge base containing mapping tables allowing normalisation of electronic inputs into coded format for storage and analysis and (3) a common database populated with longitudinal clinical data that will be periodically reviewed for accuracy and completeness.

3. **Data review module** storing missing data, error logs or unverified alerts for resolution before re-entering the common database.

4. **Standard terminology** containing expansions to existing ontologies (SNOMED-CT, UMLS, etc.).
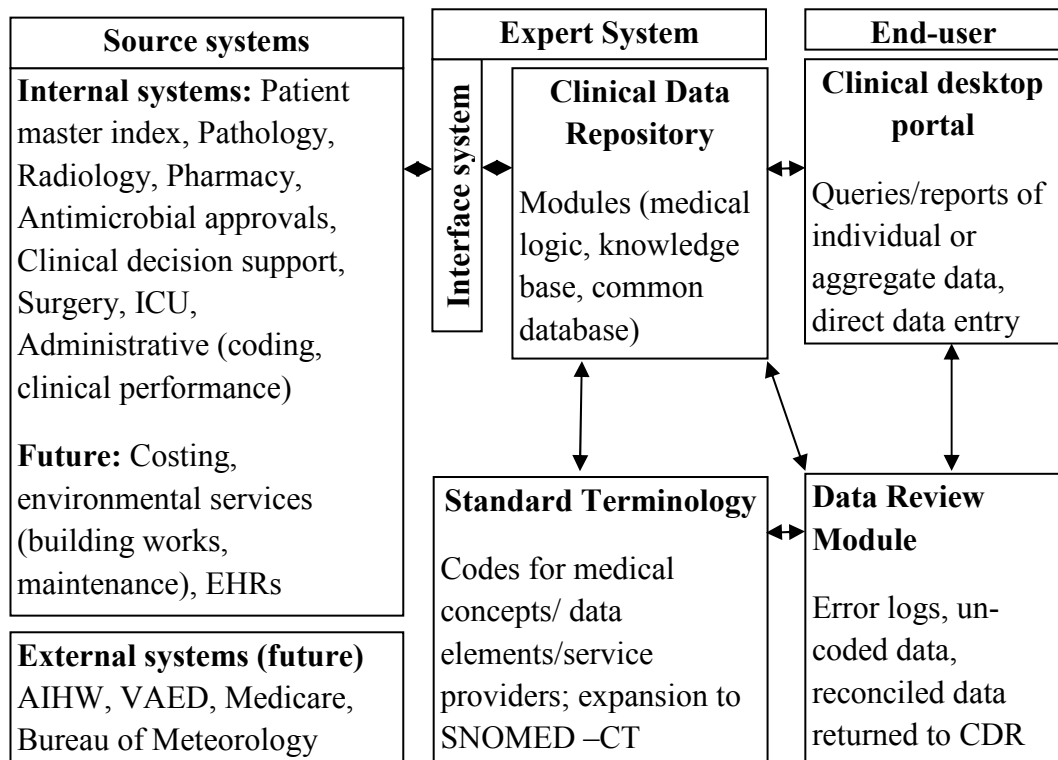
Source systems	Expert System	End-user
Internal systems: Patient master index, Pathology, Radiology, Pharmacy, Antimicrobial approvals, Clinical decision support, Surgery, ICU, Administrative (coding, clinical performance) **Future:** Costing, environmental services (building works, maintenance), EHRs	**Clinical Data Repository** Modules (medical logic, knowledge base, common database)	**Clinical desktop portal** Queries/reports of individual or aggregate data, direct data entry
External systems (future) AIHW, VAED, Medicare, Bureau of Meteorology	**Standard Terminology** Codes for medical concepts/ data elements/service providers; expansion to SNOMED –CT	**Data Review Module** Error logs, un-coded data, reconciled data returned to CDR

Interface system is shown as a vertical box between Source systems and the Expert System.

Figure 9.1 Architecture for an expert system incorporating internal and externally available information sources

Data elements extracted would include: demographic information (age, sex, LOS), co-morbidities expressed as ICD-10AM codes obtained from previous admissions, cytotoxic chemotherapy and antifungal drugs dispensed by pharmacy, antifungal approvals captured by a computerised decision support system, laboratory and radiology use (numbers, types of tests ordered and key results retrieved by NLP systems), neutropenia days, febrile events (using receipt of blood cultures as the surrogate) and pathogen data. Notifiable conditions such as IMDs would enter a notifiable-condition database.

Risk-adjusted incident rate calculation may be possible as parameters that are usually too burdensome for infection preventionists to collect manually may be extracted electronically. These include: neutropenia days ($< 0.5 \times 10^9$ cells/L);

type of chemotherapy and cycle (e.g., induction, consolidation) from pharmacy databases; patient subgroups (leukaemia, HSCT) from radiology reports or febrile events (using receipt of blood cultures as the surrogate).

Importantly, much of this work does not involve creating new technologies from inception but rather extending existing technology, using existing connections between institutions and local research repositories that are present in many Australian hospitals (Field, Kosmider et al. 2010).

9.4   Conclusion

Given the high cost, poor clinical outcomes and evolving epidemiology of IMDs in haematology-oncology patients, continuous prospective surveillance should be the standard of care. Surveillance of IMDs is a necessary step towards defining their burden, evaluating preventative interventions, recognising outbreaks, monitoring epidemiological trends in response to changing therapeutic advances and making intra- and inter-facility comparisons. Professional societies recognise the need for surveillance of mould infections especially as the immunocompromised population expands. However, at present there is no cost-effective means of performing it given the absence of a readily available and reliable laboratory prompt.

Traditional methods using manual case finding, laboratory-based reporting or coding data are labour intensive, costly, error prone, subject to underreporting and unsustainable in the long term. Addressing these challenges, we believe,

lies in the use of technology. Automated surveillance using NLP of a readily available and timely clinical resource—namely CT reports—is a more effective and efficient alternative to traditional methods with the advantage of near real-time detection. This work provides a promising glimpse into the future of surveillance for IMDs beyond well-recognised high-risk groups to poorly studied patient populations and network-wide surveillance.

The translational benefits of data generated from prospective surveillance are manifold. These include clinical registry development; clinical risk modelling with the future addition of genomic/proteomic data providing a means for individualising therapy based on clinical and genetic risk profile, clinical decision support through the triggering of guidelines or protocols and using contemporary estimates of incidence for clinical trial design and cost-effectiveness analyses. Improved identification of risk groups would lead to more targeted treatments, thereby reducing unnecessary antifungal drug use. Documents generated (e.g., mapping tables, expansion to SNOMED-CT), data infrastructure and tools such as NLP would support the electronic health record.

The model has the potential to expand as more data becomes available electronically (e.g., clinic notes, EHRs, personally controlled EHRs), or are rendered computable through technology (e.g., image analysis of digital scans) or made available via multi-institutional data linkages (e.g., the Victorian Admitted Episodes Dataset, state-wide cancer registries, Medicare, National Death Index, meteorological data). The creation of data warehouses, data

networks and information extraction technology is the toolkit required for CER and is achievable by exploiting the wealth of patient-level data available in hospitals.

Bibliography

Alangaden, G. J. (2011). Nosocomial fungal infections: Epidemiology, infection control, and prevention. *Infect Dis Clin North Am, 25*(1), 201–225. doi: S0891–5520(10)00090–5

Alanio, A., Sitterle, E., Liance, M., Farrugia, C., Foulet, F., Botterel, F., … Bretagne, S. (2011). Low prevalence of resistance to azoles in aspergillus fumigatus in a French cohort of patients treated for haematological malignancies. *J Antimicrob Chemother*. doi: dkq450

Albelda, S. M., Talbot, G. H., Gerson, S. L., Miller, W. T. & Cassileth, P. A. (1984). Role of fiberoptic bronchoscopy in the diagnosis of invasive pulmonary aspergillosis in patients with acute leukemia. *Am J Med, 76*(6), 1027–1034.

Alexander, B. D., Ashley, E. D., Reller, L. B. & Reed, S. D. (2006). Cost savings with implementation of PNA fish testing for identification of candida albicans in blood cultures. *Diagn Microbiol Infect Dis, 54*(4), 277–282. doi: S0732–8893(05)00262–2

Alffenaar, J. W., van Assen, S., van der Werf, T. S., Kosterink, J. G. & Uges, D. R. (2009). Omeprazole significantly reduces posaconazole serum trough level. *Clin Infect Dis, 48*(6), 839. doi: 10.1086/597110

Alsharif, M., Cameron, S. E., Young, J. A., Savik, K., Henriksen, J. C., Gulbahce, H. E. & Pambuccian, S. E. (2009). Time trends in fungal infections as a cause of death in hematopoietic stem cell transplant recipients: An autopsy study. *Am J Clin Pathol, 132*(5), 746–755. doi: 132/5/746

Altman, D. G. & Bland, J. M. (1994). Diagnostic tests 3: Receiver operating characteristic plots. *BMJ, 309*(6948), 188.

Ambrosioni, J., Bouchuiguir-Wafa, K. & Garbino, J. Emerging invasive zygomycosis in a tertiary care center: Epidemiology and associated risk factors. *Int J Infect Dis, 14*(suppl 3), e100–103. doi: S1201–9712(10)02289–7

Anaissie, E. J. (2007). Trial design for mold-active agents: Time to break the mold—aspergillosis in neutropenic adults. *Clin Infect Dis, 44*(10), 1298–1306. doi: CID50513

Anaissie, E. J., Kontoyiannis, D. P., O'Brien, S., Kantarjian, H., Robertson, L., Lerner, S. & Keating, M. J. (1998). Infections in patients with chronic lymphocytic leukemia treated with fludarabine. *Ann Intern Med, 129*(7), 559–566.

Ananda-Rajah, M. R., Cheng, A., Morrissey, C. O., Spelman, T., Dooley, M., Neville, A. M. & Slavin, M. (2011). Attributable hospital cost and anti-fungal treatment of invasive fungal diseases in high-risk hematology patients: An economic modeling approach. *Antimicrob Agents Chemother, 55*(5), 1953–1960. doi: AAC.01423–10

Ananda-Rajah, M. R., Grigg, A. & Slavin, M. A. (2012). Making sense of posaconazole therapeutic drug monitoring: A practical approach. *Curr Opin Infect Dis, 25*(6), 605–611. doi: 10.1097/QCO.0b013e328359a56e

Ananda-Rajah, M. R., Grigg, A., Downey, M. T., Bajel, A., Spelman, T., Cheng, A., … Slavin, M. A. (2012). Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome un-

dergoing cytotoxic chemotherapy over a 12-year period. *Haematologica, 97*(3), 459–463. doi: haematol.2011.051995

Ananda-Rajah, M. R., Martinez, D., Suominen, H., Thursky, K., Slavin, M. & Cavedon, L. (2012). Electronic surveillance of invasive fungal diseases in hematology-oncology patients using natural language processing of computed tomography reports: Towards real-time prospective surveillance. *52nd Interscience Conference on Antimicrobial Agents and Chemotherapy ASM, San Francisco.*

Ananda-Rajah, M. R., Slavin, M. A. & Thursky, K. T. (2012). The case for antifungal stewardship. *Curr Opin Infect Dis, 25*(1), 107–115. doi: 10.1097/QCO.0b013e32834e0680

Ananda-Rajah, M., Grigg, A.P., Thursky, K., Bajel, A. & Slavin, M. (2011). Prophylactic effectiveness and safety of intermittent liposomal amphotericin in high risk haematological patients. *51st Interscience Conference on Antimicrobial Agents and Chemotherapy ASM, Chicago.*

Andes, D., Pascual, A. & Marchetti, O. (2009). Antifungal therapeutic drug monitoring: Established and emerging indications. *Antimicrob Agents Chemother, 53*(1), 24–34. doi: AAC.00705–08

Apisarnthanarak, A., Yatrasert, A. & Mundy, L. M. (2010). Impact of education and an antifungal stewardship program for candidiasis at a Thai tertiary care center. *Infect Control Hosp Epidemiol, 31*(7), 722–727. doi: 10.1086/653616

Arendrup, M. C. (2009). Invasive fungal infections: Past achievements and challenges ahead. *Clin Microbiol Infect, 15*(7), 599–601. doi: CLM2914

Arendrup, M. C., Bille, J., Dannaoui, E., Ruhnke, M., Heussel, C. P. & Kibbler, C. (2012). Ecil-3 classical diagnostic procedures for the diagnosis of invasive fungal diseases in patients with leukaemia. *Bone Marrow Transplant, 47*(8), 1030–1045. doi: bmt2011246

Aronson, A. R. (2001). Effective mapping of biomedical text to the UMLS metathesaurus: The metamap program. *Proc AMIA Symp*, 17–21. doi: D010001275

Ascioglu, S., Rex, J. H., de Pauw, B., Bennett, J. E., Bille, J., Crokaert, F., … Walsh, T. J. (2002). Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: An international consensus. *Clin Infect Dis, 34*(1), 7–14. doi: CID001497

Asmundsdottir, L. R., Erlendsdottir, H., Haraldsson, G., Guo, H., Xu, J. & Gottfredsson, M. (2008). Molecular epidemiology of candidemia: Evidence of clusters of smoldering nosocomial infections. *Clin Infect Dis, 47*(2), e17–24. doi: 10.1086/589298

Auberger, J., Lass-Florl, C., Aigner, M., Clausen, J., Gastl, G. & Nachbaur, D. (2012). Invasive fungal breakthrough infections, fungal colonization and emergence of resistant strains in high-risk patients receiving antifungal prophylaxis with posaconazole: Real-life data from a single-centre institutional retrospective observational study. *J Antimicrob Chemother*. doi: dks189

Auberger, J., Lass-Florl, C., Ulmer, H., Nogler-Semenitz, E., Clausen, J., Gunsilius, E., … Nachbaur, D. (2008). Significant alterations in the epidemiology and treatment outcome of invasive fungal infections in pa-

tients with hematological malignancies. *Int J Hematol, 88*(5), 508–515. doi: 10.1007/s12185–008–0184–2

Australian Commission on Safety and Quality in Healthcare. (2011). *Antimicrobial stewardship in Australian hospitals*. Editors Duguid, M., Cruickshank, M.

Azie, N., Neofytos, D., Pfaller, M., Meier-Kriesche, H. U., Quan, S. P. & Horn, D. (2012). The path (prospective antifungal therapy) alliance(r) registry and invasive fungal infections: Update 2012. *Diagn Microbiol Infect Dis, 73*(4), 293–300. doi: S0732–8893(12)00239–8

Baddley, J. W. (2009). Pinpointing prognostic indicators of fungal infections in transplant patients. *Future Microbiol, 4*(1), 77–84. doi: 10.2217/17460913.4.1.77

Baddley, J. W. (2011). Clinical risk factors for invasive aspergillosis. *Medical Mycology, 49*(S1), S7-S12. doi: doi:10.3109/13693786.2010.505204

Baddley, J. W., Andes, D. R., Marr, K. A., Kauffman, C. A., Kontoyiannis, D. P., Ito, J. I., … Pappas, P. G. (2013). Antifungal therapy and length of hospitalization in transplant patients with invasive aspergillosis. *Med Mycol, 51*(2), 128–135. doi: 10.3109/13693786.2012.690108

Baddley, J. W., Andes, D. R., Marr, K. A., Kontoyiannis, D. P., Alexander, B. D., Kauffman, C. A., … Pappas, P. G. Factors associated with mortality in transplant patients with invasive aspergillosis. *Clin Infect Dis, 50*(12), 1559–1567. doi: 10.1086/652768

Bahl, V., Thompson, M. A., Kau, T. Y., Hu, H. M. & Campbell, D. A., Jr. (2008). Do the AHRQ patient safety indicators flag conditions that are

present at the time of hospital admission? *Med Care, 46*(5), 516–522.
doi: 10.1097/MLR.0b013e31815f537f

Bang, H. & Tsiatis, A. A. (2002). Median regression with censored cost data.
Biometrics, 58(3), 643–649.

Barnes, P. D. & Marr, K. A. (2007). Risks, diagnosis and outcomes of invasive
fungal infections in haematopoietic stem cell transplant recipients. *Br J
Haematol, 139*(4), 519–531. doi: BJH6812

Barnes, R. A. (2008). Early diagnosis of fungal infection in
immunocompromised patients. *J Antimicrob Chemother, 61*(suppl 1),
i3–6. doi: 61/suppl_1/i3

Barnes, R. A., White, P. L., Bygrave, C., Evans, N., Healy, B. & Kell, J.
(2009). Clinical impact of enhanced diagnosis of invasive fungal dis-
ease in high-risk haematology and stem cell transplant patients. *J Clin
Pathol, 62*(1), 64–69. doi: 62/1/64

Barnett, P. G. (2009). An improved set of standards for finding cost for cost-
effectiveness analysis. *Med Care, 47*(7 suppl 1), S82–88. doi:
10.1097/MLR.0b013e31819e1f3f

Baskaran, N. D., Gan, G. G. & Adeeba, K. (2008). Applying the multinational
association for supportive care in cancer risk scoring in predicting out-
come of febrile neutropenia patients in a cohort of patients. *Ann
Hematol, 87*(7), 563–569. doi: 10.1007/s00277–008–0487–7

Bell, B. P. & Khabbaz, R. F. (2013). Responding to the outbreak of invasive
fungal infections: The value of public health to Americans. *JAMA*, 1–2.
doi: 1567243

Bell, S., Benneyan, J., Best, A., Birnbaum, D., Borycki, E. M., Gallagher, T. H., … Sheps, S. (2011). Mandatory public reporting: Build it and who will come? *Stud Health Technol Inform, 164*, 346–352.

Berenguer, J., Buck, M., Witebsky, F., Stock, F., Pizzo, P. A. & Walsh, T. J. (1993). Lysis-centrifugation blood cultures in the detection of tissue-proven invasive candidiasis. Disseminated versus single-organ infection. *Diagn Microbiol Infect Dis, 17*(2), 103–109. doi: 0732–8893(93)90020–8

Bergeron, A., Porcher, R., Sulahian, A., de Bazelaire, C., Chagnon, K., Raffoux, E., … Ribaud, P. (2012). The strategy for the diagnosis of invasive pulmonary aspergillosis should depend on both the underlying condition and the leukocyte count of patients with hematologic malignancies. *Blood, 119*(8), 1831–1837; quiz 1956. doi: blood-2011–04–351601

Berrington, A. (2010). Antimicrobial prescribing in hospitals: Be careful what you measure. *J Antimicrob Chemother, 65*(1), 163–168. doi: dkp399

Bethge, W. A., Schmalzing, M., Stuhler, G., Schumacher, U., Krober, S. M., Horger, M., … Hebart, H. (2005). Mucormycoses in patients with hematologic malignancies: An emerging fungal infection. *Haematologica, 90*(suppl), ECR22.

Bitar, D., Van Cauteren, D., Lanternier, F., Dannaoui, E., Che, D., Dromer, F., … Lortholary, O. (2009). Increasing incidence of zygomycosis (mucormycosis), France, 1997–2006. *Emerg Infect Dis, 15*(9), 1395–1401. doi: 10.3201/eid1509.090334

Bochud, P. Y., Chien, J. W., Marr, K. A., Leisenring, W. M., Upton, A., Janer, M., … Boeckh, M. (2008). Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. *N Engl J Med, 359*(17), 1766–1777. doi: 359/17/1766

Bodey, G., Bueltmann, B., Duguid, W., Gibbs, D., Hanak, H., Hotchi, M., … et al. (1992). Fungal infections in cancer patients: An international autopsy survey. *Eur J Clin Microbiol Infect Dis, 11*(2), 99–109.

Boersma, W. G., Erjavec, Z., van der Werf, T. S., de Vries-Hosper, H. G., Gouw, A. S. & Manson, W. L. (2007). Bronchoscopic diagnosis of pulmonary infiltrates in granulocytopenic patients with hematologic malignancies: BAL versus PSB and PBAL. *Respir Med, 101*(2), 317–325. doi: S0954–6111(06)00232–0

Bolon, M. K., Hooper, D., Stevenson, K. B., Greenbaum, M., Olsen, M. A., Herwaldt, L., … Yokoe, D. S. (2009). Improved surveillance for surgical site infections after orthopedic implantation procedures: Extending applications for automated data. *Clin Infect Dis, 48*(9), 1223–1229. doi: 10.1086/597584

Borras, R., Rosello, P., Chilet, M., Bravo, D., de Lomas, J. G. & Navarro, D. (2010). Positive result of the aspergillus galactomannan antigen assay using bronchoalveolar lavage fluid from a patient with an invasive infection due to lichtheimia ramosa. *J Clin Microbiol, 48*(8), 3035–3036. doi: JCM.00902–10

Bow, E. J., Loewen, R., Cheang, M. S. & Schacter, B. (1995). Invasive fungal disease in adults undergoing remission-induction therapy for acute

myeloid leukemia: The pathogenetic role of the antileukemic regimen. *Clin Infect Dis, 21*(2), 361–369.

Bradley, C. A., Rolka, H., Walker, D. & Loonsk, J. (2005). Biosense: Implementation of a national early event detection and situational awareness system. *MMWR Morb Mortal Wkly Rep, 54*(suppl), 11–19. doi: su5401a4

Brenier-Pinchart, M. P., Lebeau, B., Quesada, J. L., Mallaret, M. R., Borel, J. L., Mollard, A., … Pelloux, H. (2009). Influence of internal and outdoor factors on filamentous fungal flora in hematology wards. *Am J Infect Control, 37*(8), 631–637. doi: S0196–6553(09)00595–1

Bretagne, S. (2011). Primary diagnostic approaches of invasive aspergillosis–molecular testing. *Med Mycol, 49*(suppl 1), S48–53. doi: 10.3109/13693786.2010.508186

Brown, S. H., Elkin, P. L., Rosenbloom, S. T., Fielstein, E. & Speroff, T. (2008). Equality for all: Extending automated quality measurement of free text clinical narratives. *AMIA Annu Symp Proc*, 71–75.

Brown, S. H., Speroff, T., Fielstein, E. M., Bauer, B. A., Wahner-Roedler, D. L., Greevy, R. & Elkin, P. L. (2006). Equality: Electronic quality assessment from narrative clinical reports. *Mayo Clin Proc, 81*(11), 1472–1481. doi: S0025–6196(11)61254–8

Bruno, C., Minniti, S., Vassanelli, A. & Pozzi-Mucelli, R. (2007). Comparison of CT features of aspergillus and bacterial pneumonia in severely neutropenic patients. *J Thorac Imaging, 22*(2), 160–165. doi: 10.1097/RTI.0b013e31805f6a42

Bryant, A. M., Slain, D., Cumpston, A. & Craig, M. (2011). A post-marketing evaluation of posaconazole plasma concentrations in neutropenic patients with haematological malignancy receiving posaconazole prophylaxis. *Int J Antimicrob Agents, 37*(3), 266–269. doi: S0924–8579(10)00537–6

Bueid, A., Howard, S. J., Moore, C. B., Richardson, M. D., Harrison, E., Bowyer, P. & Denning, D. W. (2010). Azole antifungal resistance in aspergillus fumigatus: 2008 and 2009. *J Antimicrob Chemother, 65*(10), 2116–2118. doi: dkq279

Buising, K. L., Thursky, K. A., Robertson, M. B., Black, J. F., Street, A. C., Richards, M. J. & Brown, G. V. (2008). Electronic antibiotic stewardship–reduced consumption of broad-spectrum antibiotics using a computerized antimicrobial approval system in a hospital setting. *J Antimicrob Chemother, 62*(3), 608–616.

Cagnoni, P. J., Walsh, T. J., Prendergast, M. M., Bodensteiner, D., Hiemenz, S., Greenberg, R. N., … Tong, K. B. (2000). Pharmacoeconomic analysis of liposomal amphotericin b versus conventional amphotericin b in the empirical treatment of persistently febrile neutropenic patients. *J Clin Oncol, 18*(12), 2476–2483.

Caillot, D., Couaillier, J. F., Bernard, A., Casasnovas, O., Denning, D. W., Mannone, L., … Guy, H. (2001). Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. *J Clin Oncol, 19*(1), 253–259.

Caira, M., Girmenia, C., Fadda, R. M., Mitra, M. E., Picardi, M., Van Lint, M. T., … Pagano, L. (2008). Invasive fungal infections in patients with acute myeloid leukemia and in those submitted to allogeneic hemopoietic stem cell transplant: Who is at highest risk? *Eur J Haematol, 81*(3), 242–243. doi: EJH1096

Caira, M., Mancinelli, M., Leone, G. & Pagano, L. (2011). Invasive aspergillosis in acute leukemias: Old and new risk factors and epidemiological trends. *Med Mycol*. doi: 10.3109/13693786.2010.509138

Caira, M., Trecarichi, E. M., Mancinelli, M., Leone, G. & Pagano, L. (2011). Uncommon mold infections in hematological patients: Epidemiology, diagnosis and treatment. *Expert Rev Anti Infect Ther, 9*(7), 881–892. doi: 10.1586/eri.11.66

Campoli, P., Al Abdallah, Q., Robitaille, R., Solis, N. V., Fielhaber, J. A., Kristof, A. S., … Sheppard, D. C. (2011). Concentration of antifungal agents within host cell membranes: A new paradigm governing the efficacy of prophylaxis. *Antimicrob Agents Chemother, 55*(12), 5732–5739. doi: AAC.00637–11

Carlisle, P. S., Gucalp, R. & Wiernik, P. H. (1993). Nosocomial infections in neutropenic cancer patients. *Infect Control Hosp Epidemiol, 14*(6), 320–324.

Carvalho, A., Cunha, C., Bistoni, F. & Romani, L. (2012). Immunotherapy of aspergillosis. *Clin Microbiol Infect, 18*(2), 120–125. doi: 10.1111/j.1469–0691.2011.03681.x

CDC. (2008). *External peer review of the division of healthcare quality promotion surveillance branch*. Centers for Disease Control and Prevention.

Accessed at

http://www.cdc.gov/nhsn/PDFs/SurveillanceBranchPeerReviewReprot_

Excerpts_MAY2008.pdf. on 25 October 2013.

Chang, C. C., Cheng, A. C., Devitt, B., Hughes, A. J., Campbell, P., Styles, K.,

… Athan, E. (2008). Successful control of an outbreak of invasive

aspergillosis in a regional haematology unit during hospital construc-

tion works. *J Hosp Infect, 69*(1), 33–38.

Chang, D. C., Burwell, L. A., Lyon, G. M., Pappas, P. G., Chiller, T. M.,

Wannemuehler, K. A., … Park, B. J. (2008). Comparison of the use of

administrative data and an active system for surveillance of invasive

aspergillosis. *Infect Control Hosp Epidemiol, 29*(1), 25–30. doi:

10.1086/524324

Chapman, W. W. (2010). Closing the gap between NLP research and clinical

practice. *Methods Inf Med, 49*(4), 317–319. doi: 10040317

Chapman, W. W., Bridewell, W., Hanbury, P., Cooper, G. F. & Buchanan, B.

G. (2001). Evaluation of negation phrases in narrative clinical reports.

Proc AMIA Symp, 105–109. doi: D010001471

Chapman, W. W., Nadkarni, P. M., Hirschman, L., D'Avolio, L. W., Savova,

G. K. & Uzuner, O. (2011). Overcoming barriers to NLP for clinical

text: The role of shared tasks and the need for additional creative solu-

tions. *J Am Med Inform Assoc, 18*(5), 540–543. doi: amiajnl-2011–

000465

Chaudhry, B., Wang, J., Wu, S., Maglione, M., Mojica, W., Roth, E., …

Shekelle, P. G. (2006). Systematic review: Impact of health information

technology on quality, efficiency, and costs of medical care. *Ann Intern Med, 144*(10), 742–752.

Chen, S. C. & Kontoyiannis, D. P. (2010). New molecular and surrogate biomarker-based tests in the diagnosis of bacterial and fungal infection in febrile neutropenic patients. *Curr Opin Infect Dis, 23*(6), 567–577. doi: 10.1097/QCO.0b013e32833ef7d1

Chen, S. C., Blyth, C. C., Sorrell, T. C. & Slavin, M. A. (2011). Pneumonia and lung infections due to emerging and unusual fungal pathogens. *Semin Respir Crit Care Med, 32*(6), 703–716. doi: 10.1055/s-0031–1295718

Chen, S., Slavin, M., Nguyen, Q., Marriott, D., Playford, E. G., Ellis, D. & Sorrell, T. (2006). Active surveillance for candidemia, Australia. *Emerg Infect Dis, 12*(10), 1508–1516.

Cheng, L. T., Zheng, J., Savova, G. K. & Erickson, B. J. (2009). Discerning tumor status from unstructured MRI reports-completeness of information in existing reports and utility of automated natural language processing. *J Digit Imaging*. doi: 10.1007/s10278–009–9215–7

Classen, D. C. (1994). Information management in infectious diseases: Survival of the fittest. *Clin Infect Dis, 19*(5), 902–909.

Clayton, P. D., Narus, S. P., Huff, S. M., Pryor, T. A., Haug, P. J., Larkin, T., … Gundersen, M. L. (2003). Building a comprehensive clinical information system from components. The approach at intermountain health care. *Methods Inf Med, 42*(1), 1–7. doi: 10.1267/METH03010001

CLSI. (2008). Reference method for broth dilution antifungal susceptibility testing of filamentous fungi: Approved standard.

Cohen, G., Hilario, M., Sax, H., Hugonnet, S. & Geissbuhler, A. (2006). Learning from imbalanced data in surveillance of nosocomial infection. *Artif Intell Med, 37*(1), 7–18. doi: S0933–3657(05)00085–0

Cohen, K. B. & Hunter, L. (2008). Getting started in text mining. *PLoS Comput Biol, 4*(1), e20. doi: 07-PLCB-MI-0330

Conte, J. E., Jr., DeVoe, C., Little, E. & Golden, J. A. (2010). Steady-state intrapulmonary pharmacokinetics and pharmacodynamics of posaconazole in lung transplant recipients. *Antimicrob Agents Chemother, 54*(9), 3609–3613. doi: AAC.01396–09

Conte, J. E., Jr., Golden, J. A., Krishna, G., McIver, M., Little, E. & Zurlinden, E. (2009). Intrapulmonary pharmacokinetics and pharmacodynamics of posaconazole at steady state in healthy subjects. *Antimicrob Agents Chemother, 53*(2), 703–707. doi: AAC.00663–08

Conway, P. H. & Clancy, C. (2009). Comparative-effectiveness research–implications of the federal coordinating council's report. *N Engl J Med, 361*(4), 328–330. doi: NEJMp0905631

Cooke, F. J. & Holmes, A. H. (2007). The missing care bundle: Antibiotic prescribing in hospitals. *Int J Antimicrob Agents, 30*(1), 25–29. doi: S0924–8579(07)00146-X

Cooley, L., Spelman, D., Thursky, K. & Slavin, M. (2007). Infection with scedosporium apiospermum and s. prolificans, Australia. *Emerg Infect Dis, 13*(8), 1170–1177.

Cordonnier, C., Pautas, C., Maury, S., Vekhoff, A., Farhat, H., Suarez, F., … Schwarzinger, M. (2009). Empirical versus preemptive antifungal ther-

apy for high-risk, febrile, neutropenic patients: A randomized, controlled trial. *Clin Infect Dis, 48*(8), 1042–1051. doi: 10.1086/597395

Cornely, O. A. & Ullmann, A. J. (2008). Numbers needed to treat with posaconazole prophylaxis to prevent invasive fungal infection and death. *Clin Infect Dis, 46*(10), 1626–1627; author reply 1627–1628. doi: 10.1086/587177

Cornely, O. A. & Ullmann, A. J. (2011). Lack of evidence for exposure-response relationship in the use of posaconazole as prophylaxis against invasive fungal infections. *Clin Pharmacol Ther, 89*(3), 351–352. doi: clpt2010261

Cornely, O. A., Helfgott, D., Langston, A., Heinz, W., Vehreschild, J. J., Vehreschild, M. J., … McCarthy, M. C. (2012). Pharmacokinetics of different dosing strategies of oral posaconazole in patients with compromised gastrointestinal function and who are at high risk for invasive fungal infection. *Antimicrob Agents Chemother, 56*(5), 2652–2658. doi: AAC.05937–11

Cornely, O. A., Maertens, J., Bresnik, M., Ebrahimi, R., Ullmann, A. J., Bouza, E., … Herbrecht, R. (2007). Liposomal amphotericin b as initial therapy for invasive mold infection: A randomized trial comparing a high-loading dose regimen with standard dosing (Ambiload trial). *Clin Infect Dis, 44*(10), 1289–1297. doi: CID41297

Cornely, O. A., Maertens, J., Winston, D. J., Perfect, J., Ullmann, A. J., Walsh, T. J., … Angulo-Gonzalez, D. (2007). Posaconazole vs. Fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med, 356*(4), 348–359. doi: 356/4/348

Cosgrove, S. E. & Carmeli, Y. (2003). The impact of antimicrobial resistance on health and economic outcomes. *Clin Infect Dis, 36*(11), 1433–1437. doi: CID30603

Courtney, R., Pai, S., Laughlin, M., Lim, J. & Batra, V. (2003). Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. *Antimicrob Agents Chemother, 47*(9), 2788–2795.

Courtney, R., Wexler, D., Radwanski, E., Lim, J. & Laughlin, M. (2004). Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. *Br J Clin Pharmacol, 57*(2), 218–222. doi: 1977

Cronin, S. & Chandrasekar, P. H. (2010). Safety of triazole antifungal drugs in patients with cancer. *J Antimicrob Chemother, 65*(3), 410–416. doi: dkp464

Cruickshank M, F. J. (2008). *Reducing harm to patients from healthcare associated infection: The role of surveillance.* Sydney, NSW: Australian Commission on Safety and Quality in Healthcare.

Cummings, J. R., Jamison, G. R., Boudreaux, J. W., Howles, M. J., Walsh, T. J. & Hayden, R. T. (2007). Cross-reactivity of non-aspergillus fungal species in the aspergillus galactomannan enzyme immunoassay. *Diagn Microbiol Infect Dis, 59*(1), 113–115. doi: S0732–8893(07)00190–3

Cunha, C. & Carvalho, A. Host genetics and invasive fungal diseases: Towards improved diagnosis and therapy? *Expert Rev Anti Infect Ther, 10*(3), 257–259. doi: 10.1586/eri.12.3

Cunha, C., Di Ianni, M., Bozza, S., Giovannini, G., Zagarella, S., Zelante, T., … Carvalho, A. (2010). Dectin-1 y238x polymorphism associates with susceptibility to invasive aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanisms of antifungal immunity. *Blood, 116*(24), 5394–5402. doi: blood-2010–04–279307

D'Avolio, L. W., Nguyen, T. M., Farwell, W. R., Chen, Y., Fitzmeyer, F., Harris, O. M. & Fiore, L. D. (2009). Evaluation of a generalizable approach to clinical information retrieval using the automated retrieval console (ARC). *J Am Med Inform Assoc, 17*(4), 375–382. doi: 17/4/375

Dalle, F., Charles, P. E., Blanc, K., Caillot, D., Chavanet, P., Dromer, F. & Bonnin, A. (2005). Cryptococcus neoformans galactoxylomannan contains an epitope(s) that is cross-reactive with aspergillus galactomannan. *J Clin Microbiol, 43*(6), 2929–2931. doi: 43/6/2929

Dasbach, E. J., Davies, G. M. & Teutsch, S. M. (2000). Burden of aspergillosis-related hospitalizations in the United States. *Clin Infect Dis, 31*(6), 1524–1528. doi: CID000220

Davey, P., Brown, E., Fenelon, L., Finch, R., Gould, I., Hartman, G., … Wiffen, P. (2005). Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*(4), CD003543. doi: 10.1002/14651858.CD003543.pub2

De Pauw, B. (2007). Prophylaxis and aspergillosis-has the principle been proven? *N Engl J Med, 356*, 409–411.

De Pauw, B. E. & Viscoli, C. (2011). Managing invasive fungal infections: Relying on clinical instincts or on a rational navigation system? *J Antimicrob Chemother, 66*(suppl 1), i55–58. doi: dkq442

De Pauw, B., Walsh, T. J., Donnelly, J. P., Stevens, D. A., Edwards, J. E., Calandra, T., … Bennett, J. E. (2008). Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus group. *Clin Infect Dis, 46*(12), 1813–1821. doi: 10.1086/588660

De With, K., Steib-Bauert, M., Knoth, H., Dorje, F., Strehl, E., Rothe, U., … Kern, W. V. (2005). Hospital use of systemic antifungal drugs. *BMC Clin Pharmacol, 5*(1), 1. doi: 1472–6904–5-1

Dellit, T. H., Owens, R. C., McGowan, J. E., Jr., Gerding, D. N., Weinstein, R. A., Burke, J. P., … Hooton, T. M. (2007). Infectious diseases society of America and the society for healthcare epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis, 44*(2), 159–177. doi: CID41270

Denning, D. W. & Hope, W. W. (2010). Therapy for fungal diseases: Opportunities and priorities. *Trends Microbiol*. doi: S0966–842X(10)00021–1

Denning, D. W. (1996). Therapeutic outcome in invasive aspergillosis. *Clin Infect Dis, 23*(3), 608–615.

Denning, D. W., Marinus, A., Cohen, J., Spence, D., Herbrecht, R., Pagano, L., … Sylvester, R. (1998). An EORTC multicentre prospective survey of invasive aspergillosis in haematological patients: Diagnosis and thera-

peutic outcome. EORTC invasive fungal infections cooperative group.
J Infect, 37(2), 173–180.

Denning, D. W., Park, S., Lass-Florl, C., Fraczek, M. G., Kirwan, M., Gore, R.,
… Perlin, D. S. (2011). High-frequency triazole resistance found in
nonculturable aspergillus fumigatus from lungs of patients with chronic
fungal disease. *Clin Infect Dis, 52*(9), 1123–1129. doi: cir179

Des Champs-Bro, B., Leroy-Cotteau, A., Mazingue, F., Pasquier, F., Francois,
N., Corm, S., … Sendid, B. (2011). Invasive fungal infections: Epide-
miology and analysis of antifungal prescriptions in onco-haematology.
J Clin Pharm Ther, 36(2), 152–160. doi: 10.1111/j.1365–
2710.2010.01166.x

Dettenkofer, M., Ebner, W., Bertz, H., Babikir, R., Finke, J., Frank, U., …
Daschner, F. D. (2003). Surveillance of nosocomial infections in adult
recipients of allogeneic and autologous bone marrow and peripheral
blood stem-cell transplantation. *Bone Marrow Transplant, 31*(9), 795–
801. doi: 10.1038/sj.bmt.1703920

Dettenkofer, M., Wenzler-Rottele, S., Babikir, R., Bertz, H., Ebner, W., Meyer,
E., … Daschner, F. D. (2005). Surveillance of nosocomial sepsis and
pneumonia in patients with a bone marrow or peripheral blood stem cell
transplant: A multicenter project. *Clin Infect Dis, 40*(7), 926–931. doi:
CID34394

Dignan, F. L., Evans, S. O., Ethell, M. E., Shaw, B. E., Davies, F. E., Dearden,
C. E., … Potter, M. N. (2009). An early CT-diagnosis-based treatment
strategy for invasive fungal infection in allogeneic transplant recipients

using caspofungin first line: An effective strategy with low mortality. *Bone Marrow Transplant, 44*(1), 51–56. doi: bmt2008427

Dimitopoulos, V., Bennett, A. & McIntosh, J. (2001). Coding productivity in Sydney public hospitals. *Health Information Management Journal, 30*(3), 1–7.

Dixon, S., McKeen, E., Tabberer, M. & Paisley, S. (2004). Economic evaluations of treatments for systemic fungal infections: A systematic review of the literature. *Pharmacoeconomics, 22*(7), 421–433. doi: 2272

Doctor, J. N., Baseman, J. G., Lober, W. B., Davies, J., Kobayashi, J., Karras, B. T. & Fuller, S. (2008). Time-tradeoff utilities for identifying and evaluating a minimum data set for time-critical biosurveillance. *Med Decis Making, 28*(3), 351–358. doi: 0272989X08317011

Dodds Ashley, E., Drew, R., Johnson, M., Danna, R., Dabrowski, D., Walker, V., … Perfect, J. (2012). Cost of invasive fungal infections in the era of new diagnostics and expanded treatment options. *Pharmacotherapy, 32*(10), 890–901. doi: 10.1002/j.1875–9114.2012.01124

Dolton, M. J., Ray, J. E., Marriott, D. & McLachlan, A. J. (2012). Posaconazole exposure-response relationship: Evaluating the utility of therapeutic drug monitoring. *Antimicrob Agents Chemother, 56*(6), 2806–2813. doi: AAC.05900–11

Donnelly, J. P. (2011). Introduction and aims. *Journal of Antimicrobial Chemotherapy, 66*(suppl 1), i3-i4. doi: 10.1093/jac/dkq436

Drew, R. H., White, R., MacDougall, C., Hermsen, E. D. & Owens, R. C., Jr. (2009). Insights from the society of infectious diseases pharmacists on antimicrobial stewardship guidelines from the Infectious Diseases Soci-

ety of America and the Society for Healthcare Epidemiology of America. *Pharmacotherapy, 29*(5), 593–607. doi: 10.1592/phco.29.5.593

Dubberke, E. R., Reske, K. A., Olsen, M. A., McDonald, L. C. & Fraser, V. J. (2008). Short- and long-term attributable costs of clostridium difficile-associated disease in nonsurgical inpatients. *Clin Infect Dis, 46*(4), 497–504. doi: 10.1086/526530

Eiden, C., Meniane, J. C., Peyriere, H., Eymard-Duvernay, S., Le Falher, G., Ceballos, P., … Hillaire-Buys, D. (2012). Therapeutic drug monitoring of posaconazole in hematology adults under posaconazole prophylaxis: Influence of food intake. *Eur J Clin Microbiol Infect Dis, 31*(2), 161–167. doi: 10.1007/s10096–011–1288–9

Eiden, C., Peyriere, H., Cociglio, M., Djezzar, S., Hansel, S., Blayac, J. P. & Hillaire-Buys, D. (2007). Adverse effects of voriconazole: Analysis of the French pharmacovigilance database. *Ann Pharmacother, 41*(5), 755–763. doi: aph.1H671

Elkin, P. L., Brown, S. H., Balas, A., Temesgen, Z., Wahner-Roedler, D., Froehling, D., … Poland, G. (2008). Biosurveillance evaluation of snomed CT'S terminology (best trial): Coverage of chief complaints. *Stud Health Technol Inform, 136*, 797–802.

Elkin, P. L., Brown, S. H., Husser, C. S., Bauer, B. A., Wahner-Roedler, D., Rosenbloom, S. T. & Speroff, T. (2006). Evaluation of the content coverage of snomed CT: Ability of snomed clinical terms to represent clinical problem lists. *Mayo Clin Proc, 81*(6), 741–748.

Elkin, P. L., Froehling, D. A., Wahner-Roedler, D. L., Brown, S. H. & Bailey, K. R. (2012). Comparison of natural language processing

biosurveillance methods for identifying influenza from encounter notes. *Ann Intern Med, 156*(1 Pt 1), 11–18. doi: 156/1_Part_1/11

Elkin, P. L., Froehling, D., Wahner-Roedler, D., Trusko, B., Welsh, G., Ma, H., … Brown, S. H. (2008). NLP-based identification of pneumonia cases from free-text radiological reports. *AMIA Annu Symp Proc*, 172–176.

Elkins, J. S., Friedman, C., Boden-Albala, B., Sacco, R. L. & Hripcsak, G. (2000). Coding neuroradiology reports for the northern Manhattan stroke study: A comparison of natural language processing and manual review. *Comput Biomed Res, 33*(1), 1–10. doi: 10.1006/cbmr.1999.1535

Ellis, D., Marriott, D., Hajjeh, R. A., Warnock, D., Meyer, W. & Barton, R. (2000). Epidemiology: Surveillance of fungal infections. *Med Mycol, 38*(suppl 1), 173–182.

Engelhart, S., Glasmacher, A., Exner, M. & Kramer, M. H. (2002). Surveillance for nosocomial infections and fever of unknown origin among adult hematology-oncology patients. *Infect Control Hosp Epidemiol, 23*(5), 244–248. doi: ICHE4180

Evans, R. S., Larsen, R. A., Burke, J. P., Gardner, R. M., Meier, F. A., Jacobson, J. A., … Hulse, R. K. (1986). Computer surveillance of hospital-acquired infections and antibiotic use. *JAMA, 256*(8), 1007–1011.

Evans, S. M., Scott, I. A., Johnson, N. P., Cameron, P. A. & McNeil, J. J. (2011). Development of clinical-quality registries in Australia: The way forward. *Med J Aust, 194*(7), 360–363. doi: eva11010_fm

Even, C., Bastuji-Garin, S., Hicheri, Y., Pautas, C., Botterel, F., Maury, S., …
Cordonnier, C. (2010). Impact of invasive fungal disease on the chemo-
therapy schedule and event-free survival in acute leukemia patients who
survived to fungal disease. A case-control study. *Haematologica, 96*(2),
337–341. doi: haematol.2010.030825

Ezzet, F., Wexler, D., Courtney, R., Krishna, G., Lim, J. & Laughlin, M.
(2005). Oral bioavailability of posaconazole in fasted healthy subjects:
Comparison between three regimens and basis for clinical dosage rec-
ommendations. *Clin Pharmacokinet, 44*(2), 211–220. doi: 4426

Farley, J. E., Srinivasan, A., Richards, A., Song, X., McEachen, J. & Perl, T.
M. (2005). Handheld computer surveillance: Shoe-leather epidemiology
in the 'palm' of your hand. *Am J Infect Control, 33*(8), 444–449. doi:
S0196–6553(05)00583–3

Farowski, F., Cornely, O. A., Vehreschild, J. J., Hartmann, P., Bauer, T.,
Steinbach, A., … Muller, C. (2010). Intracellular concentrations of
posaconazole in different compartments of peripheral blood.
Antimicrob Agents Chemother, 54(7), 2928–2931. doi: AAC.01407–09

Ferguson, P. E., Sorrell, T. C., Bradstock, K. F., Carr, P. & Gilroy, N. M.
(2009). Parainfluenza virus type 3 pneumonia in bone marrow trans-
plant recipients: Multiple small nodules in high-resolution lung com-
puted tomography scans provide a radiological clue to diagnosis. *Clin
Infect Dis*.

Field, K., Kosmider, S., Johns, J., Farrugia, H., Hastie, I., Croxford, M., …
Gibbs, P. (2010). Linking data from hospital and cancer registry data-

bases: Should this be standard practice? *Intern Med J, 40*(8), 566–573. doi: IMJ1984

Fiszman, M., Chapman, W. W., Aronsky, D., Evans, R. S. & Haug, P. J. (2000). Automatic detection of acute bacterial pneumonia from chest x-ray reports. *J Am Med Inform Assoc, 7*(6), 593–604.

Fourneret-Vivier, A., Lebeau, B., Mallaret, M. R., Brenier-Pinchart, M. P., Brion, J. P., Pinel, C., … Grillot, R. (2006). Hospital-wide prospective mandatory surveillance of invasive aspergillosis in a French teaching hospital (2000–2002). *J Hosp Infect, 62*(1), 22–28. doi: S0195–6701(05)00275–6

Frank, E., Hall, M., Trigg, L., Holmes, G. & Witten, I. H. (2004). Data mining in bioinformatics using weka. *Bioinformatics, 20*(15), 2479–2481. doi: 10.1093/bioinformatics/bth261

Freifeld, A. G., Bow, E. J., Sepkowitz, K. A., Boeckh, M. J., Ito, J. I., Mullen, C. A., … Infectious Diseases Society of, A. (2011). Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. *Clin Infect Dis, 52*(4), 427–431. doi: ciq147

Friedman, C., Knirsch, C., Shagina, L. & Hripcsak, G. (1999). Automating a severity score guideline for community-acquired pneumonia employing medical language processing of discharge summaries. *Proc AMIA Symp*, 256–260. doi: D005397

Fukuda, T., Boeckh, M., Carter, R. A., Sandmaier, B. M., Maris, M. B., Maloney, D. G., … Marr, K. A. (2003). Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell trans-

plants after nonmyeloablative conditioning. *Blood, 102*(3), 827–833. doi: 10.1182/blood-2003–02–0456

Furuno, J. P., Schweizer, M. L., McGregor, J. C. & Perencevich, E. N. (2008). Economics of infection control surveillance technology: Cost-effective or just cost? *Am J Infect Control, 36*(suppl 3), S12–17. doi: S0196–6553(07)00683–9

Garcia-Vidal, C., Upton, A., Kirby, K. A. & Marr, K. A. (2008). Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: Biological risk factors for infection according to time after transplantation. *Clin Infect Dis, 47*(8), 1041–1050. doi: 10.1086/591969

Garey, K. W., Pai, M. P., Suda, K. J., Turpin, R. S., Rege, M. D., Mingo, D. E. & Bearden, D. T. (2007). Inadequacy of fluconazole dosing in patients with candidemia based on infectious diseases society of America (IDSA) guidelines. *Pharmacoepidemiol Drug Saf, 16*(8), 919–927. doi: 10.1002/pds.1365

Garey, K. W., Rege, M., Pai, M. P., Mingo, D. E., Suda, K. J., Turpin, R. S. & Bearden, D. T. (2006). Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: A multi-institutional study. *Clin Infect Dis, 43*(1), 25–31. doi: CID39057

Georgiou, A., Ampt, A., Creswick, N., Westbrook, J. I. & Braithwaite, J. (2009). Computerized provider order entry–what are health professionals concerned about? A qualitative study in an Australian hospital. *Int J Med Inform, 78*(1), 60–70. doi: S1386–5056(08)00176–7

German, R. R., Lee, L. M., Horan, J. M., Milstein, R. L., Pertowski, C. A. & Waller, M. N. (2001). Updated guidelines for evaluating public health

surveillance systems: Recommendations from the guidelines working group. *MMWR Recomm Rep, 50*(RR-13), 1–35; quiz CE31–37.

Giacchino, M., Chiapello, N., Bezzio, S., Fagioli, F., Saracco, P., Alfarano, A., … Girmenia, C. (2006). Aspergillus galactomannan enzyme-linked immunosorbent assay cross-reactivity caused by invasive geotrichum capitatum. *J Clin Microbiol, 44*(9), 3432–3434. doi: 44/9/3432

Gil, L., Kozlowska-Skrzypczak, M., Mol, A., Poplawski, D., Styczynski, J. & Komarnicki, M. (2009). Increased risk for invasive aspergillosis in patients with lymphoproliferative diseases after autologous hematopoietic SCT. *Bone Marrow Transplant, 43*(2), 121–126. doi: bmt2008303

Girmenia, C., Frustaci, A. M., Gentile, G., Minotti, C., Cartoni, C., Capria, S., … Micozzi, A. (2012). Posaconazole prophylaxis during front-line chemotherapy of acute myeloid leukemia: A single-center, real-life experience. *Haematologica, 97*(4), 560–567. doi: haematol.2011.053058

Girmenia, C., Micozzi, A., Gentile, G., Santilli, S., Arleo, E., Cardarelli, L., … Martino, P. (2010). Clinically driven diagnostic antifungal approach in neutropenic patients: A prospective feasibility study. *J Clin Oncol*. doi: JCO.2009.21.8032

Goldman, R. L. (1992). The reliability of peer assessments of quality of care. *JAMA, 267*(7), 958–960.

Gooley, T. A., Chien, J. W., Pergam, S. A., Hingorani, S., Sorror, M. L., Boeckh, M., … McDonald, G. B. (2010). Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med, 363*(22), 2091–2101. doi: 10.1056/NEJMoa1004383

Graves, N., Birrell, F. & Whitby, M. (2005). Effect of pressure ulcers on length of hospital stay. *Infect Control Hosp Epidemiol, 26*(3), 293–297. doi: ICHE10070

Graves, N., Harbarth, S., Beyersmann, J., Barnett, A., Halton, K. & Cooper, B. (2010). Estimating the cost of health care-associated infections: Mind your p's and q's. *Clin Infect Dis, 50*(7), 1017–1021. doi: 10.1086/651110

Green, M. R. & Woolery, J. E. (2011). Optimising absorption of posaconazole. *Mycoses, 54*(6), e775–779. doi: 10.1111/j.1439–0507.2011.02020.x

Green, M. R. & Woolery, J. E. (2012). Posaconazole serum level on day 2 predicts steady state posaconazole serum level. *Ther Drug Monit, 34*(1), 118–119. doi: 10.1097/FTD.0b013e31823cef77

Greene, L. R., Cain, T. A., Khoury, R., Krystofiak, S. P., Patrick, M. & Streed, S. (2009). Apic position paper: The importance of surveillance technologies in the prevention of health care-associated infections. *Am J Infect Control, 37*, 510–513.

Greene, R. E., Schlamm, H. T., Oestmann, J. W., Stark, P., Durand, C., Lortholary, O., … Rubin, R. H. (2007). Imaging findings in acute invasive pulmonary aspergillosis: Clinical significance of the halo sign. *Clin Infect Dis, 44*(3), 373–379. doi: CID39892

Grota, P. G., Stone, P. W., Jordan, S., Pogorzelska, M. & Larson, E. (2010). Electronic surveillance systems in infection prevention: Organizational support, program characteristics, and user satisfaction. *Am J Infect Control, 38*(7), 509–514. doi: S0196–6553(10)00037–4

Gruson, D., Hilbert, G., Valentino, R., Vargas, F., Chene, G., Bebear, C., …
Cardinaud, J. P. (2000). Utility of fiberoptic bronchoscopy in
neutropenic patients admitted to the intensive care unit with pulmonary
infiltrates. *Crit Care Med, 28*(7), 2224–2230.

Gubbins, P. O., Krishna, G., Sansone-Parsons, A., Penzak, S. R., Dong, L.,
Martinho, M. & Anaissie, E. J. (2006). Pharmacokinetics and safety of
oral posaconazole in neutropenic stem cell transplant recipients.
Antimicrob Agents Chemother, 50(6), 1993–1999. doi: 50/6/1993

Guinea, J., Torres-Narbona, M., Gijon, P., Munoz, P., Pozo, F., Pelaez, T., …
Bouza, E. (2010). Pulmonary aspergillosis in patients with chronic ob-
structive pulmonary disease: Incidence, risk factors, and outcome. *Clin
Microbiol Infect, 16*(7), 870–877. doi: CLM3015

Gupta, A., Singh, M., Singh, H., Kumar, L., Sharma, A., Bakhshi, S., …
Thulkar, S. (2009). Infections in acute myeloid leukemia: An analysis
of 382 febrile episodes. *Med Oncol*. doi: 10.1007/s12032–009–9330–9

Haas, J. P., Mendonca, E. A., Ross, B., Friedman, C. & Larson, E. (2005). Use
of computerized surveillance to detect nosocomial pneumonia in neona-
tal intensive care unit patients. *Am J Infect Control, 33*(8), 439–443.
doi: S0196–6553(05)00643–7

Writing Group of the British Committee on Standards in Haematology (2008).
Guidelines on the management of invasive fungal infection during ther-
apy for haematological malignancy. [Practice Guideline, accessed at
www.bcshguidelines.com/ on 23 August 2013].

Hahn, J., Stifel, F., Reichle, A., Holler, E. & Andreesen, R. (2010). Clinical
experience with posaconazole prophylaxis–a retrospective analysis in a

haematological unit. *Mycoses, 54*(suppl 1), 12–16. doi: 10.1111/j.1439–0507.2010.01980.x

Hajjeh, R. A. & Warnock, D. W. (2001). Counterpoint: Invasive aspergillosis and the environment–rethinking our approach to prevention. *Clin Infect Dis, 33*(9), 1549–1552. doi: CID010194

Haley, R. W., Culver, D. H., White, J. W., Morgan, W. M., Emori, T. G., Munn, V. P. & Hooton, T. M. (1985). The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. *Am J Epidemiol, 121*(2), 182–205.

Halpin, H., Shortell, S. M., Milstein, A. & Vanneman, M. (2011). Hospital adoption of automated surveillance technology and the implementation of infection prevention and control programs. *Am J Infect Control, 39*(4), 270–276. doi: S0196–6553(11)00088–5

Hammond, S. P., Marty, F. M., Bryar, J. M., Deangelo, D. J. & Baden, L. R. (2010). Invasive fungal disease in patients treated for newly diagnosed acute leukemia. *Am J Hematol*. doi: 10.1002/ajh.21776

Hardak, E., Yigla, M., Avivi, I., Fruchter, O., Sprecher, H. & Oren, I. (2009). Impact of PCR-based diagnosis of invasive pulmonary aspergillosis on clinical outcome. *Bone Marrow Transplant, 44*(9), 595–599. doi: bmt200965

Hazlehurst, B., Frost, H. R., Sittig, D. F. & Stevens, V. J. (2005). Mediclass: A system for detecting and classifying encounter-based clinical events in any electronic medical record. *J Am Med Inform Assoc, 12*(5), 517–529. doi: M1771

Hazlehurst, B., Naleway, A. & Mullooly, J. (2009). Detecting possible vaccine adverse events in clinical notes of the electronic medical record. *Vaccine, 27*(14), 2077–2083. doi: S0264–410X(09)00168–6

Hebart, H., Klingspor, L., Klingebiel, T., Loeffler, J., Tollemar, J., Ljungman, P., … Einsele, H. (2009). A prospective randomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin b in patients after allo-sct. *Bone Marrow Transplant, 43*(7), 553–561. doi: bmt2008355

Heinz, W. J., Zirkel, J., Kuhn, A., Schirmer, D., Lenker, U., Keller, D. & Klinker, H. (2011). Relevance of timing for the determination of posaconazole plasma concentrations. *Antimicrob Agents Chemother, 55*, 3621–3623. doi: AAC.00062–11

Herbrecht, R., Bories, P., Moulin, J.C., Ledoux, M.P., Letscher-Bru, V. Risk stratification for invasive aspergillosis in immunocompromised patients. Ann N Y Acad Sci. 2012 Dec;1272(1):23-30. doi: 10.1111/j

Herbrecht, R., Caillot, D., Cordonnier, C., Auvrignon, A., Thiebaut, A., Brethon, B., Gangneux, J. P. (2012). Indications and outcomes of antifungal therapy in French patients with haematological conditions or recipients of haematopoietic stem cell transplantation. *J Antimicrob Chemother*. doi: dks266

Herbrecht, R., Denning, D. W., Patterson, T. F., Bennett, J. E., Greene, R. E., Oestmann, J. W., … de Pauw, B. (2002). Voriconazole versus amphotericin b for primary therapy of invasive aspergillosis. *N Engl J Med, 347*(6), 408–415. doi: 10.1056/NEJMoa020191

Hernandez-Castro, R., Arroyo-Escalante, S., Carrillo-Casas, E. M., Moncada-Barron, D., Alvarez-Verona, E., Hernandez-Delgado, L., … Lavalle-Villalobos, A. (2009). Outbreak of candida parapsilosis in a neonatal intensive care unit: A health care workers source. *Eur J Pediatr*. doi: 10.1007/s00431–009–1109–7

Hibbert, M., Gibbs, P., O'Brien, T., Colman, P., Merriel, R., Rafael, N. & Georgeff, M. (2007). The molecular medicine informatics model (MMIM). *Stud Health Technol Inform, 129*(Pt 2), 1230–1234.

Hidalgo, A., Parody, R., Martino, R., Sanchez, F., Franquet, T., Gimenez, A. & Blancas, C. (2009). Correlation between high-resolution computed tomography and galactomannan antigenemia in adult hematologic patients at risk for invasive aspergillosis. *Eur J Radiol, 71*(1), 55–60. doi: S0720–048X(08)00192–7

Hoenigl, M., Raggam, R. B., Salzer, H. J., Valentin, T., Valentin, A., Zollner-Schwetz, I., … Krause, R. (2012). Posaconazole plasma concentrations and invasive mould infections in patients with haematological malignancies. *Int J Antimicrob Agents, 39*(6), 510–513. doi: S0924–8579(12)00079–9

Hoenigl, M., Salzer, H. J., Raggam, R. B., Valentin, T., Rohn, A., Woelfler, A., … Krause, R. (2012). Impact of galactomannan testing on the prevalence of invasive aspergillosis in patients with hematological malignancies. *Med Mycol, 50*(3), 266–269. doi: 10.3109/13693786.2011.603102

Hoenigl, M., Valentin, T., Salzer, H. J., Zollner-Schwetz, I. & Krause, R. (2010). Underestimating the real burden of invasive fungal infections in

hematopoietic stem cell transplant recipients? *Clin Infect Dis, 51*(2), 253–254; author reply 254–255. doi: 10.1086/653684

Hoenigl, M., Zollner-Schwetz, I., Sill, H., Linkesch, W., Lass-Florl, C., Schnedl, W. J. & Krause, R. (2011). Epidemiology of invasive fungal infections and rationale for antifungal therapy in patients with haemato-logical malignancies. *Mycoses*. doi: MYC1881

Hope, W. W. & Denning, D. W. (2004). Invasive aspergillosis: Current and future challenges in diagnosis and therapy. *Clin Microbiol Infect, 10*(1), 2–4. doi: 809

Hope, W. W., Walsh, T. J. & Denning, D. W. (2005). Laboratory diagnosis of invasive aspergillosis. *Lancet Infect Dis, 5*(10), 609–622. doi: S1473–3099(05)70238–3

Horn, D. L., Fishman, J. A., Steinbach, W. J., Anaissie, E. J., Marr, K. A., Olyaei, A. J., … Neofytos, D. (2007). Presentation of the path alliance registry for prospective data collection and analysis of the epidemiolo-gy, therapy, and outcomes of invasive fungal infections. *Diagn Microbiol Infect Dis, 59*(4), 407–414. doi: S0732–8893(07)00261–1

Horvath, J. A. & Dummer, S. (1996). The use of respiratory-tract cultures in the diagnosis of invasive pulmonary aspergillosis. *Am J Med, 100*(2), 171–178. doi: S0002934397894557

Hota, B., Harting, B., Weinstein, R. A., Lyles, R. D., Bleasdale, S. C. & Trick, W. (2010). Electronic algorithmic prediction of central vascular cathe-ter use. *Infect Control Hosp Epidemiol, 31*(1), 4–11.

Hota, B., Lin, M., Doherty, J. A., Borlawsky, T., Woeltje, K., Stevenson, K., … Trick, W. (2009). Formulation of a model for automating infection

surveillance: Algorithmic detection of central-line associated blood-
stream infection. *J Am Med Inform Assoc, 17*(1), 42–48.

Howard, S. J. & Arendrup, M. C. (2011). Acquired antifungal drug resistance
in aspergillus fumigatus: Epidemiology and detection. *Med Mycol*. doi:
10.3109/13693786.2010.508469

Howard, S. J., Cerar, D., Anderson, M. J., Albarrag, A., Fisher, M. C.,
Pasqualotto, A. C., … Denning, D. W. (2009). Frequency and evolution
of azole resistance in aspergillus fumigatus associated with treatment
failure. *Emerg Infect Dis, 15*(7), 1068–1076.

Howard, S. J., Lestner, J. M., Sharp, A., Gregson, L., Goodwin, J., Slater, J., …
Hope, W. W. (2011). Pharmacokinetics and pharmacodynamics of
posaconazole for invasive pulmonary aspergillosis: Clinical implica-
tions for antifungal therapy. *J Infect Dis, 203*(9), 1324–1332. doi: jir023

Hripcsak, G., Friedman, C., Alderson, P. O., DuMouchel, W., Johnson, S. B. &
Clayton, P. D. (1995). Unlocking clinical data from narrative reports: A
study of natural language processing. *Ann Intern Med, 122*(9), 681–
688.

Hripcsak, G., Kuperman, G. J., Friedman, C. & Heitjan, D. F. (1999). A relia-
bility study for evaluating information extraction from radiology re-
ports. *J Am Med Inform Assoc, 6*(2), 143–150.

Hsu, J. L., Ruoss, S. J., Bower, N. D., Lin, M., Holodniy, M. & Stevens, D. A.
(2011). Diagnosing invasive fungal disease in critically ill patients. *Crit
Rev Microbiol, 37*(4), 277–312. doi: 10.3109/1040841X.2011.581223

Huang, S. S., Yokoe, D. S., Stelling, J., Placzek, H., Kulldorff, M., Kleinman,
K., … Platt, R. (2010). Automated detection of infectious disease out-

breaks in hospitals: A retrospective cohort study. *PLoS Med, 7*(2), e1000238. doi: 10.1371/journal.pmed.1000238

Humphreys, B. L., Lindberg, D. A., Schoolman, H. M. & Barnett, G. O. (1998). The unified medical language system: An informatics research collaboration. *J Am Med Inform Assoc, 5*(1), 1–11.

Iglehart, J. K. (2009). Prioritizing comparative-effectiveness research–IOM recommendations. *N Engl J Med, 361*(4), 325–328. doi: NEJMp0904133

Imai, T., Aramaki, E., Kajino, M., Miyo, K., Onogi, Y. & Ohe, K. (2007). Finding malignant findings from radiological reports using medical attributes and syntactic information. *Stud Health Technol Inform, 129*(Pt 1), 540–544.

Imhof, A., Balajee, S. A., Fredricks, D. N., Englund, J. A. & Marr, K. A. (2004). Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. *Clin Infect Dis, 39*(5), 743–746. doi: 10.1086/423274

Jang, S. H., Colangelo, P. M. & Gobburu, J. V. (2010). Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: Evaluating the need to adjust doses based on drug concentrations in plasma. *Clin Pharmacol Ther, 88*(1), 115–119. doi: clpt201064

Janssen, A., van der Bruggen, T., Haas, P. J., de Jong, P. A. & Minnema, M. C. (2011). Comparison of the occurrence of mold infection among patients receiving chemotherapy for acute leukemia versus patients undergoing stem cell transplantation. *Eur J Haematol, 87*(5), 419–425. doi: 10.1111/j.1600–0609.2011.01678.x

Jarvis, W. R. (2003). Benchmarking for prevention: The centers for disease control and prevention's national nosocomial infections surveillance (NNIS) system experience. *Infection, 31*(suppl 2), 44–48.

Jegers, M., Edbrooke, D. L., Hibbert, C. L., Chalfin, D. B. & Burchardi, H. (2002). Definitions and methods of cost assessment: An intensivist's guide. ESICM section on health research and outcome working group on cost effectiveness. *Intensive Care Med, 28*(6), 680–685. doi: 10.1007/s00134–002–1279–5

Jha, A. K., Bates, D. W., Jenter, C., Orav, E. J., Zheng, J., Cleary, P. & Simon, S. R. (2009). Electronic health records: Use, barriers and satisfaction among physicians who care for Black and Hispanic patients. *J Eval Clin Pract, 15*(1), 158–163. doi: JEP975

Jha, A. K., DesRoches, C. M., Campbell, E. G., Donelan, K., Rao, S. R., Ferris, T. G., … Blumenthal, D. (2009). Use of electronic health records in US hospitals. *N Engl J Med, 360*(16), 1628–1638. doi: NEJMsa0900592

Jha, A. K., Doolan, D., Grandt, D., Scott, T. & Bates, D. W. (2008). The use of health information technology in seven nations. *Int J Med Inform, 77*(12), 848–854. doi: S1386–5056(08)00088–9

Juliusson, G., Antunovic, P., Derolf, A., Lehmann, S., Mollgard, L., Stockelberg, D., … Hoglund, M. (2009). Age and acute myeloid leukemia: Real world data on decision to treat and outcomes from the Swedish acute leukemia registry. *Blood, 113*(18), 4179–4187. doi: blood-2008–07–172007

Kainer, M. A., Reagan, D. R., Nguyen, D. B., Wiese, A. D., Wise, M. E., Ward, J., … Jones, T. F. (2012). Fungal infections associated with con-

taminated methylprednisolone in Tennessee. *N Engl J Med, 367*(23), 2194–2203. doi: 10.1056/NEJMoa1212972

Kanda, Y., Yamamoto, R., Chizuka, A., Hamaki, T., Suguro, M., Arai, C., … Togawa, A. (2000). Prophylactic action of oral fluconazole against fungal infection in neutropenic patients. A meta-analysis of 16 randomized, controlled trials. *Cancer, 89*(7), 1611–1625. doi: 10.1002/1097–0142(20001001)89:7<1611::AID-CNCR27>3.0.CO;2-B

Kanerva, M., Ollgren, J. & Lyytikainen, O. (2010). Interhospital differences and case-mix in a nationwide prevalence survey. *J Hosp Infect, 76*(2), 135–138. doi: S0195–6701(10)00253–7

Kang, N., van Mulligen, E. M. & Kors, J. A. (2011). Comparing and combining chunkers of biomedical text. *J Biomed Inform, 44*(2), 354–360. doi: S1532–0464(10)00157–7

Kim, A., Nicolau, D. P. & Kuti, J. L. (2010). Hospital costs and outcomes among intravenous antifungal therapies for patients with invasive aspergillosis in the United States. *Mycoses*. doi: MYC1903

Klompas, M. & Yokoe, D. S. (2009). Automated surveillance of health care-associated infections. *Clin Infect Dis, 48*(9), 1268–1275. doi: 10.1086/597591

Klompas, M. (2010). Interobserver variability in ventilator-associated pneumonia surveillance. *Am J Infect Control, 38*(3), 237–239. doi: S0196–6553(09)00973–0

Klompas, M. (2012). Is a ventilator-associated pneumonia rate of zero really possible? *Curr Opin Infect Dis, 25*(2), 176–182. doi: 10.1097/QCO.0b013e3283502437

Klompas, M., Haney, G., Church, D., Lazarus, R., Hou, X. & Platt, R. (2008). Automated identification of acute hepatitis b using electronic medical record data to facilitate public health surveillance. *PLoS One, 3*(7), e2626. doi: 10.1371/journal.pone.0002626

Klompas, M., Kleinman, K. & Platt, R. (2008). Development of an algorithm for surveillance of ventilator-associated pneumonia with electronic data and comparison of algorithm results with clinician diagnoses. *Infect Control Hosp Epidemiol, 29*(1), 31–37. doi: 10.1086/524332

Klompas, M., Magill, S., Robicsek, A., Strymish, J. M., Kleinman, K., Evans, R. S., … Platt, R. (2012). Objective surveillance definitions for ventilator-associated pneumonia. *Crit Care Med, 40*(12), 3154–3161. doi: 10.1097/CCM.0b013e318260c6d9

Knirsch, C. A., Jain, N. L., Pablos-Mendez, A., Friedman, C. & Hripcsak, G. (1998). Respiratory isolation of tuberculosis patients using clinical guidelines and an automated clinical decision support system. *Infect Control Hosp Epidemiol, 19*(2), 94–100.

Kontoyiannis, D. P. (2010). Antifungal prophylaxis in hematopoietic stem cell transplant recipients: The unfinished tale of imperfect success. *Bone Marrow Transplant*. doi: bmt2010256

Kontoyiannis, D. P. (2011). Invasive mycoses: Strategies for effective management. *Am J Med, 125*(suppl 1), S25–38. doi: S0002–9343(11)00904–1

Kontoyiannis, D. P., Chamilos, G., Lewis, R. E., Giralt, S., Cortes, J., Raad, II, … Han, X. (2007). Increased bone marrow iron stores is an independent risk factor for invasive aspergillosis in patients with high-risk hemato-

logic malignancies and recipients of allogeneic hematopoietic stem cell transplantation. *Cancer, 110*(6), 1303–1306. doi: 10.1002/cncr.22909

Kontoyiannis, D. P., Lionakis, M. S., Lewis, R. E., Chamilos, G., Healy, M., Perego, C., … Raad, II. (2005). Zygomycosis in a tertiary-care cancer center in the era of aspergillus-active antifungal therapy: A case-control observational study of 27 recent cases. *J Infect Dis, 191*(8), 1350–1360. doi: JID33576

Kontoyiannis, D. P., Marr, K. A., Park, B. J., Alexander, B. D., Anaissie, E. J., Walsh, T. J., … Pappas, P. G. (2010). Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: Overview of the transplant-associated infection surveillance network (transnet) database. *Clin Infect Dis, 50*(8), 1091–1100. doi: 10.1086/651263

Kontoyiannis, D. P., Perlin, D. S., Roilides, E. & Walsh, T. J. (2013). What can we learn and what do we need to know amidst the iatrogenic outbreak of exserohilum rostratum meningitis? *Clin Infect Dis*. doi: cit283

Kontoyiannis, D. P., Wessel, V. C., Bodey, G. P. & Rolston, K. V. (2000). Zygomycosis in the 1990s in a tertiary-care cancer center. *Clin Infect Dis, 30*(6), 851–856. doi: CID990697

Kosmider, S., Jones, I., Hibbert, M., Hunter, A., McLaughlin, S., Johns, J., … Gibbs, P. (2008). Towards establishing a national colorectal cancer database: Lessons learnt from bio21 molecular medicine informatics model. *ANZ J Surg, 78*(9), 803–809. doi: ANS4655

Krishna, G., AbuTarif, M., Xuan, F., Martinho, M., Angulo, D. & Cornely, O. A. (2008). Pharmacokinetics of oral posaconazole in neutropenic pa-

tients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. *Pharmacotherapy, 28*(10), 1223–1232. doi: 10.1592/phco.28.10.1223

Krishna, G., Ma, L., Martinho, M. & O'Mara, E. (2012). A single dose phase i study to evaluate the pharmacokinetics of posaconazole new tablet and capsule formulations relative to oral suspension. *Antimicrob Agents Chemother, 56*(8), 4196–4201. doi: AAC.00222–12

Krishna, G., Martinho, M., Chandrasekar, P., Ullmann, A. J. & Patino, H. (2007). Pharmacokinetics of oral posaconazole in allogeneic hemato-poietic stem cell transplant recipients with graft-versus-host disease. *Pharmacotherapy, 27*(12), 1627–1636. doi: 10.1592/phco.27.12.1627

Krishna, G., Moton, A., Ma, L., Medlock, M. M. & McLeod, J. (2009). Phar-macokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. *Antimicrob Agents Chemother, 53*(3), 958–966. doi: AAC.01034–08

Kuhlman, J. E., Fishman, E. K. & Siegelman, S. S. (1985). Invasive pulmonary aspergillosis in acute leukemia: Characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. *Radiology, 157*(3), 611–614.

Kumar, A., Ellis, P., Arabi, Y., Roberts, D., Light, B., Parrillo, J. E., … Cha-teau, D. (2009). Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest, 136*(5), 1237–1248. doi: chest.09–0087

Labelle, A. J., Micek, S. T., Roubinian, N. & Kollef, M. H. (2008). Treatment-related risk factors for hospital mortality in candida bloodstream infec-

tions. *Crit Care Med, 36*(11), 2967–2972. doi: 10.1097/CCM.0b013e31818b3477

Lanternier, F., Dannaoui, E., Morizot, G., Elie, C., Garcia-Hermoso, D., Huerre, M., … Lortholary, O. (2012). A global analysis of mucormycosis in France: The retrozygo study (2005–2007). *Clin Infect Dis, 54*(suppl 1), S35–43. doi: cir880

Larson, E. B. (2013). Building trust in the power of 'big data' research to serve the public good. *JAMA, 309*(23), 2443–2444. doi: 1697974

Lazarus, R., Klompas, M., Campion, F. X., McNabb, S. J., Hou, X., Daniel, J., … Platt, R. (2009). Electronic support for public health: Validated case finding and reporting for notifiable diseases using electronic medical data. *J Am Med Inform Assoc, 16*(1), 18–24. doi: M2848

Leal, J. & Laupland, K. B. (2008). Validity of electronic surveillance systems: A systematic review. *J Hosp Infect, 69*(3), 220–229. doi: S0195–6701(08)00193-X

Lebeaux, D., Lanternier, F., Elie, C., Suarez, F., Buzyn, A., Viard, J. P., … Lortholary, O. (2009). Therapeutic drug monitoring of posaconazole: A monocentric study with 54 adults. *Antimicrob Agents Chemother, 53*(12), 5224–5229. doi: AAC.00939–09

Leeflang, M. M., Debets-Ossenkopp, Y. J., Visser, C. E., Scholten, R. J., Hooft, L., Bijlmer, H. A., … Vandenbroucke-Grauls, C. M. (2008). Galactomannan detection for invasive aspergillosis in immunocompromized patients. *Cochrane Database Syst Rev*(4), CD007394. doi: 10.1002/14651858.CD007394

Legrand, M., Max, A., Peigne, V., Mariotte, E., Canet, E., Debrumetz, A., …
Azoulay, E. (2012). Survival in neutropenic patients with severe sepsis
or septic shock. *Crit Care Med, 40*(1), 43–49. doi:
10.1097/CCM.0b013e31822b50c2

Lehrnbecher, T., Frank, C., Engels, K., Kriener, S., Groll, A. H. & Schwabe, D.
(2010). Trends in the postmortem epidemiology of invasive fungal in-
fections at a university hospital. *J Infect, 61*(3), 259–265. doi: S0163–
4453(10)00187–8

Leon, C., Ruiz-Santana, S., Saavedra, P., Galvan, B., Blanco, A., Castro, C., …
Hernandez-Viera, M. A. (2009). Usefulness of the 'candida score' for
discriminating between candida colonization and invasive candidiasis
in non-neutropenic critically ill patients: A prospective multicenter
study. *Crit Care Med, 37*(5), 1624–1633. doi:
10.1097/CCM.0b013e31819daa14

Leventakos, K., Lewis, R. E. & Kontoyiannis, D. P. (2010). Fungal infections
in leukemia patients: How do we prevent and treat them? *Clin Infect
Dis, 50*(3), 405–415. doi: 10.1086/649879

Lewis RE, Cahyame-Zuniga L, Leventakos K, Chamilos G, Ben-Ami R, Tam-
boli P, et al. (2013). Epidemiology and sites of involvement of invasive
fungal infections in patients with haematological malignancies: a 20-
year autopsy study. *Mycoses*. Apr 4

Lewis, G., Hall, P., Eisa, N., Deremer, D., Dobbins, R., El-Geneidy, M., Ustun,
C. (2010). Acute myelogenous leukemia patients are at low risk for in-
vasive fungal infections after high-dose cytarabine consolidations and

thus do not require prophylaxis. *Acta Haematol, 124*(4), 206–213. doi: 000321504

Lewis, R. E. (2011a). Current concepts in antifungal pharmacology. *Mayo Clin Proc, 86*(8), 805–817. doi: 86/8/805

Lewis, R. E. (2011b). Importance of pharmacokinetic considerations for selecting therapy in the treatment of invasive fungal infections. *Am J Ther*. doi: 10.1097/MJT.0b013e3181ff7e10

Lewis, R. E. (2011c). Pharmacokinetic–pharmacodynamic optimization of triazole antifungal therapy. *Current Opinion in Infectious Diseases, 24*(suppl 2), S14–S29.

Li, Y., Theuretzbacher, U., Clancy, C. J., Nguyen, M. H. & Derendorf, H. (2010). Pharmacokinetic/pharmacodynamic profile of posaconazole. *Clin Pharmacokinet, 49*(6), 379–396. doi: 2

LIBSVM. (2012). *A library for support vector machines.* Retrieved from http://ntu.Csie.Org/~cjlin/papers/libsvm.Pdf. Accessed on 6 January2012.

Lignell, A., Lowdin, E., Cars, O., Chryssanthou, E. & Sjolin, J. (2011). Posaconazole in human serum: A greater pharmacodynamic effect than predicted by the non-protein-bound serum concentration. *Antimicrob Agents Chemother, 55*(7), 3099–3104. doi: AAC.01671–10

Lin, M. Y., Hota, B., Khan, Y. M., Woeltje, K. F., Borlawsky, T. B., Doherty, J. A., … Trick, W. E. (2010). Quality of traditional surveillance for public reporting of nosocomial bloodstream infection rates. *JAMA, 304*(18), 2035–2041. doi: 304/18/2035

Lin, S. J., Schranz, J. & Teutsch, S. M. (2001). Aspergillosis case-fatality rate: Systematic review of the literature. *Clin Infect Dis, 32*(3), 358–366. doi: CID000028

Lionakis, M. S., Lewis, R. E., Torres, H. A., Albert, N. D., Raad, II & Kontoyiannis, D. P. (2005). Increased frequency of non-fumigatus aspergillus species in amphotericin b- or triazole-pre-exposed cancer patients with positive cultures for aspergilli. *Diagn Microbiol Infect Dis, 52*(1), 15–20. doi: S0732–8893(05)00011–8

Lober, W. B., Trigg, L. & Karras, B. (2004). Information system architectures for syndromic surveillance. *MMWR Morb Mortal Wkly Rep, 53*(suppl 1), 203–208.

Lortholary, O., Gangneux, J. P., Sitbon, K., Lebeau, B., de Monbrison, F., Le Strat, Y., … Bretagne, S. (2011). Epidemiological trends in invasive aspergillosis in France: The saif network (2005–2007). *Clin Microbiol Infect, 17*(12), 1882–1889. doi: 10.1111/j.1469–0691.2011.03548.x

Low, C. Y. & Rotstein, C. (2011). Emerging fungal infections in immunocompromised patients. *F1000 Med Rep, 3*, 14. doi: 10.3410/M3–14

MacDougall, C. & Polk, R. E. (2005). Antimicrobial stewardship programs in health care systems. *Clin Microbiol Rev, 18*(4), 638–656. doi: 18/4/638

Maertens, J., Groll, A. H., Cordonnier, C., de la Cámara, R., Roilides, E. & Marchetti, O. (2011). Treatment and timing in invasive mould disease. *Journal of Antimicrobial Chemotherapy, 66*(suppl 1), i37-i43. doi: 10.1093/jac/dkq440

Maertens, J., Marchetti, O., Herbrecht, R., Cornely, O. A., Fluckiger, U., Frere, P., … Cordonnier, C. (2011). European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: Summary of the ecil 3–2009 update. *Bone Marrow Transplant*. doi: bmt2010175

Maertens, J., Theunissen, K., Verhoef, G., Verschakelen, J., Lagrou, K., Verbeken, E., … Van Eldere, J. (2005). Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: A prospective feasibility study. *Clin Infect Dis, 41*(9), 1242–1250. doi: CID36798

Malagola, M., Peli, A., Damiani, D., Candoni, A., Tiribelli, M., Martinelli, G., … Russo, D. (2008). Incidence of bacterial and fungal infections in newly diagnosed acute myeloid leukaemia patients younger than 65 yr treated with induction regimens including fludarabine: Retrospective analysis of 224 cases. *Eur J Haematol, 81*(5), 354–363. doi: EJH1122

Marks, D. I., Pagliuca, A., Kibbler, C. C., Glasmacher, A., Heussel, C. P., Kantecki, M., … Cook, G. (2011). Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. *Br J Haematol*. doi: 10.1111/j.1365–2141.2011.08838.x

Maro, J. C., Platt, R., Holmes, J. H., Strom, B. L., Hennessy, S., Lazarus, R. & Brown, J. S. (2009). Design of a national distributed health data network. *Ann Intern Med, 151*(5), 341–344. doi: 0000605–200909010–00140

Marom, E. M. & Kontoyiannis, D. P. (2011). Imaging studies for diagnosing invasive fungal pneumonia in immunocompromised patients. *Curr Opin Infect Dis, 24*(4), 309–314. doi: 10.1097/QCO.0b013e328348b2e1

Marr, K. A. (2010). Fungal infections in oncology patients: Update on epidemiology, prevention, and treatment. *Curr Opin Oncol*.

Marr, K. A., Balajee, S. A., McLaughlin, L., Tabouret, M., Bentsen, C. & Walsh, T. J. (2004). Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: Variables that affect performance. *J Infect Dis, 190*(3), 641–649. doi: 10.1086/422009

Marr, K. A., Carter, R. A., Boeckh, M., Martin, P. & Corey, L. (2002). Invasive aspergillosis in allogeneic stem cell transplant recipients: Changes in epidemiology and risk factors. *Blood, 100*(13), 4358–4366. doi: 10.1182/blood-2002–05–1496

Marr, K. A., Carter, R. A., Crippa, F., Wald, A. & Corey, L. (2002). Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis, 34*(7), 909–917. doi: CID011064

Marr, K. A., Laverdiere, M., Gugel, A. & Leisenring, W. (2005). Antifungal therapy decreases sensitivity of the aspergillus galactomannan enzyme immunoassay. *Clin Infect Dis, 40*(12), 1762–1769. doi: CID35631

Martino, R. & Viscoli, C. (2006). Empirical antifungal therapy in patients with neutropenia and persistent or recurrent fever of unknown origin. *Br J Haematol, 132*(2), 138–154. doi: BJH5838

Martino, R., Parody, R., Fukuda, T., Maertens, J., Theunissen, K., Ho, A., …
Einsele, H. (2006). Impact of the intensity of the pretransplantation
conditioning regimen in patients with prior invasive aspergillosis un-
dergoing allogeneic hematopoietic stem cell transplantation: A retro-
spective survey of the infectious diseases working party of the european
group for blood and marrow transplantation. *Blood, 108*(9), 2928–2936.
doi: blood-2006–03–008706

Martino, R., Pinana, J. L., Parody, R., Valcarcel, D., Sureda, A., Brunet, S., …
Sierra, J. (2009). Lower respiratory tract respiratory virus infections in-
crease the risk of invasive aspergillosis after a reduced-intensity alloge-
neic hematopoietic sct. *Bone Marrow Transplant, 44*(11), 749–756. doi:
bmt200978

Martino, R., Subira, M., Rovira, M., Solano, C., Vazquez, L., Sanz, G. F., …
De la Camara, R. (2002). Invasive fungal infections after allogeneic pe-
ripheral blood stem cell transplantation: Incidence and risk factors in
395 patients. *Br J Haematol, 116*(2), 475–482. doi: 3259

Maschmeyer, G., Beinert, T., Buchheidt, D., Cornely, O. A., Einsele, H.,
Heinz, W., … Mattiuzzi, G. (2009). Diagnosis and antimicrobial thera-
py of lung infiltrates in febrile neutropenic patients: Guidelines of the
infectious diseases working party of the german society of haematology
and oncology. *Eur J Cancer, 45*(14), 2462–2472. doi: S0959–
8049(09)00340–2

McCowan, I., Moore, D. & Fry, M. J. (2006). Classification of cancer stage
from free-text histology reports. *Conf Proc IEEE Eng Med Biol Soc, 1*,
5153–5156.

McKnight, L. K., Wilcox, A. & Hripcsak, G. (2002). The effect of sample size and disease prevalence on supervised machine learning of narrative data. *Proc AMIA Symp*, 519–522. doi: D020002508

McLaughlin, A. M., Hardt, J., Canavan, J. B. & Donnelly, M. B. (2009). Determining the economic cost of ICU treatment: A prospective 'micro-costing' study. *Intensive Care Med, 35*(12), 2135–2140. doi: 10.1007/s00134–009–1622–1

Melton, G. B. & Hripcsak, G. (2005). Automated detection of adverse events using natural language processing of discharge summaries. *J Am Med Inform Assoc, 12*(4), 448–457. doi: M1794

Meltzer, M. I. (2001). Introduction to health economics for physicians. *Lancet, 358*(9286), 993–998. doi: S0140–6736(01)06107–4

Mendonca, E. A., Haas, J., Shagina, L., Larson, E. & Friedman, C. (2005). Extracting information on pneumonia in infants using natural language processing of radiology reports. *J Biomed Inform, 38*(4), 314–321. doi: S1532–0464(05)00016-X

Mengoli, C., Cruciani, M., Barnes, R. A., Loeffler, J. & Donnelly, J. P. (2009). Use of PCR for diagnosis of invasive aspergillosis: Systematic review and meta-analysis. *Lancet Infect Dis, 9*(2), 89–96. doi: S1473–3099(09)70019–2

Mennink-Kersten, M. A., Donnelly, J. P. & Verweij, P. E. (2004). Detection of circulating galactomannan for the diagnosis and management of invasive aspergillosis. *Lancet Infect Dis, 4*(6), 349–357. doi: 10.1016/S1473–3099(04)01045-X

Menzin, J., Lang, K. M., Friedman, M., Dixon, D., Marton, J. P. & Wilson, J. (2005). Excess mortality, length of stay, and costs associated with serious fungal infections among elderly cancer patients: Findings from linked seer-medicare data. *Value Health, 8*(2), 140–148. doi: VHE4004

Menzin, J., Meyers, J. L., Friedman, M., Korn, J. R., Perfect, J. R., Langston, A. A., … Papadopoulos, G. (2011). The economic costs to United States hospitals of invasive fungal infections in transplant patients. *Am J Infect Control, 39*(4), e15–20. doi: S0196–6553(10)00795–9

Menzin, J., Meyers, J. L., Friedman, M., Perfect, J. R., Langston, A. A., Danna, R. P. & Papadopoulos, G. (2009). Mortality, length of hospitalization, and costs associated with invasive fungal infections in high-risk patients. *Am J Health Syst Pharm, 66*(19), 1711–1717. doi: 66/19/1711

Meyer, E., Schwab, F., Gastmeier, P., Ruden, H. & Heininger, A. (2007). Antifungal use in intensive care units. *J Antimicrob Chemother, 60*(3), 619–624. doi: dkm255

Meystre, S. M., Savova, G. K., Kipper-Schuler, K. C. & Hurdle, J. F. (2008). Extracting information from textual documents in the electronic health record: A review of recent research. *Yearb Med Inform*, 128–144. doi: me08010128

Mezger, M., Kneitz, S., Wozniok, I., Kurzai, O., Einsele, H. & Loeffler, J. (2008). Proinflammatory response of immature human dendritic cells is mediated by dectin-1 after exposure to aspergillus fumigatus germ tubes. *J Infect Dis, 197*(6), 924–931. doi: 10.1086/528694

Mezger, M., Steffens, M., Beyer, M., Manger, C., Eberle, J., Toliat, M. R., … Loeffler, J. (2008). Polymorphisms in the chemokine (c-x-c motif) lig-

and 10 are associated with invasive aspergillosis after allogeneic stem-cell transplantation and influence cxcl10 expression in monocyte-derived dendritic cells. *Blood, 111*(2), 534–536. doi: blood-2007–05–090928

Miceli, M. H. & Lee, S. A. (2011). Emerging moulds: Epidemiological trends and antifungal resistance. *Mycoses*. doi: 10.1111/j.1439–0507.2011.02032.x

Michallet, M., Benet, T., Sobh, M., Kraghel, S., El Hamri, M., Cannas, G., … Vanhems, P. (2012). Invasive aspergillosis: An important risk factor on the short- and long-term survival of acute myeloid leukemia (AML) patients. *Eur J Clin Microbiol Infect Dis, 31*(6), 991–997. doi: 10.1007/s10096–011–1397–5

Milito, M. A., Kontoyiannis, D. P., Lewis, R. E., Liu, P., Mawlawi, O. R., Truong, M. T. & Marom, E. M. (2010). Influence of host immunosuppression on CT findings in invasive pulmonary aspergillosis. *Med Mycol, 48*(6), 817–823. doi: 10.3109/13693780903514872

Mol, P. G., Rutten, W. J., Gans, R. O., Degener, J. E. & Haaijer-Ruskamp, F. M. (2004). Adherence barriers to antimicrobial treatment guidelines in teaching hospital, the netherlands. *Emerg Infect Dis, 10*(3), 522–525.

Morgan, J., Meltzer, M. I., Plikaytis, B. D., Sofair, A. N., Huie-White, S., Wilcox, S., … Teutsch, S. M. (2005). Excess mortality, hospital stay, and cost due to candidemia: A case-control study using data from population-based candidemia surveillance. *Infect Control Hosp Epidemiol, 26*(6), 540–547. doi: ICHE10710

Morrell, M., Fraser, V. J. & Kollef, M. H. (2005). Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: A potential risk factor for hospital mortality. *Antimicrob Agents Chemother, 49*(9), 3640–3645. doi: 49/9/3640

Morrissey, C. O., Chen, S. C., Sorrell, T. C., Milliken, S., Bardy, P. G., Bradstock, K. F., … Slavin, M. A. (2013). Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: A randomised controlled trial. *Lancet Infect Dis, 13*(6), 519–528. doi: S1473–3099(13)70076–8

Murali, S. & Langston, A. (2009). Advances in antifungal prophylaxis and empiric therapy in patients with hematologic malignancies. *Transpl Infect Dis, 11*(6), 480–490. doi: TID441

Murdoch, T. B. & Detsky, A. S. (2013). The inevitable application of big data to health care. *JAMA, 309*(13), 1351–1352. doi: 1674245

Murff, H. J., FitzHenry, F., Matheny, M. E., Gentry, N., Kotter, K. L., Crimin, K., … Speroff, T. (2011). Automated identification of postoperative complications within an electronic medical record using natural language processing. *JAMA, 306*(8), 848–855. doi: 306/8/848

Nadkarni, P. M., Ohno-Machado, L. & Chapman, W. W. (2012). Natural language processing: An introduction. *J Am Med Inform Assoc, 18*(5), 544–551. doi: amiajnl-2011–000464

Naggie, S. & Perfect, J. R. (2009). Molds: Hyalohyphomycosis, phaeohyphomycosis, and zygomycosis. *Clin Chest Med, 30*(2), 337–353, vii-viii. doi: S0272–5231(09)00022–7

NEHTA. (2009). National e-health transition authority strategic plan 2009/10 to 2011/12.

Neofytos, D., Fishman, J. A., Horn, D., Anaissie, E., Chang, C. H., Olyaei, A., … Marr, K. A. (2013). Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transpl Infect Dis, 12*(3), 220–229. doi: TID492

Neofytos, D., Horn, D., Anaissie, E., Steinbach, W., Olyaei, A., Fishman, J., … Marr, K. (2009). Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: Analysis of multicenter prospective antifungal therapy (path) alliance registry. *Clin Infect Dis, 48*(3), 265–273. doi: 10.1086/595846

Neofytos, D., Lu, K., Hatfield-Seung, A., Blackford, A., Marr, K. A., Treadway, S., … Karp, J. (2013). Epidemiology, outcomes, and risk factors of invasive fungal infections in adult patients with acute myelogenous leukemia after induction chemotherapy. *Diagn Microbiol Infect Dis, 75*(2), 144–149. doi: S0732–8893(12)00403–8

Neofytos, D., Treadway, S., Ostrander, D., Alonso, C. D., Dierberg, K. L., Nussenblatt, V., … Marr, K. A. (2013). Epidemiology, outcomes, and mortality predictors of invasive mold infections among transplant recipients: A 10-year, single-center experience. *Transpl Infect Dis, 15*(3), 233–242. doi: 10.1111/tid.12060

Neoh, C. F., Snell, G. I., Kotsimbos, T., Levvey, B., Morrissey, C. O., Slavin, M. A., … Kong, D. C. (2011). Antifungal prophylaxis in lung transplantation–a world-wide survey. *Am J Transplant, 11*(2), 361–366. doi: 10.1111/j.1600–6143.2010.03375.x

Neubauer, W. C., Engelhardt, M., Konig, A., Hieke, S., Jung, M., Bertz, H. & Kummerer, K. (2010). Therapeutic drug monitoring of posaconazole in hematology patients: Experience with a new high-performance liquid chromatography-based method. *Antimicrob Agents Chemother, 54*(9), 4029–4032. doi: AAC.00150–10

Nguyen, A., Moore, J., Lawley, M., Hansen, D. & Colquist, S. (2011). Automatic extraction of cancer characteristics from free-text pathology reports for cancer notifications. *Stud Health Technol Inform, 168*, 117–124.

Nguyen, A., Moore, J., Zuccon, G., Lawley, M. & Colquist, S. (2012). Classification of pathology reports for cancer registry notifications. *Stud Health Technol Inform, 178*, 150–156.

Nguyen, Q. & Reid, B. (2005). A comparison of two sources of data on fungaemia in two hospitals. *HIM J, 34*(3), 88–93.

Nicolle, M. C., Benet, T., Thiebaut, A., Bienvenu, A. L., Voirin, N., Duclos, A., … Vanhems, P. (2011). Invasive aspergillosis in patients with hematologic malignancies: Incidence and description of 127 cases enrolled in a single institution prospective survey from 2004 to 2009. *Haematologica, 96*(11), 1685–1691. doi: haematol.2011.044636

Nivoix, Y., Velten, M., Letscher-Bru, V., Moghaddam, A., Natarajan-Ame, S., Fohrer, C., … Herbrecht, R. (2008). Factors associated with overall and attributable mortality in invasive aspergillosis. *Clin Infect Dis, 47*(9), 1176–1184.

Nosari, A. M., Caira, M., Pioltelli, M. L., Fanci, R., Bonini, A., Cattaneo, C., … Pagano, L. (2012). Hema e-chart registry of invasive fungal infec-

tions in haematological patients: Improved outcome in recent years in mould infections. *Clin Microbiol Infect*. doi: 10.1111/1469–0691.12014

Nouer, S. A., Nucci, M., Kumar, N. S., Grazziutti, M., Restrepo, A. & Anaissie, E. (2011). Baseline platelet count and creatinine clearance rate predict the outcome of neutropenia-related invasive aspergillosis. *Clin Infect Dis, 54*(12), e173–183. doi: cis298

Nucci, M. & Anaissie, E. (2009). Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. *Clin Infect Dis, 49*(8), 1211–1225. doi: 10.1086/605664

Nucci, M., Nouer, S. A., Grazziutti, M., Kumar, N. S., Barlogie, B. & Anaissie, E. (2010). Probable invasive aspergillosis without prespecified radiologic findings: Proposal for inclusion of a new category of aspergillosis and implications for studying novel therapies. *Clin Infect Dis, 51*(11), 1273–1280. doi: 10.1086/657065

Oren, I., Haddad, N., Finkelstein, R. & Rowe, J. M. (2001). Invasive pulmonary aspergillosis in neutropenic patients during hospital construction: Before and after chemoprophylaxis and institution of hepa filters. *Am J Hematol, 66*(4), 257–262. doi: 10.1002/ajh.1054

Ostrosky-Zeichner, L. (2012). Invasive mycoses: Diagnostic challenges. *Am J Med, 125*(suppl 1), S14–24. doi: S0002–9343(11)00903-X

Pagano, L. & Lumb, J. (2011). Update on invasive fungal disease. *Future Microbiol, 6*(9), 985–989. doi: 10.2217/fmb.11.85

Pagano, L., Akova, M., Dimopoulos, G., Herbrecht, R., Drgona, L. & Blijlevens, N. (2011). Risk assessment and prognostic factors for mould-

related diseases in immunocompromised patients. *J Antimicrob Chemother, 66*(suppl 1), i5–14. doi: dkq437

Pagano, L., Caira, M., Candoni, A., Offidani, M., Fianchi, L., Martino, B., … Nosari, A. (2006). The epidemiology of fungal infections in patients with hematologic malignancies: The seifem-2004 study. *Haematologica, 91*(8), 1068–1075.

Pagano, L., Caira, M., Candoni, A., Offidani, M., Martino, B., Specchia, G., … Nosari, A. (2010). Invasive aspergillosis in patients with acute myeloid leukemia: A seifem-2008 registry study. *Haematologica, 95*(4), 644–650. doi: haematol.2009.012054

Pagano, L., Caira, M., Nosari, A., Rossi, G., Locatelli, F., Viale, P. & Aversa, F. (2010). Hema e-chart: Italian registry for prospective analysis of epidemiology, management and outcome of febrile events in patients with hematological malignancies. *J Chemother, 22*(1), 20–24.

Pagano, L., Caira, M., Nosari, A., Van Lint, M. T., Candoni, A., Offidani, M., … Aversa, F. (2007). Fungal infections in recipients of hematopoietic stem cell transplants: Results of the seifem b-2004 study–sorveglianza epidemiologica infezioni fungine nelle emopatie maligne. *Clin Infect Dis, 45*(9), 1161–1170. doi: CID50874

Pagano, L., Caira, M., Nosari, A., Viale, P., Rossi, G. & Aversa, F. (2009). Continuous surveillance of invasive fungal infection: A realistic goal for the near future. *Clin Infect Dis, 48*(12), 1801; author reply 1801–1803. doi: 10.1086/599229

Pagano, L., Caira, M., Offidani, M., Martino, B., Candoni, A., Valentini, C. G., … Aversa, F. (2010). Adherence to international guidelines for the

treatment of invasive aspergillosis in acute myeloid leukaemia: Feasibility and utility (seifem-2008b study). *J Antimicrob Chemother, 65*(9), 2013–2018. doi: dkq240

Pagano, L., Caira, M., Picardi, M., Candoni, A., Melillo, L., Fianchi, L., … Nosari, A. (2007). Invasive aspergillosis in patients with acute leukemia: Update on morbidity and mortality–seifem-c report. *Clin Infect Dis, 44*(11), 1524–1525. doi: CID50497

Pagano, L., Fianchi, L. & Caira, M. (2008). Pulmonary aspergillosis in hematologic malignancies: Lights and shadows. *Haematologica, 93*(11), 1611–1616. doi: 93/11/1611

Pagano, L., Offidani, M., Fianchi, L., Nosari, A., Candoni, A., Piccardi, M., … Del Favero, A. (2004). Mucormycosis in hematologic patients. *Haematologica, 89*(2), 207–214.

Pagano, L., Valentini, C. G., Fianchi, L. & Caira, M. (2009). The role of neutrophils in the development and outcome of zygomycosis in haematological patients. *Clin Microbiol Infect, 15*(suppl 5), 33–36. doi: CLM2977

Pagano, L., Valentini, C. G., Posteraro, B., Girmenia, C., Ossi, C., Pan, A., … Viviani, M. (2009). Zygomycosis in italy: A survey of fimua-ECMM (federazione italiana di micopatologia umana ed animale and european confederation of medical mycology). *J Chemother, 21*(3), 322–329.

Pakyz, A. L., Gurgle, H. E. & Oinonen, M. J. (2011). Antifungal use in hospitalized adults in U.S. academic health centers. *Am J Health Syst Pharm, 68*(5), 415–418. doi: 68/5/415

Panackal, A. A., Li, H., Kontoyiannis, D. P., Mori, M., Perego, C. A., Boeckh, M. & Marr, K. A. (2010). Geoclimatic influences on invasive aspergillosis after hematopoietic stem cell transplantation. *Clin Infect Dis, 50*(12), 1588–1597. doi: 10.1086/652761

Pappas, P. G., Alexander, B. D., Andes, D. R., Hadley, S., Kauffman, C. A., Freifeld, A., … Chiller, T. M. (2010). Invasive fungal infections among organ transplant recipients: Results of the transplant-associated infection surveillance network (transnet). *Clin Infect Dis, 50*(8), 1101–1111. doi: 10.1086/651262

Pappas, P. G., Kauffman, C. A., Andes, D., Benjamin, D. K., Jr., Calandra, T. F., Edwards, J. E., Jr., … Sobel, J. D. (2009). Clinical practice guidelines for the management of candidiasis: 2009 update by the infectious diseases society of America. *Clin Infect Dis, 48*(5), 503–535. doi: 10.1086/596757

Pappas, P. G., Kontoyiannis, D. P., Perfect, J. R. & Chiller, T. M. (2013). Real-time treatment guidelines: Considerations during the exserohilum rostratum outbreak in the United States. *Antimicrob Agents Chemother*. doi: AAC.00205–13

Parize, P., Rammaert, B. & Lortholary, O. (2012). Emerging invasive fungal diseases in transplantation. *Curr Infect Dis Rep, 14*(6), 668–675. doi: 10.1007/s11908–012–0296-y

Park, B. J., Pappas, P. G., Wannemuehler, K. A., Alexander, B. D., Anaissie, E. J., Andes, D. R., … Kontoyiannis, D. P. (2011). Invasive non-aspergillus mold infections in transplant recipients, United States,

2001–2006. *Emerg Infect Dis, 17*(10), 1855–1864. doi:
10.3201/eid1710.110087

Parody, R., Martino, R., Rovira, M., Vazquez, L., Vazquez, M. J., de la
Camara, R., … Sanz, G. F. (2006). Severe infections after unrelated do-
nor allogeneic hematopoietic stem cell transplantation in adults: Com-
parison of cord blood transplantation with peripheral blood and bone
marrow transplantation. *Biol Blood Marrow Transplant, 12*(7), 734–
748. doi: S1083–8791(06)00253–9

Partridge-Hinckley, K., Liddell, G. M., Almyroudis, N. G. & Segal, B. H.
(2009). Infection control measures to prevent invasive mould diseases
in hematopoietic stem cell transplant recipients. *Mycopathologia,
168*(6), 329–337. doi: 10.1007/s11046–009–9247-z

Pascual, A., Calandra, T., Bolay, S., Buclin, T., Bille, J. & Marchetti, O.
(2008). Voriconazole therapeutic drug monitoring in patients with inva-
sive mycoses improves efficacy and safety outcomes. *Clin Infect Dis,
46*(2), 201–211. doi: 10.1086/524669

Paterson, D. L. & Singh, N. (1999). Invasive aspergillosis in transplant recipi-
ents. *Medicine (Baltimore), 78*(2), 123–138.

Patterson, J. E., Zidouh, A., Miniter, P., Andriole, V. T. & Patterson, T. F.
(1997). Hospital epidemiologic surveillance for invasive aspergillosis:
Patient demographics and the utility of antigen detection. *Infect Control
Hosp Epidemiol, 18*(2), 104–108.

Pea, F., Furlanut, M. & Viale, P. (2009). What should be the first-choice strat-
egy to maximize posaconazole exposure in daily clinical practice?

Antimicrob Agents Chemother, 53(8), 3608–3609; author reply 3609–3610. doi: 53/8/3608

Perkhofer, S., Lass-Florl, C., Hell, M., Russ, G., Krause, R., Honigl, M., … Greil, R. (2010). The nationwide austrian aspergillus registry: A prospective data collection on epidemiology, therapy and outcome of invasive mould infections in immunocompromised and/or immunosuppressed patients. *Int J Antimicrob Agents, 36*(6), 531–536. doi: S0924–8579(10)00369–9

Petrikkos, G., Skiada, A., Lortholary, O., Roilides, E., Walsh, T. J. & Kontoyiannis, D. P. (2012). Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis, 54*(suppl 1), S23–34. doi: cir866

Pfaller, M. A., Diekema, D. J., Gibbs, D. L., Newell, V. A., Ellis, D., Tullio, V., … Ling, T. A. (2010). Results from the artemis disk global antifungal surveillance study, 1997 to 2007: A 10.5-year analysis of susceptibilities of candida species to fluconazole and voriconazole as determined by clsi standardized disk diffusion. *J Clin Microbiol, 48*(4), 1366–1377. doi: JCM.02117–09

Pfaller, M. A., Messer, S. A., Hollis, R. J. & Jones, R. N. (2002). Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin b against 239 clinical isolates of aspergillus spp. and other filamentous fungi: Report from sentry antimicrobial surveillance program, 2000. *Antimicrob Agents Chemother, 46*(4), 1032–1037.

Pfeiffer, C. D., Fine, J. P. & Safdar, N. (2006). Diagnosis of invasive aspergillosis using a galactomannan assay: A meta-analysis. *Clin Infect Dis, 42*(10), 1417–1427. doi: CID38501

Polk, R. E., Fox, C., Mahoney, A., Letcavage, J. & MacDougall, C. (2007). Measurement of adult antibacterial drug use in 130 US hospitals: Comparison of defined daily dose and days of therapy. *Clin Infect Dis, 44*(5), 664–670. doi: CID40490

Pollack, M., Heugel, J., Xie, H., Leisenring, W., Storek, J., Young, J. A., … Boeckh, M. (2011). An international comparison of current strategies to prevent herpesvirus and fungal infections in hematopoietic cell transplant recipients. *Biol Blood Marrow Transplant, 17*(5), 664–673. doi: S1083–8791(10)00328–9

Polsky, D. & Glick, H. (2009). Costing and cost analysis in randomized controlled trials: Caveat emptor. *Pharmacoeconomics, 27*(3), 179–188.

Pongas, G. N., Lewis, R. E., Samonis, G. & Kontoyiannis, D. P. (2009). Voriconazole-associated zygomycosis: A significant consequence of evolving antifungal prophylaxis and immunosuppression practices? *Clin Microbiol Infect, 15*(suppl 5), 93–97. doi: CLM2988

Portugal, R. D., Garnica, M. & Nucci, M. (2009). Index to predict invasive mold infection in high-risk neutropenic patients based on the area over the neutrophil curve. *J Clin Oncol, 27*(23), 3849–3854. doi: JCO.2008.21.0856

Prentice, H. G., Kibbler, C. C. & Prentice, A. G. (2000). Towards a targeted, risk-based, antifungal strategy in neutropenic patients. *Br J Haematol, 110*(2), 273–284. doi: bjh2014

Quan, C. & Spellberg, B. Mucormycosis, pseudallescheriasis, and other uncommon mold infections. *Proc Am Thorac Soc, 7*(3), 210–215. doi: 7/3/210

Raad, II, Graybill, J. R., Bustamante, A. B., Cornely, O. A., Gaona-Flores, V., Afif, C., … Ullmann, A. J. (2006). Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. *Clin Infect Dis, 42*(12), 1726–1734. doi: CID38706

Ram, R., Gafter-Gvili, A., Raanani, P., Yeshurun, M., Shpilberg, O., Dreyer, J., … Paul, M. (2009). Surveillance of infectious complications in hemato-oncological patients. *Isr Med Assoc J, 11*(3), 133–137.

Ramirez, E., Garcia-Rodriguez, J., Borobia, A. M., Ortega, J. M., Lei, S., Barrios-Fernandez, A., … Frias, J. (2011). Use of antifungal agents in pediatric and adult high-risk areas. *Eur J Clin Microbiol Infect Dis*. doi: 10.1007/s10096–011–1315-x

Reichenberger, F., Habicht, J. M., Gratwohl, A. & Tamm, M. (2002). Diagnosis and treatment of invasive pulmonary aspergillosis in neutropenic patients. *Eur Respir J, 19*(4), 743–755.

Reichenberger, F., Habicht, J., Matt, P., Frei, R., Soler, M., Bolliger, C. T., … Tamm, M. (1999). Diagnostic yield of bronchoscopy in histologically proven invasive pulmonary aspergillosis. *Bone Marrow Transplant, 24*(11), 1195–1199. doi: 10.1038/sj.bmt.1702045

Rentz, A. M., Halpern, M. T. & Bowden, R. (1998). The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. *Clin Infect Dis, 27*(4), 781–788.

Riedel, A., Choe, L., Inciardi, J., Yuen, C., Martin, T. & Guglielmo, B. J. (2007). Antifungal prophylaxis in chemotherapy-associated neutropenia: A retrospective, observational study. *BMC Infect Dis, 7*, 70. doi: 1471–2334–7-70

Rieger, C. T., Cornely, O. A., Hoppe-Tichy, T., Kiehl, M., Knoth, H., Thalheimer, M., … Ostermann, H. (2012). Treatment cost of invasive fungal disease (IFD) in patients with acute myelogenous leukaemia (AML) or myelodysplastic syndrome (MDS) in german hospitals. *Mycoses*. doi: 10.1111/j.1439–0507.2012.02193.x

Roberts, R. R., Hota, B., Ahmad, I., Scott, R. D., 2nd, Foster, S. D., Abbasi, F., … Weinstein, R. A. (2009). Hospital and societal costs of antimicrobial-resistant infections in a chicago teaching hospital: Implications for antibiotic stewardship. *Clin Infect Dis, 49*(8), 1175–1184. doi: 10.1086/605630

Roden, M. M., Zaoutis, T. E., Buchanan, W. L., Knudsen, T. A., Sarkisova, T. A., Schaufele, R. L., … Walsh, T. J. (2005). Epidemiology and outcome of zygomycosis: A review of 929 reported cases. *Clin Infect Dis, 41*(5), 634–653. doi: CID36019

Rolka, H., Walker, D. W., English, R., Katzoff, M. J., Scogin, G. & Neuhaus, E. (2012). CDC's vision for public health surveillance in the 21st century. *MMWR / July 27, 61*.

Ruping, M. J., Heinz, W. J., Kindo, A. J., Rickerts, V., Lass-Florl, C., Beisel, C., … Cornely, O. A. (2009). Forty-one recent cases of invasive zygomycosis from a global clinical registry. *J Antimicrob Chemother, 65*(2), 296–302. doi: dkp430

343

Sabatelli, F., Patel, R., Mann, P. A., Mendrick, C. A., Norris, C. C., Hare, R.,
… McNicholas, P. M. (2006). In vitro activities of posaconazole, flu-
conazole, itraconazole, voriconazole, and amphotericin b against a large
collection of clinically important molds and yeasts. *Antimicrob Agents
Chemother, 50*(6), 2009–2015. doi: 50/6/2009

Saegeman, V., Maertens, J., Ectors, N., Meersseman, W. & Lagrou, K. (2010).
Epidemiology of mucormycosis: Review of 18 cases in a tertiary care
hospital. *Med Mycol, 48*(2), 245–254. doi: 912824506

Saegeman, V., Maertens, J., Meersseman, W., Spriet, I., Verbeken, E. &
Lagrou, K. (2010). Increasing incidence of mucormycosis in university
hospital, belgium. *Emerg Infect Dis, 16*(9), 1456–1458. doi:
10.3201/eid1609.100276

Safdar, A., Rodriguez, G. H., De Lima, M. J., Petropoulos, D., Chemaly, R. F.,
Worth, L. L., … Champlin, R. E. (2007). Infections in 100 cord blood
transplantations: Spectrum of early and late posttransplant infections in
adult and pediatric patients 1996–2005. *Medicine (Baltimore), 86*(6),
324–333. doi: 10.1097/MD.0b013e31815c52b0

Sansone-Parsons, A., Krishna, G., Calzetta, A., Wexler, D., Kantesaria, B.,
Rosenberg, M. A. & Saltzman, M. A. (2006). Effect of a nutritional
supplement on posaconazole pharmacokinetics following oral admin-
istration to healthy volunteers. *Antimicrob Agents Chemother, 50*(5),
1881–1883. doi: 50/5/1881

Santini, V. (2012). Novel therapeutic strategies: Hypomethylating agents and
beyond. *Hematology Am Soc Hematol Educ Program, 2012*, 65–73.
doi: 2012/1/65

Savel, T. G. & Foldy, S. (2012). The role of public health informatics in enhancing public health surveillance. *MMWR Surveill Summ, 61*(suppl), 20–24. doi: su6103a5

Sax, H. & Pittet, D. (2002). Interhospital differences in nosocomial infection rates: Importance of case-mix adjustment. *Arch Intern Med, 162*(21), 2437–2442. doi: ioi10880

Schelenz, S., Barnes, R. A., Kibbler, C. C., Jones, B. L. & Denning, D. W. (2009). Standards of care for patients with invasive fungal infections within the united kingdom: A national audit. *J Infect, 58*(2), 145–153. doi: S0163–4453(08)00412-X

Segal, B. H., Almyroudis, N. G., Battiwalla, M., Herbrecht, R., Perfect, J. R., Walsh, T. J. & Wingard, J. R. (2007). Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. *Clin Infect Dis, 44*(3), 402–409. doi: CID40555

Shah, D. N., Yau, R., Weston, J., Lasco, T. M., Salazar, M., Palmer, H. R. & Garey, K. W. (2011). Evaluation of antifungal therapy in patients with candidaemia based on susceptibility testing results: Implications for antimicrobial stewardship programmes. *J Antimicrob Chemother, 66*(9), 2146–2151. doi: dkr244

Shannon, V. R., Andersson, B. S., Lei, X., Champlin, R. E. & Kontoyiannis, D. P. (2010). Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem

cell transplantation. *Bone Marrow Transplant, 45*(4), 647–655. doi:
bmt2009203

Shepard, J. R., Addison, R. M., Alexander, B. D., Della-Latta, P., Gherna, M.,
Haase, G., Fiandaca, M. J. (2008). Multicenter evaluation of the can-
dida albicans/candida glabrata peptide nucleic acid fluorescent in situ
hybridization method for simultaneous dual-color identification of c.
Albicans and c. Glabrata directly from blood culture bottles. *J Clin
Microbiol, 46*(1), 50–55. doi: JCM.01385–07

Shields, R. K., Clancy, C. J., Vadnerkar, A., Kwak, E. J., Silveira, F. P.,
Massih, R. C., … Nguyen, M. H. (2010). Posaconazole serum concen-
trations among cardiothoracic transplant recipients: Factors impacting
trough levels and correlation with clinical response to therapy.
Antimicrob Agents Chemother, 55(3), 1308–1311. doi: AAC.01325–10

Shimodaira, K., Okubo, Y., Nakayama, H., Wakayama, M., Shinozaki, M.,
Ishiwatari, T., … Shibuya, K. (2012). Trends in the prevalence of inva-
sive fungal infections from an analysis of annual records of autopsy
cases of toho university. *Mycoses, 55*(5), 435–443. doi:
10.1111/j.1439–0507.2012.02169.x

Shoham, S. & Marr, K. A. (2012). Treatment of iatrogenic fungal infections: A
black mold defines a new gray zone in medicine. *Ann Intern Med,
158*(3), 208–210. doi: 1390612

Singh, N. (2005). Invasive aspergillosis in organ transplant recipients: New
issues in epidemiologic characteristics, diagnosis, and management.
Med Mycol, 43(suppl 1), S267–270.

Sinko, J., Csomor, J., Nikolova, R., Lueff, S., Krivan, G., Remenyi, P., …
Masszi, T. (2008). Invasive fungal disease in allogeneic hematopoietic
stem cell transplant recipients: An autopsy-driven survey. *Transpl In-
fect Dis, 10*(2), 106–109. doi: TID264

Siwek, G. T., Dodgson, K. J., de Magalhaes-Silverman, M., Bartelt, L. A.,
Kilborn, S. B., Hoth, P. L., … Pfaller, M. A. (2004). Invasive
zygomycosis in hematopoietic stem cell transplant recipients receiving
voriconazole prophylaxis. *Clin Infect Dis, 39*(4), 584–587. doi:
10.1086/422723

Skiada, A., Pagano, L., Groll, A., Zimmerli, S., Dupont, B., Lagrou, K., …
Petrikkos, G. (2011). Zygomycosis in europe: Analysis of 230 cases ac-
crued by the registry of the european confederation of medical mycolo-
gy (ECMM) working group on zygomycosis between 2005 and 2007.
Clin Microbiol Infect, 17(12), 1859–1867. doi: 10.1111/j.1469–
0691.2010.03456.x

Slavin, M. A. (2008). Introduction to the updated Australian and new zealand
consensus guidelines for the use of antifungal agents in the haematolo-
gy/oncology setting, 2008. *Intern Med J, 38*(6b), 457–467. doi:
IMJ1649

Slavin, M. A., Heath, C. H., Thursky, K. A., Morrissey, C. O., Szer, J., Ling, L.
M., … Grigg, A. P. (2008). Antifungal prophylaxis in adult stem cell
transplantation and haematological malignancy. *Intern Med J, 38*(6b),
468–476. doi: IMJ1723

Slavin, M. A., Osborne, B., Adams, R., Levenstein, M. J., Schoch, H. G.,
Feldman, A. R., … Bowden, R. A. (1995). Efficacy and safety of flu-

conazole prophylaxis for fungal infections after marrow transplanta-

tion–a prospective, randomized, double-blind study. *J Infect Dis,*

171(6), 1545–1552.

Slavin, M., Fastenau, J., Sukarom, I., Mavros, P., Crowley, S. & Gerth, W. C.

(2004). Burden of hospitalization of patients with candida and

aspergillus infections in Australia. *Int J Infect Dis, 8*(2), 111–120. doi:

S1201971203000110

Slobbe, L., Polinder, S., Doorduijn, J. K., Lugtenburg, P. J., el Barzouhi, A.,

Steyerberg, E. W. & Rijnders, B. J. (2008). Outcome and medical costs

of patients with invasive aspergillosis and acute myelogenous leuke-

mia-myelodysplastic syndrome treated with intensive chemotherapy:

An observational study. *Clin Infect Dis, 47*(12), 1507–1512. doi:

10.1086/591531

SNOMED-CT. (2013, accessed at http://www.ihtsdo.org/snomed-CT on 28

August).

Sorror, M. L., Maris, M. B., Storb, R., Baron, F., Sandmaier, B. M., Maloney,

D. G. & Storer, B. (2005). Hematopoietic cell transplantation (HCT)-

specific comorbidity index: A new tool for risk assessment before al-

logeneic HCT. *Blood, 106*(8), 2912–2919. doi: 2005–05–2004

Springer J, Morton CO, Perry M, Heinz WJ, Paholcsek M, Alzheimer M,

Rogers, T.R., Barnes, R.A., Einsele, H., Loeffler, J. & White, P. L.

(2013) Multicenter comparison of serum and whole-blood specimens

for detection of Aspergillus DNA in high-risk hematological patients. *J*

Clin Microbiol. ;51(5):1445-50. doi: 10.1128/JCM.03322-12

Steinbach, W. J., Marr, K. A., Anaissie, E. J., Azie, N., Quan, S. P., Meier-Kriesche, H. U., … Horn, D. L. (2012). Clinical epidemiology of 960 patients with invasive aspergillosis from the path alliance registry. *J Infect, 65*(5), 453–464. doi: S0163–4453(12)00220–4

Stergiopoulou, T., Meletiadis, J., Roilides, E., Kleiner, D. E., Schaufele, R., Roden, M., … Walsh, T. J. (2007). Host-dependent patterns of tissue injury in invasive pulmonary aspergillosis. *Am J Clin Pathol, 127*(3), 349–355. doi: G4225V1P20523H64

Stevenson, K. B., Khan, Y., Dickman, J., Gillenwater, T., Kulich, P., Myers, C., … Mangino, J. E. (2008). Administrative coding data, compared with cdc/nhsn criteria, are poor indicators of health care-associated infections. *Am J Infect Control, 36*(3), 155–164. doi: S0196–6553(08)00087–4

Stone, M. (1974). Cross-validation choice and assessment of statistical predictions (with discussion). *Journal of the Royal Statistical Society, 36*(2), 111–147.

Stone, P. W. (2009). Changes in medicare reimbursement for hospital-acquired conditions including infections. *Am J Infect Control, 37*(9), A17–18. doi: S0196–6553(09)00656–7

Stone, P. W., Dick, A., Pogorzelska, M., Horan, T. C., Furuya, E. Y. & Larson, E. (2009). Staffing and structure of infection prevention and control programs. *Am J Infect Control, 37*(5), 351–357. doi: S0196–6553(08)00900–0

STRIDE Stanford Translational Research Integrated Database Environment (2013). Retrieved from https://clinicalinformatics.Stanford.Edu/research/stride.html on August 23.

Sun, H. Y. & Singh, N. (2009). Characterisation of breakthrough invasive mycoses in echinocandin recipients: An evidence-based review. *Int J Antimicrob Agents, 35*(3), 211–218. doi: S0924–8579(09)00454–3

Swanink, C. M., Meis, J. F., Rijs, A. J., Donnelly, J. P. & Verweij, P. E. (1997). Specificity of a sandwich enzyme-linked immunosorbent assay for detecting aspergillus galactomannan. *J Clin Microbiol, 35*(1), 257–260.

Tablan, O. C., Anderson, L. J., Besser, R., Bridges, C. & Hajjeh, R. (2004). Guidelines for preventing health-care–associated pneumonia, 2003: Recommendations of cdc and the healthcare infection control practices advisory committee. *MMWR Recomm Rep, 53*(RR-3), 1–36. doi: rr5303a1

Tarrand, J. J., Lichterfeld, M., Warraich, I., Luna, M., Han, X. Y., May, G. S. & Kontoyiannis, D. P. (2003). Diagnosis of invasive septate mold infections. A correlation of microbiological culture and histologic or cytologic examination. *Am J Clin Pathol, 119*(6), 854–858. doi: 10.1309/EXBV-YAUP-ENBM-285Y

Tavanti, A., Naglik, J. R. & Osherov, N. Host-fungal interactions: Pathogenicity versus immunity. *Int J Microbiol, 2012*, 562480. doi: 10.1155/2012/562480

Thacker, S. B., Qualters, J. R. & Lee, L. M. (2012). Public health surveillance in the United States: Evolution and challenges. *MMWR Surveill Summ, 61*(suppl 1), 3–9. doi: su6103a2

Thompson, G. R., Kontoyiannis, D. P. & Patterson, T. F. (2013). Real-world experience in the midst of an exserohilum meningitis outbreak. *JAMA, 309*(23), 2493–2495. doi: 1697947

Thompson, G. R., Rinaldi, M. G., Pennick, G., Dorsey, S. A., Patterson, T. F. & Lewis, J. S. (2009). Posaconazole therapeutic drug monitoring: A reference laboratory experience. *Antimicrob Agents Chemother, 53*(5), 2223–2224. doi: AAC.00240–09

Thors, V. S., Bierings, M. B., Melchers, W. J., Verweij, P. E. & Wolfs, T. F. (2010). Pulmonary aspergillosis caused by a pan-azole-resistant aspergillus fumigatus in a 10-year-old boy. *Pediatr Infect Dis J, 30*(3), 268–270. doi: 10.1097/INF.0b013e3182037879

Thursky, K. A. & Mahemoff, M. (2007). User-centered design techniques for a computerised antibiotic decision support system in an intensive care unit. *Int J Med Inform, 76*(10), 760–768.

Thursky, K. A., Worth, L. J., Seymour, J. F., Miles Prince, H. & Slavin, M. A. (2006). Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab. *Br J Haematol, 132*(1), 3–12.

Thursky, K., Byrnes, G., Grigg, A., Szer, J. & Slavin, M. (2004). Risk factors for post-engraftment invasive aspergillosis in allogeneic stem cell transplantation. *Bone Marrow Transplant, 34*(2), 115–121.

Tokars, J. I., Richards, C., Andrus, M., Klevens, M., Curtis, A., Horan, T., … Cardo, D. (2004). The changing face of surveillance for health care-associated infections. *Clin Infect Dis, 39*(9), 1347–1352. doi: CID33816

Tomanek, K., Wermter, J. & Hahn, U. (2007). A reappraisal of sentence and token splitting for life sciences documents. *Stud Health Technol Inform, 129*(Pt 1), 524–528.

Tomblyn, M., Chiller, T., Einsele, H., Gress, R., Sepkowitz, K., Storek, J., … Boeckh, M. A. (2009). Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: A global perspective. *Biol Blood Marrow Transplant, 15*(10), 1143–1238.

Tomblyn, M., Chiller, T., Einsele, H., Gress, R., Sepkowitz, K., Storek, J., … Boeckh, M. J. (2009). Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: A global perspective. Preface. *Bone Marrow Transplant, 44*(8), 453–455.

Tong, K. B., Lau, C. J., Murtagh, K., Layton, A. J. & Seifeldin, R. (2009). The economic impact of aspergillosis: Analysis of hospital expenditures across patient subgroups. *Int J Infect Dis, 13*(1), 24–36. doi: S1201–9712(08)00092–1

Toth, N. R., Chambers, R. M. & Davis, S. L. (2010). Implementation of a care bundle for antimicrobial stewardship. *Am J Health Syst Pharm, 67*(9), 746–749. doi: 67/9/746

Trick, W. E., Chapman, W. W., Wisniewski, M. F., Peterson, B. J., Solomon, S. L. & Weinstein, R. A. (2003). Electronic interpretation of chest radiograph reports to detect central venous catheters. *Infect Control Hosp Epidemiol, 24*(12), 950–954. doi: ICHE6713

Trifilio, S., Singhal, S., Williams, S., Frankfurt, O., Gordon, L., Evens, A., … Mehta, J. (2007). Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole. *Bone Marrow Transplant, 40*(5), 451–456. doi: 1705754

Tsitsikas, D. A., Morin, A., Araf, S., Murtagh, B., Johnson, G., Vinnicombe, S., … Agrawal, S. G. (2012). Impact of the revised (2008) EORTC/MSG definitions for invasive fungal disease on the rates of diagnosis of invasive aspergillosis. *Med Mycol, 50*(5), 538–542. doi: 10.3109/13693786.2011.630040

Ullmann, A. J., Cornely, O. A., Burchardt, A., Hachem, R., Kontoyiannis, D. P., Topelt, K., … Raad, I. (2006). Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. *Antimicrob Agents Chemother, 50*(2), 658–666. doi: 50/2/658

Ullmann, A. J., Lipton, J. H., Vesole, D. H., CHANDRASEKAR, P., Langston, A., Tarantolo, S. R., … Durrant, S. (2007). Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med, 356*(4), 335–347. doi: 356/4/335

Upton, A., Kirby, K. A., Carpenter, P., Boeckh, M. & Marr, K. A. (2007). Invasive aspergillosis following hematopoietic cell transplantation: Outcomes and prognostic factors associated with mortality. *Clin Infect Dis, 44*(4), 531–540. doi: CID40731

van Burik, J. A., Carter, S. L., Freifeld, A. G., High, K. P., Godder, K. T., Papanicolaou, G. A., … Kernan, N. A. (2007). Higher risk of cytomegalovirus and aspergillus infections in recipients of t cell-depleted unre-

lated bone marrow: Analysis of infectious complications in patients treated with t cell depletion versus immunosuppressive therapy to prevent graft-versus-host disease. *Biol Blood Marrow Transplant, 13*(12), 1487–1498. doi: S1083–8791(07)00440–5

Van Campenhout, H., Marbaix, S., Derde, M. P. & Annemans, L. (2008). Voriconazole treatment of invasive aspergillosis: Real-world versus health-economic model results. *Clin Drug Investig, 28*(8), 509–521. doi: 2886

van der Linden, J. W., Jansen, R. R., Bresters, D., Visser, C. E., Geerlings, S. E., Kuijper, E. J., … Verweij, P. E. (2009). Azole-resistant central nervous system aspergillosis. *Clin Infect Dis, 48*(8), 1111–1113. doi: 10.1086/597465

van der Velden, W. J., Blijlevens, N. M. & Donnelly, J. P. Genetic variants and the risk for invasive mould disease in immunocompromised hematology patients. *Curr Opin Infect Dis, 24*(6), 554–563. doi: 10.1097/QCO.0b013e32834ab1f4

Vehreschild, J. J., Ruping, M. J., Wisplinghoff, H., Farowski, F., Steinbach, A., Sims, R., … Cornely, O. A. (2010). Clinical effectiveness of posaconazole prophylaxis in patients with acute myelogenous leukaemia (AML): A 6 year experience of the Cologne AML cohort. *J Antimicrob Chemother, 65*(7), 1466–1471. doi: dkq121

Verweij, P. E., Camps, S. M., Kema, G. H. & Melchers, W. J. (2011). Comment on: Low prevalence of resistance to azoles in aspergillus fumigatus in a French cohort of patients treated for haematological malignancies. *J Antimicrob Chemother, 66*(4), 954–955. doi: dkr008

354

Verweij, P. E., Kerremans, J. J., Voss, A. & Meis, J. F. (2000). Fungal contamination of tobacco and marijuana. *JAMA, 284*(22), 2875. doi: jlt1213

Verweij, P. E., Snelders, E., Kema, G. H., Mellado, E. & Melchers, W. J. (2009). Azole resistance in aspergillus fumigatus: A side-effect of environmental fungicide use? *Lancet Infect Dis, 9*(12), 789–795. doi: S1473–3099(09)70265–8

Walsh, T. J., Anaissie, E. J., Denning, D. W., Herbrecht, R., Kontoyiannis, D. P., Marr, K. A., … Patterson, T. F. (2008). Treatment of aspergillosis: Clinical practice guidelines of the infectious diseases society of America. *Clin Infect Dis, 46*(3), 327–360. doi: 10.1086/525258

Walsh, T. J., Finberg, R. W., Arndt, C., Hiemenz, J., Schwartz, C., Bodensteiner, D., … Holcenberg, J. S. (1999). Liposomal amphotericin b for empirical therapy in patients with persistent fever and neutropenia. National institute of allergy and infectious diseases mycoses study group. *N Engl J Med, 340*(10), 764–771. doi: 10.1056/NEJM199903113401004

Walsh, T. J., Hiemenz, J. & Pizzo, P. A. (1994). Evolving risk factors for invasive fungal infections–all neutropenic patients are not the same. *Clin Infect Dis, 18*(5), 793–798.

Walsh, T. J., Raad, I., Patterson, T. F., Chandrasekar, P., Donowitz, G. R., Graybill, R., … Perfect, J. R. (2007). Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: An externally controlled trial. *Clin Infect Dis, 44*(1), 2–12.

Walsh, T. J., Teppler, H., Donowitz, G. R., Maertens, J. A., Baden, L. R., Dmoszynska, A., ... dePauw, B. E. (2004). Caspofungin versus liposomal amphotericin b for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med, 351*(14), 1391–1402. doi: 10.1056/NEJMoa040446

Wang, Z., Shah, A. D., Tate, A. R., Denaxas, S., Shawe-Taylor, J. & Hemingway, H. (2012). Extracting diagnoses and investigation results from unstructured text in electronic health records by semi-supervised machine learning. *PLoS One, 7*(1), e30412. doi: 10.1371/journal.pone.0030412

Warris, A., Klaassen, C. H., Meis, J. F., De Ruiter, M. T., De Valk, H. A., Abrahamsen, T. G., ... Verweij, P. E. (2003). Molecular epidemiology of aspergillus fumigatus isolates recovered from water, air, and patients shows two clusters of genetically distinct strains. *J Clin Microbiol, 41*(9), 4101–4106.

Weber, D. J., Peppercorn, A., Miller, M. B., Sickbert-Benett, E. & Rutala, W. A. (2009). Preventing healthcare-associated aspergillus infections: Review of recent cdc/hicpac recommendations. *Med Mycol, 47*(suppl 1), S199–209. doi: 909318741

Weng, C., Levine, B. A. & Mun, S. K. (2009). Software architecture and engineering for patient records: Current and future. *Mil Med, 174*(suppl 5), 27–34.

Wengenack, N. L. & Binnicker, M. J. (2009). Fungal molecular diagnostics. *Clin Chest Med, 30*(2), 391–408, viii. doi: S0272–5231(09)00027–6

Wenzel, R., Del Favero, A., Kibbler, C., Rogers, T., Rotstein, C., Mauskopf, J., ... Marciniak, A. (2005). Economic evaluation of voriconazole com-

pared with conventional amphotericin b for the primary treatment of aspergillosis in immunocompromised patients. *J Antimicrob Chemother, 55*(3), 352–361. doi: dkh535

Wernitz, M. H., Keck, S., Swidsinski, S., Schulz, S. & Veit, S. K. (2005). Cost analysis of a hospital-wide selective screening programme for methicillin-resistant staphylococcus aureus (MRSA) carriers in the context of diagnosis related groups (DRG) payment. *Clin Microbiol Infect, 11*(6), 466–471. doi: CLM1153

Wilson, L. S., Reyes, C. M., Stolpman, M., Speckman, J., Allen, K. & Beney, J. (2002). The direct cost and incidence of systemic fungal infections. *Value Health, 5*(1), 26–34.

Wingard, J. R., Carter, S. L., Walsh, T. J., Kurtzberg, J., Small, T. N., Baden, L. R., … Marr, K. A. (2010). Randomized double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection (IFI) after allo hematopoietic cell transplantation (HCT). *Blood*. doi: blood-2010–02–268151

Wingard, J. R., Herbrecht, R., Mauskopf, J., Schlamm, H. T., Marciniak, A. & Roberts, C. S. (2007). Resource use and cost of treatment with voriconazole or conventional amphotericin b for invasive aspergillosis. *Transpl Infect Dis, 9*(3), 182–188. doi: TID210

Wingard, J. R., Ribaud, P., Schlamm, H. T. & Herbrecht, R. (2008). Changes in causes of death over time after treatment for invasive aspergillosis. *Cancer, 112*(10), 2309–2312. doi: 10.1002/cncr.23441

Winston, D. J., Bartoni, K., Territo, M. C. & Schiller, G. J. (2010). Efficacy, safety, and breakthrough infections associated with standard long-term

posaconazole antifungal prophylaxis in allogeneic stem-cell transplant recipients. *Biol Blood Marrow Transplant*. doi: S1083–8791(10)00198–9

Winthrop, K. L. & Chiller, T. (2009). Preventing and treating biologic-associated opportunistic infections. *Nat Rev Rheumatol, 5*(7), 405–410. doi: nrrheum.2009.105

Wisniewski, M. F., Kieszkowski, P., Zagorski, B. M., Trick, W. E., Sommers, M. & Weinstein, R. A. (2003). Development of a clinical data warehouse for hospital infection control. *J Am Med Inform Assoc, 10*(5), 454–462. doi: 10.1197/jamia.M1299

Worth, L. J., Blyth, C. C., Booth, D. L., Kong, D. C., Marriott, D., Cassumbhoy, M., … Wilkes, J. R. (2008). Optimizing antifungal drug dosing and monitoring to avoid toxicity and improve outcomes in patients with haematological disorders. *Intern Med J, 38*(6b), 521–537. doi: IMJ1726

Wright, M. O., Perencevich, E. N., Novak, C., Hebden, J. N., Standiford, H. C. & Harris, A. D. (2004). Preliminary assessment of an automated surveillance system for infection control. *Infect Control Hosp Epidemiol, 25*(4), 325–332. doi: ICHE7913

Xu, H., Anderson, K., Grann, V. R. & Friedman, C. (2004). Facilitating cancer research using natural language processing of pathology reports. *Stud Health Technol Inform, 107*(Pt 1), 565–572. doi: D040004468

Yokoe, D., Casper, C., Dubberke, E., Lee, G., Munoz, P., Palmore, T., … Donnelly, J. P. (2009). Infection prevention and control in health-care

facilities in which hematopoietic cell transplant recipients are treated. *Bone Marrow Transplant, 44*(8), 495–507.

Zaas, A. K., Liao, G., Chien, J. W., Weinberg, C., Shore, D., Giles, S. S., … Schwartz, D. A. (2008). Plasminogen alleles influence susceptibility to invasive aspergillosis. *PLoS Genet, 4*(6), e1000101. doi: 10.1371/journal.pgen.1000101

Zilberberg, M. D., Kollef, M. H., Arnold, H., Labelle, A., Micek, S. T., Kothari, S. & Shorr, A. F. (2010). Inappropriate empiric antifungal therapy for candidemia in the ICU and hospital resource utilization: A retrospective cohort study. *BMC Infect Dis, 10*, 150. doi: 1471–2334–10–150

Making sense of posaconazole therapeutic drug monitoring: a practical approach

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Purpose of review
Therapeutic drug monitoring (TDM) may be an important adjunct to optimizing the use of posaconazole.

Recent findings
Limited clinical studies suggest that an exposure–response relationship for posaconazole exists for the treatment of established invasive fungal diseases (IFDs), with emerging but less compelling data supporting its role in prophylaxis. The high prevalence of subtherapeutic levels has not translated to high prophylactic failure rates perhaps because of preferential uptake by effector cells important in the front-line defence against *Aspergillus* species. Nevertheless, TDM would appear prudent in patients deemed at highest risk for IFD with correction of patient modifiable factors and attention to drug administration important in optimizing drug exposure. TDM performed within a few days after commencing posaconazole may be predictive of steady-state levels, thus minimizing the delay in obtaining results in addition to identifying a subset of patients who may remain persistently subtherapeutic and also resistant to dose-escalation. Trough levels may be supplanted by untimed levels at steady state, thereby expanding the practicalities of TDM. We propose that TDM becomes one of the several measures in an integrated approach to IFD prevention combining screening of high-risk haematology patients for invasive aspergillosis at presentation, together with prospective surveillance for IFD, explicit criteria for switching to an alternative prophylactic agent and adherence to infection control practices.

Summary
Growing evidence supports the value of TDM for posaconazole to identify patients who may benefit from correction of modifiable factors impacting bioavailability, dosage adjustment or switch to an alternative agent.

Keywords
antifungal, fungal infections, posaconazole, therapeutic drug monitoring

INTRODUCTION

The increasing uptake of posaconazole as antifungal prophylaxis has been driven by the trial evidence demonstrating its efficacy in high-risk haematology–oncology patients [1,2], its favourable toxicity profile over the long term [3] and a recognition of the high health and economic burden of invasive fungal diseases (IFDs) [4–6] with a predominance of mold pathogens in the current era [4,5,7,8]. The clinical effectiveness of posaconazole appears to be similar to trial experience, with several centres reporting low IFD breakthrough rates ranging from 3 to 7.5% [9–12]. However, there have been isolated reports of higher than expected breakthrough rates of 13% [13,14], which may be a consequence of the intensive diagnostic strategies employing galactomannan [13] or the absence of adjuvant therapeutic drug monitoring (TDM) at these centres, or both.

An important question is the influence of the introduction of posaconazole prophylaxis on fungal epidemiology in patients with acute leukaemia undergoing intensive chemotherapy or allogeneic haematopoietic stem cell transplant (HSCT) recipients. Reports from single centres document a reduction in the incidence of invasive aspergillosis

KEY POINTS

- Posaconazole therapeutic drug monitoring provides an objective measure of drug exposure and may guide prescribing.

- Higher plasma posaconazole levels are associated with improved clinical response in patients with established invasive fungal diseases on salvage therapy.

- Predictors of low plasma posaconazole levels are well established, but identifying patients at high risk of prophylactic failure is more difficult and not necessarily contingent upon plasma levels.

- The prophylactic efficacy of posaconazole appears to be mediated by high concentrations in host cell membranes, thus explaining the observed discrepancy between low serum levels which are commonplace and prophylactic efficacy.

- Levels performed at day 3 may be predictive of steady-state concentrations.

- Untimed serum levels at steady state are a reliable alternative to the traditional premorning dose trough level, thus expanding the practicalities of TDM.

from 4.9 to 3.3% ($P = 0.04$) [12] and a shift to non-*Aspergillus* molds with the mucormycetes prominent [14], but these observations need to be corroborated by large-scale surveillance studies.

Unpredictable bioavailability associated with high interpatient (up to 68% in adult patients) and intrapatient variability [15–17] means that TDM is increasingly being used to guide prescribing, although its impact on patient outcomes is less well studied. Rather than an appraisal of pharmacokinetic and pharmacodynamic aspects of posaconazole which can be found elsewhere [18,19,20■], we will outline the controversies surrounding its use and contextualize the role of TDM in IFD treatment and prevention, cognisant that this is an evolving area of research.

HOW SHOULD POSACONAZOLE LEVELS BE INTERPRETED?

Limited clinical studies suggest that an exposure–response relationship for posaconazole exists [17,21,22]. Improved outcomes with progressively higher plasma concentrations in patients with established disease [21] have been observed, but therapeutic targets for either treatment or prophylaxis are undefined and hampered by the variability of parameters [e.g., area under curve (AUC), minimum inhibitory concentration (MIC) average, trough and maximum concentration] reported in

the literature with no clear pharmacokinetic/pharmacodynamic index predictive of efficacy in molds [18].

THRESHOLDS FOR CURATIVE INTENT

In patients with established infection, TDM is advisable based on the pharmacokinetic dataset of 67 patients from a salvage study of 107 patients with invasive aspergillosis, which showed improved outcomes with progressively higher maximum or average steady-state plasma concentrations of posaconazole [21]. Response rates were 24, 53, 53 and 75% corresponding to mean plasma levels of 134, 411, 719 and 1250 ng/ml, but the timing of TDM was not recorded. On the basis of this study, it seems reasonable for curative intent to aim for an average concentration at a steady state of at least 1 ng/ml, although in practice this may be difficult to achieve.

THRESHOLDS FOR PROPHYLAXIS

An early expert recommendation proposed a trough TDM target of 0.5 μg/ml for prophylaxis [23], which corresponded to the concentration required to suppress growth in 90% of most *Aspergillus* isolates *in vitro* (i.e. the MIC_{90} being 500 μg/ml for *Aspergillus fumigatus* and *Aspergillus flavus* but 1.0 μg/ml for *Aspergillus niger*) [24,25].

Given the wide therapeutic index of posaconazole, a threshold of 500 ng/ml may be regarded as conservative and 700 ng/ml has been proposed by Jang *et al.* [22] based on a post-hoc analysis of a subset of patients with pharmacokinetic data from the posaconazole registration trials (i.e. 252 of 600, 42% from [2] and 215 of 602, 36% from [1]). However, an exposure–response relationship for IFD prophylaxis is difficult to establish when studies are underpowered for this endpoint. In this analysis, patients were stratified according to quartile posaconazole average (Cavg) steady-state concentrations [22]. Higher quartiles were associated with lower clinical failure defined as a composite of receipt of empiric antifungal therapy, premature discontinuation, survival and proven/probable IFDs. By logistic regression, clinical failure was shown to be substantially higher, at greater than 25–35%, when Cavg concentrations were less than 700 ng/ml [22]. Importantly, in this analysis the major factor driving clinical failure was receipt of empiric antifungal therapy rather than IFD or death [26■]. Of note, the number of treatment emergent (i.e. during prophylaxis) IFDs was too low for meaningful analysis (11 of 14 IFDs were treatment emergent) [26■], and in three patients who developed IFDs

Cavg concentrations were greater than 1500 ng/ml [22]. Furthermore, in three patients plasma posaconazole concentrations were sampled 3–7 weeks prior to IFD onset [26•]. In light of these shortcomings, a cautious interpretation of this TDM target is warranted.

Again, separate post-hoc analyses of the pharmacokinetic dataset from the registration trials are conflicting. In patients with graft vs. host disease (GVHD), median Cavg concentrations at steady state were lower among five patients who developed proven or probable IFDs (611 ng/ml) compared to 241 patients without IFD (922 ng/ml) [17]. In contrast, among the higher risk acute myeloid leukaemia (AML)/myelodysplastic syndrome (MDS) patients receiving intensive chemotherapy, there was no difference in mean Cavg levels at steady state between the six patients who developed IFDs (457 ng/ml) compared with the 188 uninfected patients (586 ng/ml) [16]. Importantly, a survival benefit in the posaconazole arm of the latter study was observed despite 25% of patients having Cavg levels of less than 319 ng/ml [16].

In routine practice, subtherapeutic posaconazole levels, based on provisional targets of 500 or 700 ng/ml, are common, ranging from 44 to 76% [27–31], but because numbers of breakthrough IFDs are few, observational real-world studies also do not unequivocally validate the putative threshold concentrations described for prophylaxis. In a retrospective study of patients with mostly haematological malignancies, 44% (16 of 36) of patients receiving posaconazole prophylaxis had levels less than 500 ng/ml after 5 days therapy; the two patients who subsequently developed IFDs had levels of 310 and 190 ng/ml [28]. In a prospective study of 63 HSCT patients, despite 74% having levels less than 0.70 mg/l (median 0.44 mg/l) at steady state, only one patient, with a level of 0.11 mg/l, developed an IFD [30]. Similarly, a prospective study of 34 haematology patients, in whom 31 received posaconazole prophylactically, found that 71% of patients had levels less than 0.5 µg/ml; among three patients developing breakthrough IFDs steady-state levels were 0.28, less than 0.20 and 0.31 µg/ml prior to prophylaxis failure [31]. A retrospective evaluation of posaconazole steady-state concentrations in patients with chemotherapy-induced neutropenia for AML/MDS showed that 3 of 21 patients who developed breakthrough IFDs had levels less than 0.5 µg/ml, but overall most patients were subtherapeutic with 76.2 and 90.5% failing to reach the targets of 0.5 and 0.7 µg/ml, respectively [29]. It is noteworthy that in a small prospective study two patients developed breakthrough IFDs, despite attaining posaconazole levels of 900µg/l at IFD

onset [32]. It is unclear if TDM can further improve the prophylactic efficacy of posaconazole given the fact that even outside the controlled conditions of clinical trials, breakthrough IFDs remain uncommon despite subtherapeutic levels being commonplace.

CELLULAR CONCENTRATIONS OF POSACONAZOLE AND EFFICACY

There is much debate about the relevance of posaconazole levels in serum as an indicator of effective prophylaxis and therapy. Using a murine model of inhalational aspergillosis, Howard *et al.* [33] showed that a 24-h serum AUC:MIC target associated with a 90% maximal antifungal effect (as measured by galactomannan kinetics) was 440, which is unfeasible in practice because 800 mg/day is estimated to deliver an AUC:MIC of only 100–150 in patients. However, whether the AUC:MIC is the appropriate pharmacokinetic/pharmacodynamic parameter for *Aspergillus* and *Candida* species is contentious as underlined by a proof-of-principle study showing higher than expected antifungal activity against *Candida* spp. of unbound drug at concentrations far below the MIC, suggesting flux from the protein-bound fraction to the fungal target [34].

The prophylactic efficacy of posaconazole may be explained by preferential penetration of drug from serum into cells important in the front-line defence against *Aspergillus* species. Concentrations in alveolar cells and monocytes are 22–67 times plasma concentrations [35–37], which is above the MIC_{90} of *Aspergillus* for the entire 12-h dosing interval. In addition, a recent in-vitro study [38•] demonstrated inhibition of fungal growth in pulmonary epithelial cells and macrophages upon exposure of drug-exposed cells to *Aspergillus* conidia after a relatively brief exposure (4 h) to posaconazole, which persisted for up to 48 h. Resistance to infection occurred at cellular concentrations above 80–100 µg/ml, which is the steady-state level in alveolar cells isolated from healthy volunteers receiving 400 mg b.d. of posaconazole [35].

WHAT ARE THE INDICATIONS FOR POSACONAZOLE THERAPEUTIC DRUG MONITORING?

Patients with established infection should have TDM, while for prophylaxis our recommendation includes either those patients at highest risk for IFD or if concerns regarding bioavailability prevail as summarized in the list below.

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TDM is recommended for the following indications:

(1) treatment of established fungal infection;
(2) impaired gastrointestinal absorption, for example, presence of diarrhoea, mucositis, poor oral intake, vomiting;
(3) compliance concerns;
(4) coadministration of drugs known to either impair absorption or increase clearance, for example, proton pump inhibitors;
(5) patients at highest risk for development of fungal infection, for example, relapsed or refractory disease, anticipated duration of neutropenia greater than 14 days.

CAN POSACONAZOLE THERAPEUTIC DRUG MONITORING BE PERFORMED PRIOR TO STEADY STATE?

TDM should ideally be performed at steady state; however, this entails a delay of at least 7 days in addition to the turn-around time for results. Of interest, recent clinical studies [39■,40] corroborate a pharmacokinetic computer simulation suggesting that levels at day 2 may be predictive of steady-state concentrations [41]. Cornely *et al.* [39■] in a study of 49 AML patients, many of whom had chemotherapy-related gastrointestinal disease, demonstrated that levels at day 3 were predictive of levels at day 8 (R^2 0.64), with 22 of the 30 patients (73%) who achieved a mean level of 250 ng/ml at day 3 reaching a threshold of 500 ng/ml by day 8. Similarly, a small retrospective study of 16 patients undergoing intensive chemotherapy for acute leukaemia and receiving posaconazole 200 mg t.d.s., administered with a series of adjuvant interventions described elsewhere [42■], showed that the majority (14 of 16) experienced a doubling or near doubling ($\geq$150%) of serum levels when levels after the fourth dose on day 2 were compared with trough levels on day 7 [40]. These findings suggest that for a proportion of patients, day 3 measurements may be predictive of steady-state levels, thereby potentially allowing earlier dose modification or interventions to optimize drug exposure.

ARE POSACONAZOLE TROUGH LEVELS NECESSARY?

Posaconazole has a prolonged half-life of 35 h [18,37] and its frequent dosing results in a relatively flat concentration–time profile at steady state [39■] which may be exploited for TDM purposes. Heinz *et al.* [43] in a pharmacokinetic study of 25 haematology patients showed a less than 20% variation in levels between a trough and 4 h after dose in 60% of patients despite intentionally selecting a dosing regimen (400 mg b.d.) associated with the highest daily pharmacokinetic variability; corresponding mean levels at trough, 4 h and 8 h after dose were 645, 687 and 616 ng/ml, respectively. These findings indicate that at steady state, untimed levels may be a reliable alternative to the trough level which is typically collected prior to the morning dose, thus enhancing the practicalities of TDM especially when there is a pressing need to optimize drug exposure in light of either breakthrough IFD or absorption concerns.

WHAT TO DO WHEN POSACONAZOLE LEVELS ARE 'SUBTHERAPEUTIC'

Addressing modifiable patient factors and optimizing drug delivery (summarized in Table 1) are the initial steps in safeguarding the effectiveness of posaconazole. Posaconazole should be coadministered with either a high-fat meal, nutritional supplement or nonfat meal, but if that is not possible then at the minimum with an acidic beverage. Avoidance of proton pump inhibitors and histamine antagonists in addition to drugs which increase posaconazole drug clearance is advisable. Dose fractionation, for example, 200 mg q.i.d. rather than 400 mg b.d., is of greatest benefit in fasting patients, but in fed patients 400 mg b.d. with food is associated with a higher exposure (AUC), lower variability than 200 mg q.i.d. [46,47] and compliance benefits. One centre reported successful attainment of therapeutic levels at steady state in five haematology–oncology patients following introduction of a 'posaconazole bundle' aimed at maximizing absorption with a series of strictly enforced interventions [42■].

IS INCREASING THE DAILY DOSE OF POSACONAZOLE EFFECTIVE?

Available data would suggest that dose-escalation in an attempt to increase posaconazole drug exposure is unlikely to be effective. Jang *et al.* [22] recommended dose-escalation beyond the saturable limit of 800 mg/day [50], proposing 1200 mg/day if levels were less than 350 ng/ml on day 2 or less than 700 ng/ml on day 7 [22]. Cornely *et al.* [39■] recently tested this hypothesis in a cohort of AML patients with gastrointestinal compromise randomized to three regimens (200 mg t.d.s., 400 mg b.d. and 400 mg t.d.s.) after receiving standard prophylactic doses (200 mg t.d.s.) for 8 days. They identified a subset of patients with persistently low levels who were resistant to dose-escalation. Among the 12 patients who did not achieve a mean plasma concentration of 250 ng/ml on day 8, 75% (9 of 12) did not attain the target of 500 ng/ml at day 15

Table 1. Safeguarding posaconazole with attention to modifiable patient factors and drug delivery

Recommendation	Comment	References
Co-administer posaconazole during or within 10–20 min of either:		
1. High-fat meal if tolerated or	Four-fold increase in exposure relative to fasting state with a meal containing 841 calories comprising 52% fat	[44]
2. Nutritional supplement (e.g. Boost Plus-14g fat) if solids poorly tolerated or	2.6-fold increase in exposure relative to fasting state	[45]
3. Nonfat meal or	Approximately 2.6-fold increase in exposure relative to fasting state	[44]
4. Acidic beverage (e.g. ginger ale 12 oz) if solids poorly tolerated	70% increase in exposure relative to fasting state	[46]
If daily dose is 800 mg/day, choice of regimen (400 mg b.d. or 200 q.i.d.) is largely dependent on prandial status:	Effect of food most marked only with 400 mg b.d. rather than 200 mg q.i.d. dosing.	[46–48]
1. In fed state, 400 mg b.d. with high-fat meal	Higher exposure and lower variability than 200 mg q.i.d. in fasting state; better compliance than q.i.d. dosing but dose fractionation preferred in fasting state	
2. If fasting conditions, then 200 mg q.i.d. preferred		
Avoidance of proton pump inhibitors in all patients in the absence of a specific indication	Decreases exposure by 32%; antacids potential alternatives	[32,46,49]
Avoidance of drugs known to increase posaconazole clearance or impair absorption, for example, cimetidine, phenytoin, rifamycin derivatives	–	[18]

following dose-escalation to 800 or 1200 mg/day. Consistent with these findings is the observation that no increase in plasma concentrations was seen in healthy volunteers or neutropenic patients administered 1200 mg/day compared to 800 mg/day [50,51]. Shields *et al.* [52] describe dose-escalation in 7 of 17 heart or lung transplant recipients from 800 to 1200 mg daily as being largely ineffective with only 2 of 7 patients achieving trough levels greater than 0.5 μg/ml, the exception being three patients subsequently given 1600 mg/day who achieved levels of at least 1 μg/ml but at the cost of dose-limiting gastrointestinal and hepatic toxicity.

AREAS OF CONTENTION

In clinical trials, posaconazole at prophylactic doses and without TDM was associated with significant reductions in proven/probable invasive aspergillosis, making the need for TDM for this indication questionable. Furthermore, efficacy was demonstrated despite the presence of incipient invasive aspergillosis at trial recruitment in a subset of patients as evidenced by a positive serum galactomannan which was returned in 4% each of posaconazole (12 of 304) and comparator groups (13 of 298) with AML/MDS [1] and in 7% (21 of 301) and 10% (10 of 299) of posaconazole and fluconazole patients, respectively (Merck Sharp Dohme data on file) with severe GVHD [2]. A recent observational

study from France reported the presence of invasive aspergillosis at admission in 11% of hospitalized haematology–oncology patients of whom 76% had AML, but this is likely an underestimate of the true incidence as investigation was clinician initiated rather than protocol driven [12]. Replicating or improving trial outcomes in routine practice is dependent on several measures, among them, attention to drug delivery and perhaps, although unproven at this stage, consideration towards screening for invasive aspergillosis at initial presentation in order to identify those patients requiring treatment rather than prophylaxis.

There is no standard approach for the selection of an alternative when discontinuation of posaconazole is contemplated. As it is an effective prophylactic agent, ceasing posaconazole is not a trivial issue and we believe that criteria for switch should be explicit and endorsed in unit protocols. TDM, rather than bedside assessment alone (e.g. frequency of diarrhoea/vomiting or oral intake), provides an objective measure of absorption which may inform the decision to switch provided it is available in a timely manner. Difficulties arise for the subset of asymptomatic patients at highest risk for IFD with persistently low levels despite optimization of drug delivery. In this group, options include performing enhanced surveillance for IFD using regular biomarkers, for example, galactomannan, *Aspergillus* PCR, beta-ᴅ-glucan and high-resolution computed

tomography screening; switching to alternative antifungal prophylaxis, which in our setting is typically intermittent liposomal amphotericin [53] or intravenous voriconazole; or posaconazole dose-escalation, with or without fractionation, to 800 mg/day, accepting that this may not be effective in increasing serum levels.

CONCLUSION

Posaconazole TDM does not unequivocally stratify patients into high and low risk for prophylactic or therapeutic failure, but it does provide an objective measure of drug exposure and the subsequent opportunity to individualize therapy while also augmenting clinician confidence in using the drug. The solid tablet and capsule formulations will address some of the shortcomings of the oral suspension given their higher bioavailability and less variability [54], but until they become available optimizing the use of posaconazole entails attention to drug delivery and modifiable patient factors. As important, however, is adherence to infection control standards [55] and prospective surveillance for IFDs in order to evaluate the effectiveness of preventive interventions such as antifungal prophylaxis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
■ of special interest
■■ of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007; 356:348–359.
2. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007; 356:335–347.
3. Raad II, Graybill JR, Bustamante AB, et al. Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. Clin Infect Dis 2006; 42:1726–1734.
4. Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis 2010; 50:1091–1100.
5. Pagano L, Caira M, Candoni A, et al. Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 Registry Study. Haematologica 2010; 95:644–650.
6. Ananda-Rajah MR, Cheng A, Morrissey CO, et al. Attributable hospital cost and antifungal treatment of invasive fungal diseases in high-risk hematology patients: an economic modeling approach. Antimicrob Agents Chemother 2011; 55:1953–1960.

7. Park BJ, Pappas PG, Wannemuehler KA, et al. Invasive non-Aspergillus mold infections in transplant recipients, United States, 2001–2006. Emerg Infect Dis 2011; 17:1855–1864.
8. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica 2006; 91:1068–1075.
9. Ananda-Rajah MR, Grigg A, Downey MT, et al. Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period. Haematologica 2012; 97:459–463.
10. Winston DJ, Bartoni K, Territo MC, Schiller GJ. Efficacy, safety and breakthrough infections associated with standard long-term posaconazole antifungal prophylaxis in allogeneic stem-cell transplant recipients. Biol Blood Marrow Transplant 2011; 17:507–515.
11. Vehreschild JJ, Ruping MJ, Wisplinghoff H, et al. Clinical effectiveness of posaconazole prophylaxis in patients with acute myelogenous leukaemia (AML): a 6 year experience of the Cologne AML cohort. J Antimicrob Chemother 2010; 65:1466–1471.
12. Nicolle MC, Benet T, Thiebaut A, et al. Invasive aspergillosis in patients with hematologic malignancies: incidence and description of 127 cases enrolled in a single institution prospective survey from 2004 to 2009. Haematologica 2011; 96:1685–1691.
13. Girmenia C, Frustaci AM, Gentile G, et al. Posaconazole prophylaxis during front-line chemotherapy of acute myeloid leukemia: a single-center, real-life experience. Haematologica 2012; 97:560–567.
14. Auberger J, Lass-Florl C, Aigner M, et al. Invasive fungal breakthrough infections, fungal colonization and emergence of resistant strains in high-risk patients receiving antifungal prophylaxis with posaconazole: real-life data from a single-centre institutional retrospective observational study. J Antimicrob Chemother 2012; 67:2268–2273.
15. Gubbins PO, Krishna G, Sansone-Parsons A, et al. Pharmacokinetics and safety of oral posaconazole in neutropenic stem cell transplant recipients. Antimicrob Agents Chemother 2006; 50:1993–1999.
16. Krishna G, AbuTarif M, Xuan F, et al. Pharmacokinetics of oral posaconazole in neutropenic patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. Pharmacotherapy 2008; 28:1223–1232.
17. Krishna G, Martinho M, Chandrasekar P, et al. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. Pharmacotherapy 2007; 27:1627–1636.
18. Li Y, Theuretzbacher U, Clancy CJ, et al. Pharmacokinetic/pharmacodynamic profile of posaconazole. Clin Pharmacokinet 2010; 49:379–396.
19. Lewis RE. Pharmacokinetic–pharmacodynamic optimization of triazole antifungal therapy. Curr Opin Infect Dis 2011; 24 (Suppl. 2):S14–S29.
20. Dolton MJ, Ray JE, Marriott D, McLachlan AJ. Posaconazole exposure–
■ response relationship: evaluating the utility of therapeutic drug monitoring. Antimicrob Agents Chemother 2012; 56:2806–2813.
Update on the studies for and against an exposure–response relationship for posaconazole.
21. Walsh TJ, Raad I, Patterson TF, Chandrasekar P, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis 2007; 44:2–12.
22. Jang SH, Colangelo PM, Gobburu JV. Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma. Clin Pharmacol Ther 2010; 88:115–119.
23. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother 2009; 53:24–34.
24. Pfaller MA, Messer SA, Hollis RJ, Jones RN. Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of Aspergillus spp. and other filamentous fungi: report from SENTRY Antimicrobial Surveillance Program, 2000. Antimicrob Agents Chemother 2002; 46:1032–1037.
25. Sabatelli F, Patel R, Mann PA, et al. In vitro activities of posaconazole, fluconazole, itraconazole, voriconazole, and amphotericin B against a large collection of clinically important molds and yeasts. Antimicrob Agents Chemother 2006; 50:2009–2015.
26. Cornely OA, Ullmann AJ. Lack of evidence for exposure-response relationship
■ in the use of posaconazole as prophylaxis against invasive fungal infections. Clin Pharmacol Ther 2011; 89:351–352.
This response highlights the shortcomings of Jang et al.'s analysis [22] supporting a threshold for prophylaxis.
27. Thompson GR 3rd, Rinaldi MG, Pennick G, et al. Posaconazole therapeutic drug monitoring: a reference laboratory experience. Antimicrob Agents Chemother 2009; 53:2223–2224.
28. Lebeaux D, Lanternier F, Elie C, et al. Therapeutic drug monitoring of posaconazole: a monocentric study with 54 adults. Antimicrob Agents Chemother 2009; 53:5224–5229.
29. Bryant AM, Slain D, Cumpston A, Craig M. A postmarketing evaluation of posaconazole plasma concentrations in neutropenic patients with haematological malignancy receiving posaconazole prophylaxis. Int J Antimicrob Agents 2011; 37:266–269.

30. Eiden C, Meniane JC, Peyriere H, *et al.* Therapeutic drug monitoring of posaconazole in hematology adults under posaconazole prophylaxis: influence of food intake. Eur J Clin Microbiol Infect Dis 2012; 31:161–167.

31. Hoenigl M, Raggam RB, Salzer HJ, *et al.* Posaconazole plasma concentrations and invasive mould infections in patients with haematological malignancies. Int J Antimicrob Agents 2012; 39:510–513.

32. Neubauer WC, Engelhardt M, Konig A, *et al.* Therapeutic drug monitoring of posaconazole in hematology patients: experience with a new high-performance liquid chromatography-based method. Antimicrob Agents Chemother 2010; 54:4029–4032.

33. Howard SJ, Lestner JM, Sharp A, *et al.* Pharmacokinetics and pharmacodynamics of posaconazole for invasive pulmonary aspergillosis: clinical implications for antifungal therapy. J Infect Dis 2011; 203:1324–1332.

34. Lignell A, Lowdin E, Cars O, Chryssanthou E, *et al.* Posaconazole in human serum: a greater pharmacodynamic effect than predicted by the nonprotein-bound serum concentration. Antimicrob Agents Chemother 2011; 55:3099–3104.

35. Conte JE Jr, Golden JA, Krishna G, *et al.* Intrapulmonary pharmacokinetics and pharmacodynamics of posaconazole at steady state in healthy subjects. Antimicrob Agents Chemother 2009; 53:703–707.

36. Farowski F, Cornely OA, Vehreschild JJ, *et al.* Intracellular concentrations of posaconazole in different compartments of peripheral blood. Antimicrob Agents Chemother 2010; 54:2928–2931.

37. Conte JE Jr, DeVoe C, Little E, Golden JA. Steady-state intrapulmonary pharmacokinetics and pharmacodynamics of posaconazole in lung transplant recipients. Antimicrob Agents Chemother 2010; 54:3609–3613.

38. Campoli P, Al Abdallah Q, Robitaille R, *et al.* Concentration of antifungal
■ agents within host cell membranes: a new paradigm governing the efficacy of prophylaxis. Antimicrob Agents Chemother 2011; 55:5732–5739.
An experimental study demonstrating how high cellular levels of posaconazole account for its cytoprotective effect.

39. Cornely OA, Helfgott D, Langston A, *et al.* Pharmacokinetics of different
■ dosing strategies of oral posaconazole in patients with compromised gastrointestinal function and who are at high risk for invasive fungal infection. Antimicrob Agents Chemother 2012; 56:2652–2658.
A subset of patients may remain 'subtherapeutic' irrespective of dose-escalation. In the remaining patients, day 3 levels are predictive of levels at steady state.

40. Green MR, Woolery JE. Posaconazole serum level on day 2 predicts steady state posaconazole serum level. Ther Drug Monit 2012; 34:118–119.

41. Noxafil_ (Posaconazole) application no. 022003. Clinical Pharmacology and Biopharmaceutics Review(s). http://www.accessdata.fda.gov/drug. [Accessed 26 June 2012]

42. Green MR, Woolery JE. Optimising absorption of posaconazole. Mycoses
■ 2011; 54:e775–e779.
Optimizing posaconazole administration using a care-bundle approach.

43. Heinz WJ, Zirkel J, Kuhn A, *et al.* Relevance of timing for the determination of posaconazole plasma concentrations. Antimicrob Agents Chemother 2011; 55:3621–3623.

44. Courtney R, Wexler D, Radwanski E, *et al.* Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. Br J Clin Pharmacol 2004; 57:218–222.

45. Sansone-Parsons A, Krishna G, Calzetta A, *et al.* Effect of a nutritional supplement on posaconazole pharmacokinetics following oral administration to healthy volunteers. Antimicrob Agents Chemother 2006; 50:1881–1883.

46. Krishna G, Moton A, Ma L, *et al.* Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. Antimicrob Agents Chemother 2009; 53:958–966.

47. Pea F, Furlanut M, Viale P. What should be the first-choice strategy to maximize posaconazole exposure in daily clinical practice? Antimicrob Agents Chemother 2009; 53:3608–3609; author reply 609–610.

48. Ezzet F, Wexler D, Courtney R, *et al.* Oral bioavailability of posaconazole in fasted healthy subjects: comparison between three regimens and basis for clinical dosage recommendations. Clin Pharmacokinet 2005; 44:211–220.

49. Alffenaar JW, van Assen S, van der Werf TS, *et al.* Omeprazole significantly reduces posaconazole serum trough level. Clin Infect Dis 2009; 48:839.

50. Courtney R, Pai S, Laughlin M, *et al.* Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. Antimicrob Agents Chemother 2003; 47:2788–2795.

51. Ullmann AJ, Cornely OA, Burchardt A, *et al.* Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. Antimicrob Agents Chemother 2006; 50:658–666.

52. Shields RK, Clancy CJ, Vadnerkar A, *et al.* Posaconazole serum concentrations among cardiothoracic transplant recipients: factors impacting trough levels and correlation with clinical response to therapy. Antimicrob Agents Chemother 2010; 55:1308–1311.

53. Ananda-Rajah M, Grigg AP, Thursky K, *et al.* Prophylactic effectiveness & safety of intermittent liposomal amphotericin in high risk haematological patients [abstract]. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy, 17–20 September 2011, Chicago. American Society for Microbiology; 2011; abstr. M-280.

54. Krishna G, Ma L, Martinho M, O'Mara E. A single dose phase I study to evaluate the pharmacokinetics of posaconazole new tablet and capsule formulations relative to oral suspension. Antimicrob Agents Chemother 2012; 56:4196–4201.

55. Weber DJ, Peppercorn A, Miller MB, *et al.* Preventing healthcare-associated Aspergillus infections: review of recent CDC/HICPAC recommendations. Med Mycol 2009; 47 (Suppl. 1):S199–S209.

The case for antifungal stewardship

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Purpose of review
Antimicrobial stewardship (AMS) has overwhelmingly focussed on antibiotics while antifungal agents have been largely neglected despite the few published audits of antifungal drug use demonstrating clear deficiencies in prescribing behaviour. In this review, we outline not only the elements of antifungal stewardship (AFS) in common with AMS but also features specific to antifungal drugs, combined with insights from our experience in AFS.

Recent findings
Invasive fungal diseases (IFDs) have a lower institutional incidence relative to infections caused by multiresistant bacteria, but their health and economic burden are substantial. Pharmacy costs inclusive of antifungal agents are a major determinant of IFD-attributable hospital cost. High drug costs and the toxicities of antifungal agents are the principal rationale for AFS while antifungal resistance is an emerging but less prevalent issue. The high mortality/morbidity associated with IFDs, including adverse impact on curative chemotherapy, combined with suboptimal diagnostic tools, has driven the overuse of antifungal drugs. De-escalation of empiric therapy is one of the most challenging aspects of AFS to implement. Nonculture-based tests may enhance AFS, but refinement of both target populations and clinical pathways incorporating their use is required. Performance indicators including structural, process and outcome measures are integral for demonstrating the value of AFS programmes.

Summary
Practice guidelines adapted to the local context are the cornerstone of AFS. Local epidemiology informs the choice of antifungal agents for the prevention and management of IFDs, underscoring the need for surveillance. Adherence to minimum standards of prescribing ensures that clinical outcomes are optimized and drug toxicities minimized, thus meeting healthcare quality and safety goals.

Keywords
antifungal agents, antifungal stewardship, fungal infections

INTRODUCTION

Antimicrobial stewardship (AMS) has largely focussed on the judicious use of antibiotics while antifungal agents have received less attention. However, it is likely that the practice of antifungal stewardship (AFS) has been commonplace at many institutions for years, principally because of the high cost of antifungal drugs and the specialized patients to whom they apply. Antifungal agents are usually on restricted formularies in hospitals, requiring the input of experts such as infectious diseases physicians and pharmacists who are knowledgeable of local fungal epidemiology, susceptibility patterns and current clinical literature to guide prescribing. AMS has been defined as the 'ongoing effort by a healthcare institution to optimise antimicrobial use in order to improve patient outcomes, ensure cost effective therapy and reduce adverse sequelae' [1]. Inappropriate antibiotic use is associated with collateral damage, namely the emergence of bacterial resistance, adding to the burden of hospital acquired infection, patient morbidity, mortality and cost [2,3]. As a result, there has been a call to arms in recent years promoting the institution and strengthening of hospital AMS programmes [4]. However, although these programmes broadly include antifungal agents, data on optimizing rather than auditing their use in clinical settings is scarce [5].

Similar to the diminishing pipeline of new antibiotic choices in the face of escalating global

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KEY POINTS

- The high costs and high contribution of antifungal agents to the management of invasive fungal diseases (IFDs) along with their recognized toxicities is the principal justification for antifungal stewardship (AFS).

- Antifungal drug resistance is an emerging but likely under-recognized problem, which is of concern given the lack of new antifungal drugs in development.

- Practice guidelines adapted to the local context following collaboration with institutional leaders are the cornerstone of AFS and should be available at the point of care with linkage to expert prescribers.

- Local fungal epidemiology informs the choice of IFD prevention and management measures, underscoring the importance of surveillance.

- Practice guidelines support prescribing but underappreciate the challenges of de-escalation, especially in the empiric context.

resistance, novel antifungal agents are few [6] and the range of fungal pathogens along with the population at risk continues to expand. However, although bacterial resistance has been the impetus behind the initiation and strengthening of antibiotic stewardship programmes in hospitals, fungal resistance is less of a problem being confined to certain contexts. Triazole resistance in *Aspergillus fumigatus* has been described in both azole-naive [7–9] and azole-exposed patients [7,8,10] mostly in patients with cavitatory disease [10], but also in patients with allergic aspergillosis and cancer patients with invasive aspergillosis [7]. Alarmingly, high rates have been reported in the Netherlands, with 6–12.8% of clinical isolates harbouring resistance which has been associated with clinical failure of azole therapy [10–13]. Resistance appears to be geographically restricted to some settings within Europe but not others [9]. Extensive use of azoles in agriculture is responsible [11], but the problem is likely under-recognized because of a paucity of field studies [14]. Amongst *Candida* species, the issue of resistance largely applies to fluconazole and to a lesser extent the echinocandins [15]. Longitudinal data from laboratory surveillance shows that fluconazole resistance amongst *Candida albicans* and *Candida parasilopsis* is uncommon, but *Candida glabrata* resistance may exceed 15% [16]. Breakthrough candidaemia on caspofungin therapy has been documented in 2.4% of patients, being typically associated with prolonged therapy when source control of sepsis was not achieved [15].

PRINCIPLES OF STEWARDSHIP

Optimizing the use of currently available antifungal agents is principally driven by their high cost and attendant toxicities. We will focus on haematology–oncology patients because they are high users of antifungal agents [17] and have an established record of practice guidelines, but the principles discussed are applicable to other high users including intensive care unit (ICU) and solid-organ transplant (SOT) recipients. We will highlight some of the shared tenets with antibiotic stewardship and features peculiar to antifungal agents, while providing practical examples from our own experience in over 10 years of guideline development [18▪▪,19], implementation and computerized decision-support systems (CDSSs) [20,21] along with engagement with end-users and institutional stakeholders.

THE HEALTH AND ECONOMIC BURDEN OF INVASIVE FUNGAL DISEASES

Patients with acute myeloid leukaemia (AML) are at high risk for invasive fungal diseases (IFDs), particularly following remission-induction chemotherapy or treatment for refractory or relapsed disease [22], with historical rates of IFD complicating high-dose cytarabine-based chemotherapy reaching 36% [23]. In recent clinical trials, IFD incidence rates in patients with AML/myelodysplastic syndrome (MDS) were higher than in allo-haematological stem cell transplant (HSCT) recipients [24–27], a finding consistent with earlier (1999–2003) Italian registry data showing IFD incidences of 16.9 and 8.2% amongst AML and allo-HSCT patients, respectively [28].

The low incidence of IFD (3.2%) recently reported by the TRANSNET consortium amongst HSCT recipients 12 months from transplantation is due to 60% of the denominator comprising autologous recipients who had the lowest incidence (1.2%) of IFDs overall [29]. In fact, amongst HLA-mismatched related and unrelated allo-HSCT recipients, IFD incidence rates were 8.1 and 7.7%, respectively, with wide inter-institutional variation noted ranging from 3.1 to 20.6% amongst six sites with a high case-load [29]. Marked institutional variation in IFD incidence is likely due to differences in case-mix, treatment practices, infection control and possibly geoclimatic factors [30]. Mold infections predominated with invasive aspergillosis and zygomycoses accounting for 46 and 8%, respectively, followed by invasive candidiasis (28%) [29].

Although improvements in the short-term survival of invasive aspergillosis are encouraging, crude mortality remains considerable at 33–47% [22,31–33], and for patients surviving IFD the

prospect of delays or modifications to curative chemotherapy may compromise long-term prognosis [23,34]. For HSCT recipients invasive candidiasis is not a benign disease, with a 12-month mortality similar to invasive aspergillosis of 67 and 75%, respectively [29].

Studies using large administrative datasets have reported that antifungal agents contribute 7–15% of total treatment costs of patients with IFDs [35–37], but this may be an underestimate. A recent single-centre study of haematology–oncology patients, using patient-level data and activity-based costing methods (a highly regarded costing tool [38]), showed that pharmacy costs accounted for 64% of the difference in mean hospital cost per patient [39""]. Antifungal agents accounted for 27% of the overall difference ($P < 0.001$) with no significant differences seen in ward costs between infected and uninfected controls (27%, $P = 0.091$) [39""]. The proportion of pharmacy (60%) to ward (31%) costs persisted at 12 weeks follow-up, suggesting that the finding was robust [39""].

Pharmacoeconomic analyses are best informed by estimates of attributable cost. However, disentangling the effect of underlying illness in complex patients with cancer is challenging. Cost determination methods for IFDs have included gross costs [40,41], expert opinion [42] and clinical trial data [43,44]; but studies reporting attributable cost are few [35,39"",45–47], and those using patient-level data are even rarer [39"",47]. Attributable mean invasive aspergillosis-associated medical cost in patients with AML/MDS has been estimated to be €15 280 [47]; but given the skewed nature of health outcomes, reporting the mean may potentially overstate costs because of the effect of outlier patients. Median costs, in contrast, represent a conservative estimate which in one study resulted in an IFD attributable hospital cost of AU$30 957 (95% confidence interval, CI AU$2368 to AU$59 546; $P = 0.034$), approximating at purchasing power parity US$21 203 (95% CI US$1622 to US$40 784) and €15 788 (95% CI €1208 to €30 368) [39""]. Costly antifungal treatment [C-AT, defined as liposomal amphotericin B, voriconazole, posaconazole, caspofungin expressed as defined daily doses (DDDs) per IFD hospitalization] was described as an alternative resource metric which may be more generalizable than cost alone, being independent of country and inflation. IFD was associated with an excess of 17 DDDs of C-AT (95% CI 15–19 DDDs; $P < 0.001$) per case patient [39""].

It is the high mortality and morbidity of IFDs coupled with diagnostic uncertainty where culture positive rates in patients with confirmed invasive aspergillosis are only 30–50% [48], which drives the overuse of antifungal agents.

ESSENTIAL ELEMENTS OF AN ANTIFUNGAL STEWARDSHIP PROGRAMME

These are well described for AMS [4,18""] but are applicable to AFS also.

Implementation of antifungal guidelines

Practice guidelines are the starting point on the AFS roadmap. Ideally, guidelines should be available at the point of care, whether embedded in CDSS or hospital intranet, and linked to access to expert prescribers such as infectious diseases physicians or clinical pharmacists. Integration into the decision-making process and work-flow of prescribers, who are typically busy junior staff, is likely to enhance their uptake. Clinical care pathways for the management of IFDs have recently been proposed as a means of integrating clinical guidelines with diagnostic protocols in a feasible way for multidisciplinary teams to deliver [49""].

Guidelines adapted to the local context

The many national and international guidelines for the management of patients with IFDs [19,50–53,54""] are designed to assist clinicians in providing appropriate evidence-based care. Although little is known about their impact on provider behaviour, it is clear that adaptation to local circumstances with input from senior clinicians is likely to increase acceptance rates [55]. We accommodated deviations from national guidelines [19] with, for example, the use of intermittent liposomal amphotericin prophylaxis in patients intolerant of azole drugs [56], thereby increasing the acceptance of guidelines by our haematologists, their sense of ownership of the document and satisfaction with process.

Few studies have evaluated the translation of guidelines into practice. An evaluation of 136 cases of invasive aspergillosis from an Italian registry (2004–2007) found poor compliance with Infectious Diseases Society of America (IDSA) and European Conference on Infections in Leukaemia (ECIL) recommendations for first-line therapy, being 55 and 28%, respectively [57]. Noncompliance with guidelines did not impact mortality but guideline adherence was associated with improved short-term clinical outcome. The authors concluded that guidelines are often inapplicable to daily practice, perhaps because patients with multiple comorbidities and organ dysfunction are excluded from the clinical

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trials which ultimately inform practice guidelines. A cautious interpretation of this study is warranted as this was a post hoc evaluation, used guidelines which were either outdated (IDSA 2000) or just published (ECIL 2007), examined appropriateness which is one of several components of prescribing quality and used a controversial endpoint, namely attributable rather than overall mortality assessed at 120 days rather than 6 weeks which may be regarded as a more accurate time point for IFD-related outcomes [58].

Given that empiric antifungal therapy (EAFT) accounts for the majority of inpatient antifungal prescription ranging from 62 to 72% [22,59] and recent recommendations advocating either voriconazole [54**] or posaconazole prophylaxis [52,54**] in high-risk haematology patients, these are the areas which at a minimum should be addressed by institutional guidelines.

Preprescription approval with postprescription review and feedback

Restrictive interventions such as formulary restriction and preprescription approval are more than three times more influential than persuasive interventions, such as education, on prescribing behaviour [60]. Our web-based approval system allows doctors to obtain approval for standard (e.g. guideline concordant) and nonstandard or guideline discordant indications [21]. All approvals are reviewed by the infectious diseases service within 24–48 h, but dispensing is not withheld pending infectious diseases review because it is impractical in a busy clinical service and risks unintended patient harm such as delaying the initiation of potentially life-saving therapy. Postprescription review and feedback is a core activity of AMS [4,18**], whereby deficiencies in prescribing practice are identified by the AFS team and prescribers educated. In our setting, both methods are employed in a multifaceted approach using high visibility of AFS teams on regular rounds to build trust and encourage discussion with prescribers.

ANTIFUNGAL THERAPY: OPPORTUNITIES FOR IMPROVEMENT

Drug de-escalation and limiting empiric antifungal therapy are particular areas which require active guidance from AFS teams.

The challenges of de-escalation

Therapeutic streamlining is recommended by the IDSA in the management of candidiasis and invasive aspergillosis [51,52], but current guidelines under-appreciate the challenges of de-escalation in the empiric context [61]. Even when susceptibility results are available to guide therapy, clinicians are often reluctant to de-escalate therapy when a seriously ill patient is improving on broad-spectrum treatment. A recent study of patients with candidaemia reported that less than 40% of echinocandin-treated patients with fluconazole-susceptible isolates were de-escalated to fluconazole and only 50% of patients with less severe disease or *C. albicans* underwent de-escalation [62]. The solution, therefore, lies in building clinical confidence around de-escalation, but this is hampered by the suboptimal diagnosis of IFDs using current tests.

Restraining empiric antifungal use relies on improved diagnostics

A diagnostic-driven strategy or preemptive approach incorporating nonculture-based tests (NCBTs) such as galactomannan and *Aspergillus* PCR along with computed tomography (CT) aims to curtail unnecessary antifungal drug use and has best been studied in neutropenic patients. Most studies to date have shown a reduction in antifungal use [63–66], but the practice has attracted an experimental grading in the recent ECIL-3 guidelines [54**] because non-inferiority of the preemptive approach in a subgroup of leukaemic patients at very high risk of IFD (i.e. undergoing remission-induction chemotherapy) could not be demonstrated with certainty in one open-label randomized study, although no overall difference in mortality was seen between groups [66]. Indeed, similar concerns were raised by Girmenia *et al.* [67] who after comparing an intensive diagnostic approach to standard care, instituted posaconazole prophylaxis for patients with AML because of their high incidence of IFD. A lack of a consensus definition, target population, utility in patients on mold-active prophylaxis and cost-effectiveness need to be resolved before the preemptive approach is widely accepted.

Harnessing the excellent negative predicative value of NCBTs may be the most appropriate means of using them by excluding invasive aspergillosis with confidence [68**]. A meta-analysis of mainly haematological patients concluded that the serum galactomannan assay for probable/proven invasive aspergillosis had a low postive predictive value of 31% (95% CI 26–53%) but a high negative predictive value (NPV) of 98% (95% CI 97–99%) [69]. Similarly, studies have used the NPV of PCR as a screening tool in allo-HSCT and high-risk haematology patients to demonstrate no excess in mortality amongst patients in whom EAFT was

withheld [64,70] and in one setting realized savings in antifungal drug expenditure [64].

Advances in molecular tests [71**,72] will likely enhance AFS efforts. Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF) is emerging as a powerful tool for the rapid and reliable identification of *Candida* and *Aspergillus* species with the additional advantage of lower costs than conventional methods [73,74]. Similarly, rapid identification of azole resistance in culture-negative samples in patients with pulmonary aspergillosis using ultrasensitive real-time *Aspergillus* PCR has recently been reported [7], but the clinical relevance of this finding needs assessment.

Measuring the performance of an AFS programme: quality and quantity of prescribing

Demonstrating the continued benefit of an AFS programme to hospital administrators, drug committees and senior clinicians relies on the cyclical monitoring of process, outcome and structural measures (presented in Table 1) relevant to the prevention and management of IFDs. Initial goals should be modest and achievable in order to demonstrate success of the programme in the short term (i.e. 'quick wins'). For example, targeting a few high-cost antifungal drugs which may have suboptimal use such as liposomal amphotericin, the echinocandins or intravenous voriconazole may be preferable to demonstrating a reduction in all antifungal drugs.

In addition to clinical audit, population-level surveys are a useful means of identifying areas requiring attention. Schelenz *et al.* [76] reported several deficiencies in clinical and laboratory standards amongst UK hospitals including delayed initiation of antifungal therapy and central catheter-line removal in patients with candidaemia, low provision of on-site galactomannan testing and suboptimal morphological fungal description. In a recent survey, lung transplant clinicians flagged the need for structural measures, namely consensus guidelines on antifungal prophylaxis [77].

Process and outcome measures

Measurement of antifungal consumption and the use of this data to benchmark institutions is problematic because of differences in case-mix (e.g. transplant centres, ICU workload) or institutional practices (e.g. local guidelines, transplant practices) [78]. Unit or ward-specific usage data should at a minimum include high users such as haematology–oncology and ICU patients [17,78,79]. Antifungal drug consumption in DDDs [80] has several limitations [81,82] and tends to overestimate the use for fluconazole, itraconazole and amphotericin B [17]. Usage data is commonly reported as a mean [17,78], but a distribution (median, IQR) should be considered because it is more resistant to outlier patients who skew all resource metrics including length of stay (LOS), C-AT and hospital cost [39**]. However, quantitative data, although relatively simple to obtain, is inherently limited by a lack of information on the appropriateness of prescribing [17,83].

The minimum standards of prescribing antimicrobials are well documented [4,18**]. Cooke and Holmes [84] proposed a care bundle, denoting adherence to its individual elements, as a means of gauging the health of an institution's AMS programme, a proposition which has been recently tested [85]. From an AFS perspective, maintaining high prescribing standards could be regarded as a surrogate for patient safety and improved clinical outcomes as it ensures that the most effective antifungal agent is being given and that drug-related adverse events are being minimized.

A clear association between appropriateness and timeliness of antimicrobial administration and clinical outcomes in sepsis/infectious diseases has been demonstrated [86,87] and IFDs are no exception. For patients with invasive candidiasis, the association between inadequate dosing or delayed initiation of antifungal therapy and increased LOS, healthcare costs, morbidity and mortality is well established [87–89]. Inadequate dosing of fluconazole is an independent predictor of mortality [90] and is common [90,91], being present in approximately half of critically ill patients and two-thirds of non-ICU patients in one single centre [90].

Improved diagnosis of IFD is central to guiding antifungal therapy but dependent on the timeliness and completeness of the diagnostic work-up. Characteristic radiological features of invasive aspergillosis such as the halo sign are associated with improved clinical response but, being transient, present in 88–96% of patients at day 0–1 but only 22–37% by day 7 [92], underscoring the importance of early CT scanning when IFD is suspected. Similarly, the diagnostic yield from bronchoscopy in HSCT recipients 100 days after transplant declines after clinical presentation (75% at day 1, 40% at day 5 and 14% at day 10) [93], indicating that referral should be prompt. Indeed, a single centre specializing in the management of patients with multiple myeloma endeavours to confirm the diagnosis of invasive aspergillosis using host, clinical and radiologic criteria within 24–48 h [32]. Another modality, bronchoalveolar lavage fluid-based PCR

Table 1. Performance measures for an AFS program

Characteristic	Comments
Process measures	
Antifungal drug consumption	No information on appropriateness of therapy
	Measured in defined daily doses, prescribed daily doses or days of therapy adjusted for bed occupancy
	Large fluctuations in small populations (e.g. the ward level), because of the effect of outlier patients
Minimum standards of prescribing	
Documentation of treatment rationale	The reason(s) for prescription should be recorded in the medical record
Dose optimization using therapeutic drug monitoring (TDM)	Resources should be available to ensure that the pharmacokinetic/ pharmacodynamic endpoints proposed for voriconazole which optimize clinical efficacy and minimize toxicity are rapidly attained [75]
	The utility of TDM for posoconazole is unclear
	TDM for itraconazole is well established
Therapeutic streamlining	
De-escalation of empiric antifungal therapy	Assisted by the high negative predictive value of NCBTs such as galactomannan and *Aspergillus* PCR in the appropriate clinical context
	Best studied in neutropenic patients
De-escalation from broad to narrower spectrum drugs	Guided by susceptibility results and clinical response
Intravenous to oral switch therapy	Can decrease health-care costs/adverse events without compromising outcomes
	Suitable for agents with high oral bioavailability, for example, voriconazole
Timeliness and completeness of diagnostic investigations when IFD suspected	Improved diagnosis to guide therapy, such as ceasing or modifying antifungal therapy
Concordance of prescribing with institutional guidelines using an indication-driven approach	Clinical audit can be a labour-intensive process requiring chart review, online tools, for example, computerized decision support system or point prevalence surveys.
	May be best performed targeting areas where there is reasonable quality evidence and/or institutional guidelines, for example, antifungal prophylaxis in patients with AML undergoing intensive chemotherapy or use of empiric antifungal therapy
	Includes timeliness, appropriateness and adequacy of initial antifungal therapy
Outcome measures	
IFD incidence in targeted groups	Targeted surveillance of patients at highest risk for IFDs, that is, allogeneic HSCT recipients and patients with AML undergoing chemotherapy for initial remission; refractory or relapsed disease.
	Requires prospective surveillance
	Evolves in response to changing practices, for example, formulary changes
Antifungal drug expenditure	Patient quality and safety initiatives encompass AFS programmes and should not be driven by cost
	Subject to fluctuations in purchase contracts, formulary changes, variations in ordering
	Targeting specific high-cost drugs, for example, liposomal amphotericin, intravenous voriconazole, echinocandins, is an efficient means of demonstrating value of an AFS programme
Structural measures	At a minimum includes an antifungal drug policy or locally adapted practice guidelines

AFS, antifungal stewardship; AML, acute myeloid leukaemia; HSCT, haematological stem cell transplant; IFD, invasive fungal disease; TDM, therapeutic drug monitoring.

diagnosis, in one study was associated with improved inpatient mortality compared with probable invasive aspergillosis (80 vs. 35.6%, $P < 0.003$) because the latter represents a more advanced stage of disease [94].

Clinical audit as a core AFS activity should evaluate the impact of formulary changes on IFD incidence. At our institution, consecutive use of fluconazole, itraconazole, voriconazole and posaconazole prophylaxis in 216 patients with AML/MDS undergoing high-dose cytarabine-based chemotherapy was associated with an incremental reduction in breakthrough IFD incidence of 25, 16, 14 and 3%, respectively [95]. In contrast, intermittent liposomal amphotericin prophylaxis appears to be less effective with a breakthrough IFD incidence of 6.9%, prompting a review of our dosing regimen [56].

CONCLUSION

Relative to infections caused by multiresistant bacteria, IFDs have a lower institutional incidence but a high health and economic burden which is likely to increase over time as the population of at-risk individuals expands [96]. Institutional variation in incidence rates [29], emerging but underrecognized antifungal resistance [97] and evolving treatment practices underscores the importance of centres knowing their local epidemiology, which can only be achieved with surveillance. The cornerstone of AFS is the implementation of institutional guidelines which should largely accord with international or national standards augmented by provider audit and feedback, the quality use of medicine indicators and performance measures [18••,84]. An orchestrated effort requiring multidisciplinary team engaging and consensus building with end-users is vital for mission success. It is incumbent upon AFS programmes to demonstrate value to hospital administrators and although a reduction in healthcare costs is regarded as a secondary goal of AMS [4], it is a common justification for stewardship programmes [98] which should be exploited by AFS programmes also, given the high costs and high contribution of antifungal agents to the management and prevention of IFDs.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
■ of special interest
■■ of outstanding interest

1. MacDougall C, Polk RE. Antimicrobial stewardship programs in healthcare systems. Clin Microbiol Rev 2005; 18:638–656.
2. Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. Clin Infect Dis 2003; 36:1433–1437.
3. Roberts RR, Hota B, Ahmad I, *et al.* Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. Clin Infect Dis 2009; 49:1175–1184.
4. Dellit TH, Owens RC, McGowan JE, *et al.* Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007; 44:159–177.
5. Apisarnthanarak A, Yatrasert A, Mundy LM. Impact of education and an antifungal stewardship program for candidiasis at a Thai tertiary care center. Infect Control Hosp Epidemiol 2010; 31:722–727.
6. Denning DW, Hope WW. Therapy for fungal diseases: opportunities and priorities. Trends Microbiol 2010; 18:195–204.
7. Denning DW, Park S, Lass-Florl C, *et al.* High-frequency triazole resistance found in nonculturable Aspergillus fumigatus from lungs of patients with chronic fungal disease. Clin Infect Dis 2011; 52:1123–1129.
8. Bueid A, Howard SJ, Moore CB, *et al.* Azole antifungal resistance in Aspergillus fumigatus: 2008 and 2009. J Antimicrob Chemother 2010; 65:2116–2118.
9. Alanio A, Sitterle E, Liance M, *et al.* Low prevalence of resistance to azoles in Aspergillus fumigatus in a French cohort of patients treated for haematological malignancies. J Antimicrob Chemother 2011; 66:371–374.
10. Howard SJ, Cerar D, Anderson MJ, *et al.* Frequency and evolution of azole resistance in Aspergillus fumigatus associated with treatment failure. Emerg Infect Dis 2009; 15:1068–1076.
11. Verweij PE, Snelders E, Kema GH, *et al.* Azole resistance in Aspergillus fumigatus: a side-effect of environmental fungicide use? Lancet Infect Dis 2009; 9:789–795.
12. Van der Linden JW, Jansen RR, Bresters D, *et al.* Azole-resistant central nervous system aspergillosis. Clin Infect Dis 2009; 48:1111–1113.
13. Thors VS, Bierings MB, Melchers WJ, *et al.* Pulmonary aspergillosis caused by a pan-azole-resistant Aspergillus fumigatus in a 10-year-old boy. Pediatr Infect Dis J 2010; 30:268–270.
14. Verweij PE, Camps SM, Kema GH, Melchers WJ. Comment on low prevalence of resistance to azoles in Aspergillus fumigatus in a French cohort of patients treated for haematological malignancies. J Antimicrob Chemother 2011; 66:954–955.
15. Sun HY, Singh N. Characterisation of breakthrough invasive mycoses in echinocandin recipients: an evidence-based review. Int J Antimicrob Agents 2009; 35:211–218.
16. Pfaller MA, Diekema DJ, Gibbs DL, *et al.* Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-year analysis of susceptibilities of Candida species to fluconazole and voriconazole as determined by CLSI standardized disk diffusion. J Clin Microbiol 2010; 48:1366–1377.
17. De With K, Steib-Bauert M, Knoth H, *et al.* Hospital use of systemic antifungal drugs. BMC Clin Pharmacol 2005; 5:1.
18. Antimicrobial Stewardship in Australian Hospitals. In: Duguid M, Cruickshank
■■ M, editor. Australian Commission on Safety and Quality in Healthcare. 1st ed. 2011. http://www.health.gov.au/internet/safety/publishing.nsf/Content/compubs_AMS-44471 [accessed 4 October 2011]
A practical guide on implementation of antimicrobial stewardship in the hospital setting.
19. Slavin MA. Introduction to the updated Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting. Intern Med J 2008; 38:457–467.
20. Thursky KA, Mahemoff M. User-centered design techniques for a computerised antibiotic decision support system in an intensive care unit. Int J Med Inform 2007; 76:760–768.

21. Buising KL, Thursky KA, Robertson MB, *et al.* Electronic antibiotic steward-ship – reduced consumption of broad-spectrum antibiotics using a compu-terized antimicrobial approval system in a hospital setting. J Antimicrob Chemother 2008; 62:608–616.
22. Pagano L, Caira M, Candoni A, *et al.* Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study. Haematologica 2010; 95:644–650.
23. Bow EJ, Loewen R, Cheang MS, Schacter B. Invasive fungal disease in adults undergoing remission-induction therapy for acute myeloid leukemia: the patho-genetic role of the antileukemic regimen. Clin Infect Dis 1995; 21:361–369.
24. Cornely OA, Maertens J, Winston DJ, *et al.* Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007; 356:348–359.
25. Wingard JR, Carter SL, Walsh TJ, *et al.* Randomized double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection (IFI) after allo hematopoietic cell transplantation (HCT). Blood 2010; 116:5111–5118.
26. Ullmann AJ, Lipton JH, Vesole DH, *et al.* Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007; 356:335–347.
27. Marks DI, Pagliuca A, Kibbler CC, *et al.* Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell trans-plantation. Br J Haematol 2011; 155:318–327.
28. Caira M, Girmenia C, Fadda RM, *et al.* Invasive fungal infections in patients with acute myeloid leukemia and in those submitted to allogeneic hemopoietic stem cell transplant: who is at highest risk? Eur J Haematol 2008; 81:242–243.
29. Kontoyiannis DP, Marr KA, Park BJ, *et al.* Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis 2010; 50:1091–1100.
30. Panackal AA, Li H, Kontoyiannis DP, Mori M, *et al.* Geoclimatic influences on invasive aspergillosis after hematopoietic stem cell transplantation. Clin Infect Dis 2010; 50:1588–1597.
31. Perkhofer S, Lass-Florl C, Hell M, *et al.* The Nationwide Austrian Aspergillus Registry: a prospective data collection on epidemiology, therapy and outcome of invasive mould infections in immunocompromised and/or immunosup-pressed patients. Int J Antimicrob Agents 2010; 36:531–536.
32. Nucci M, Nouer SA, Grazziutti M, *et al.* Probable invasive aspergillosis without prespecified radiologic findings: proposal for inclusion of a new category of aspergillosis and implications for studying novel therapies. Clin Infect Dis 2010; 51:1273–1280.
33. Neofytos D, Horn D, Anaissie E, *et al.* Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis 2009; 48:265–273.
34. Even C, Bastuji-Garin S, Hicheri Y, *et al.* Impact of invasive fungal disease on the chemotherapy schedule and event-free survival in acute leukemia patients who survived to fungal disease. A case–control study. Haematologica 2010; 96:337–341.
35. Wilson LS, Reyes CM, Stolpman M, *et al.* The direct cost and incidence of systemic fungal infections. Value Health 2002; 5:26–34.
36. Rentz AM, Halpern MT, Bowden R. The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. Clin Infect Dis 1998; 27:781–788.
37. Kim A, Nicolau DP, Kuti JL. Hospital costs and outcomes among intravenous antifungal therapies for patients with invasive aspergillosis in the United States. Mycoses 2010; 54:e301–e312.
38. Barnett PG. An improved set of standards for finding cost for cost-effective-ness analysis. Med Care 2009; 47 (7 Suppl. 1):S82–S88.
39. Ananda-Rajah MR, Cheng A, Morrissey CO, *et al.* Attributable hospital cost
■■ and antifungal treatment of invasive fungal diseases in high-risk hematology patients: an economic modeling approach. Antimicrob Agents Chemother 2011; 55:1953–1960.
Retrospective case–control study which estimates attributable hospital cost of IFDs after adjustment for key high-cost variables. Cost estimates in Australian/US dollars and Euro are useful for business case proposals supporting antifungal stewardship programmes.
40. Tong KB, Lau CJ, Murtagh K, Layton AJ, *et al.* The economic impact of aspergillosis: analysis of hospital expenditures across patient subgroups. Int J Infect Dis 2009; 13:24–36.
41. Kim A, Nicolau DP, Kuti JL. Hospital costs and outcomes among intravenous antifungal therapies for patients with invasive aspergillosis in the United States. Mycoses 2010; 54:e301–e312.
42. Van Campenhout H, Marbaix S, Derde MP, Annemans L. Voriconazole treatment of invasive aspergillosis: real-world versus health-economic model results. Clin Drug Invest 2008; 28:509–521.
43. Wenzel R, Del Favero A, Kibbler C, *et al.* Economic evaluation of voriconazole compared with conventional amphotericin B for the primary treatment of aspergillosis in immunocompromised patients. J Antimicrob Chemother 2005; 55:352–361.
44. Wingard JR, Herbrecht R, Mauskopf J, *et al.* Resource use and cost of treatment with voriconazole or conventional amphotericin B for invasive aspergillosis. Transpl Infect Dis 2007; 9:182–188.
45. Menzin J, Meyers JL, Friedman M, *et al.* Mortality, length of hospitalization, and costs associated with invasive fungal infections in high-risk patients. Am J Health Syst Pharm 2009; 66:1711–1717.
46. Morgan J, Meltzer MI, Plikaytis BD, *et al.* Excess mortality, hospital stay, and cost due to candidemia: a case–control study using data from population-based candidemia surveillance. Infect Control Hosp Epidemiol 2005; 26:540–547.
47. Slobbe L, Polinder S, Doorduijn JK, *et al.* Outcome and medical costs of patients with invasive aspergillosis and acute myelogenous leukemia–mye-lodysplastic syndrome treated with intensive chemotherapy: an observational study. Clin Infect Dis 2008; 47:1507–1512.
48. Hope WW, Walsh TJ, Denning DW. Laboratory diagnosis of invasive asper-gillosis. Lancet Infect Dis 2005; 5:609–622.
49. Donnelly JP. Introduction and aims. J Antimicrob Chemother 2011; 66
■■ (Suppl. 1):i3–i4.
This supplement is an update on current diagnostics and treatment strategies for patients at risk for IFDs incorporated into clinical care pathways.
50. Maschmeyer G, Beinert T, Buchheidt D, *et al.* Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients: guidelines of the infectious diseases working party of the German Society of Haematology and Oncology. Eur J Cancer 2009; 45:2462–2472.
51. Pappas PG, Kauffman CA, Andes D, *et al.* Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:503–535.
52. Walsh TJ, Anaissie EJ, Denning DW, *et al.* Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008; 46:327–360.
53. Writing Group of the British Committee on Standards in Haematology. Guidelines on the management of invasive fungal infection during therapy for haematological malignancy 2008. http://www.bcshguidelines.com/ [accessed 4 October 2011].
54. Maertens J, Marchetti O, Herbrecht R, *et al.* European guidelines for antifungal
■■ management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3-2009 update. Bone Marrow Transplant 2011; 46:709–718.
An excellent discussion on varying treatment and preventive strategies for IFDs incorporating results of recent clinical trials.
55. Mol PG, Rutten WJ, Gans RO, *et al.* Adherence barriers to antimicrobial treatment guidelines in teaching hospital, the Netherlands. Emerg Infect Dis 2004; 10:522–525.
56. Ananda-Rajah MR, Grigg AP, Thursky K, *et al.* Prophylactic effectiveness & safety of intermittent liposomal amphotericin in high risk haematological patients [abstract]. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy; ASM, Chicago. 2011. Abstr. no. M-280.
57. Pagano L, Caira M, Offidani M, *et al.* Adherence to international guidelines for the treatment of invasive aspergillosis in acute myeloid leukaemia: feasibility and utility (SEIFEM-2008B study). J Antimicrob Chemother 2010; 65:2013–2018.
58. Wingard JR, Ribaud P, Schlamm HT, Herbrecht R. Changes in causes of death over time after treatment for invasive aspergillosis. Cancer 2008; 112:2309–2312.
59. Des Champs-Bro B, Leroy-Cotteau A, Mazingue F, *et al.* Invasive fungal infections: epidemiology and analysis of antifungal prescriptions in onco-haematology. J Clin Pharm Ther 2011; 36:152–160.
60. Davey P, Brown E, Fenelon L, *et al.* Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2005; CD003543.
61. Freifeld AG, Bow EJ, Sepkowitz KA, *et al.* Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2011; 52:427–431.
62. Shah DN, Yau R, Weston J, *et al.* Evaluation of antifungal therapy in patients with candidaemia based on susceptibility testing results: implications for antimicrobial stewardship programmes. J Antimicrob Chemother 2011; 66:2146–2151.
63. Maertens J, Theunissen K, Verhoef G, *et al.* Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis 2005; 41:1242–1250.
64. Barnes RA, White PL, Bygrave C, *et al.* Clinical impact of enhanced diagnosis of invasive fungal disease in high-risk haematology and stem cell transplant patients. J Clin Pathol 2009; 62:64–69.
65. Morrissey O, Slavin M; for the Australia and New Zealand Mycology Interest Group and Australasian Leukaemia Lymphoma Group. Randomized con-trolled trial of two diagnostic strategies for invasive aspergillosis (IA) in high-risk hematology patients [abstract]. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy; ASM, Chicago. 2011. Abstr. no. M-1136.
66. Cordonnier C, Pautas C, Maury S, *et al.* Empirical versus preemptive anti-fungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. Clin Infect Dis 2009; 48:1042–1051.
67. Girmenia C, Micozzi A, Gentile G, *et al.* Clinically driven diagnostic antifungal approach in neutropenic patients: a prospective feasibility study. J Clin Oncol 2010; 28:667–674.

68. Maertens J, Groll AH, Cordonnier C, *et al.* Treatment and timing in invasive mould disease. J Antimicrob Chemother 2011; 66 (Suppl. 1):i37–i43.
■■ A nuanced discussion of current approaches to antifungal prophylaxis, early treatment (empirical and preemptive therapy) and treatment of confirmed IFDs in haematology–oncology patients.

69. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis 2006; 42:1417–1427.

70. Hebart H, Klingspor L, Klingebiel T, *et al.* A prospective randomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin B in patients after allo-SCT. Bone Marrow Transplant 2009; 43:553–561.

71. Chen SC, Kontoyiannis DP. New molecular and surrogate biomarker-based tests in the diagnosis of bacterial and fungal infection in febrile neutropenic patients. Curr Opin Infect Dis 2010; 23:567–577.
■■ An overview of advances in the nonculture-based diagnostics which may enhance antifungal stewardship efforts in the future.

72. Bretagne S. Primary diagnostic approaches of invasive aspergillosis – molecular testing. Med Mycol 2011; 49 (Suppl. 1):S48–S53.

73. Pinto A, Halliday C, Zahra M, *et al.* Matrix-assisted laser desorption ionization–time of flight mass spectrometry identification of yeasts is contingent on robust reference spectra. Plos One 2011; 6:e25712.

74. Alanio A, Beretti JL, Dauphin B, *et al.* Matrix-assisted laser desorption ionization time-of-flight mass spectrometry for fast and accurate identification of clinically relevant *Aspergillus* species. Clin Microbiol Infect 2010; 17:750–755.

75. Lewis RE. Pharmacokinetic–pharmacodynamic optimization of triazole antifungal therapy. Curr Opin Infect Dis 2011; 24 (Suppl. 2):S14–S29.

76. Schelenz S, Barnes RA, Kibbler CC, *et al.* Standards of care for patients with invasive fungal infections within the United Kingdom: a national audit. J Infect 2009; 58:145–153.

77. Neoh CF, Snell GI, Kotsimbos T, *et al.* Antifungal prophylaxis in lung transplantation – a world-wide survey. Am J Transplant 2011; 11:361–366.

78. Meyer E, Schwab F, Gastmeier P, *et al.* Antifungal use in intensive care units. J Antimicrob Chemother 2007; 60:619–624.

79. Ramirez E, Garcia-Rodriguez J, Borobia AM, *et al.* Use of antifungal agents in pediatric and adult high-risk areas. Eur J Clin Microbiol Infect Dis 2011 [Epub ahead of print].

80. WHO Collaborating Centre for Drug Statistics Methodology. http://www.whocc.no [accessed 2 October 2011].

81. Berrington A. Antimicrobial prescribing in hospitals: be careful what you measure. J Antimicrob Chemother 2010; 65:163–168.

82. Polk RE, Fox C, Mahoney A, *et al.* Measurement of adult antibacterial drug use in 130 US hospitals: comparison of defined daily dose and days of therapy. Clin Infect Dis 2007; 44:664–670.

83. Pakyz AL, Gurgle HE, Oinonen MJ. Antifungal use in hospitalized adults in U.S. academic health centers. Am J Health Syst Pharm 2011; 68:415–418.

84. Cooke FJ, Holmes AH. The missing care bundle: antibiotic prescribing in hospitals. Int J Antimicrob Agents 2007; 30:25–29.

85. Toth NR, Chambers RM, Davis SL. Implementation of a care bundle for antimicrobial stewardship. Am J Health Syst Pharm 2010; 67:746–749.

86. Kumar A, Ellis P, Arabi Y, *et al.* Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 2009; 136:1237–1248.

87. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of Candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother 2005; 49:3640–3645.

88. Garey KW, Rege M, Pai MP, *et al.* Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multiinstitutional study. Clin Infect Dis 2006; 43:25–31.

89. Zilberberg MD, Kollef MH, Arnold H, *et al.* Inappropriate empiric antifungal therapy for candidemia in the ICU and hospital resource utilization: a retrospective cohort study. BMC Infect Dis 2010; 10:150.

90. Labelle AJ, Micek ST, Roubinian N, Kollef MH. Treatment-related risk factors for hospital mortality in Candida bloodstream infections. Crit Care Med 2008; 36:2967–2972.

91. Garey KW, Pai MP, Suda KJ, *et al.* Inadequacy of fluconazole dosing in patients with candidemia based on Infectious Diseases Society of America (IDSA) guidelines. Pharmacoepidemiol Drug Saf 2007; 16:919–927.

92. Marom EM, Kontoyiannis DP. Imaging studies for diagnosing invasive fungal pneumonia in immunocompromised patients. Curr Opin Infect Dis 2011; 24:309–314.

93. Shannon VR, Andersson BS, Lei X, *et al.* Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem cell transplantation. Bone Marrow Transplant 2010; 45:647–655.

94. Hardak E, Yigla M, Avivi I, *et al.* Impact of PCR-based diagnosis of invasive pulmonary aspergillosis on clinical outcome. Bone Marrow Transplant 2009; 44:595–599.

95. Ananda-Rajah MR, Grigg AP, Downey MT, *et al.* 10 years of azole prophylaxis in acute myeloid leukaemia patients: a retrospective study of fluconazole, itraconazole, voriconazole and posaconazole in an Australian Tertiary Center [abstract]. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy; ASM, San Francisco. 2009. Abstr. no. M-1053.

96. Juliusson G, Antunovic P, Derolf A, *et al.* Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. Blood 2009; 113:4179–4187.

97. Howard SJ, Arendrup MC. Acquired antifungal drug resistance in *Aspergillus fumigatus*: epidemiology and detection. Med Mycol 2011; 49 (Suppl. 1): S90–S95.

98. Drew RH, White R, MacDougall C, *et al.* Insights from the Society of Infectious Diseases Pharmacists on antimicrobial stewardship guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Pharmacotherapy 2009; 29:593–607.

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Appendix 3

Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period

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ABSTRACT

Post-induction aplasia for acute myeloid leukemia/myelodysplastic syndrome is a high-risk period for invasive fungal diseases. The effectiveness of fluconazole, itraconazole solution, voriconazole and posaconazole prophylaxis used consecutively from December 1998 to January 2010 in patients with acute myeloid leukemia/ myelodysplastic syndrome undergoing remission-induction chemotherapy was retrospectively evaluated. A total of 216 consecutive patients received 573 prophylaxis courses. Breakthrough-invasive fungal disease incidence in fluconazole, itraconazole, voriconazole, posaconazole recipients was 25%, 16%, 14% and 3%, respectively. Voriconazole/posconazole *versus* fluconazole/itraconazole combined was associated with significant reductions in breakthrough-invasive fungal disease incidence (20% *vs.* 8%, *P*=0.011), premature discontinuations (46% *vs.* 22% *P*<0.001) and empiric antifungal treatment (31% *vs.* 8.5%, *P*<0.001). Microbiologically confirmed infections were molds. Posaconazole compared to other drugs was associated with fewer courses requiring computed-tomography (43% *vs.* 26%, *P*<0.001). Adoption of voriconazole/posaconazole has decreased invasive fungal disease incidence, empiric antifungal treatment and for posaconazole, computed-tomography demand, with effectiveness of posaconazole comparable to clinical trial experience.

Key words: fungal infections, prophylaxis, acute myeloid leukemia, voriconazole, posaconazole.

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Introduction

Post-induction aplasia for acute myeloid leukemia (AML)/myelodysplastic syndromes (MDS) is a period at high-risk for invasive fungal disease (IFD).[1,2] Invasive aspergillosis (IA) remains the commonest cause of IFD and crude mortality remains considerable at 33-47%.[1,3,4] For patients surviving IFDs, delays or modifications to curative chemotherapy may compromise long-term prognosis.[2,5] Poor clinical outcomes coupled with diagnostic uncertainty underlies the rationale for antifungal prophylaxis, the efficacy of which in preventing IFD and improving short-term survival has best been demonstrated for posaconazole in AML/MDS patients receiving remission-induction chemotherapy.[6]

Despite recognition of the high health and economic burden of IFD,[7] non-selective broad-spectrum prophylaxis has raised concerns about expenditure, overtreatment and emergent drug-resistance[8] as only a subset[9] of AML patients develop IFD. Currently, a more targeted use of prophylaxis is hampered by limited knowledge of local fungal epidemiology[10] and an evolving but incomplete understanding of patient-level risk. Over ten years, we have continuously given antifungal prophylaxis in AML/MDS patients undergoing intensive chemotherapy characterized by use of fluconazole, itraconazole, voriconazole and posaconazole. We retrospectively reviewed the relative effectiveness and safety of azole antifungal prophylaxis with particular attention to the newer triazoles compared to fluconazole/itraconazole.

Design and Methods

Study design and setting

The Royal Melbourne Hospital is a 690-bed adult university-affiliated tertiary hospital that performs 45 allogeneic hematologic stem

cell transplants (HSCT) annually. Consecutive patients with AML/MDS undergoing remission-induction chemotherapy from December 1998-January 2010, who received one day or more of azole prophylaxis, defining a course, were included. Prophylaxis consisting of fluconazole 400 mg daily, itraconazole solution 2.5 mg/kg bd, voriconazole 200 mg bd and posaconazole 200 mg tds co-administered with fatty food, was started at 1-2 days prior to cytoreductive chemotherapy and continued until: neutrophil recovery to more than 0.5cells/L, occurrence of a confirmed or suspected IFD, drug-related toxicity/intolerance, or the patient's condition becoming palliative. Oral administration was preferred with intravenous dosing of either fluconazole or voriconazole reserved for when gastrointestinal absorption was considered inadequate.

Suspicion of IFD lead to high-resolution computed tomography (HR-CT) introduced routinely in 2003, and lung sampling (i.e. bronochoalveolar lavage/biopsy) as tolerated. Galactomannan (GM) or beta-D-glucan assays were not used. AML treatment protocols were predominantly anthracycline and cytarabine based. Neutropenic fever was treated with cefepime prior to 2005 and piperacillin-tazobactam thereafter. Empiric antifungal therapy (EAFT), usually liposomal amphotericin, was typically initiated, once voriconazole and posaconazole prophylaxis became routine, in the presence of HR-CT changes suspicious for IFD. G-CSF was used as part of trial protocols or at the physician's discretion when expected neutropenia duration was 18-days or over. The majority of patients received proton-pump inhibitors for stress ulcer prophylaxis. Therapeutic drug monitoring (TDM) was not routine.

High efficiency particulate air-filtration (HEPA) was extended from five to all rooms in April 2005. However, the vast majority of patients were nursed in HEPA-filtered rooms from 1996-2005.

Clinical data, definitions and imaging review

Collected information included host and treatment-related characteristics, receipt of total parenteral nutrition (TPN) as a surrogate marker of severe mucositis and chest/sinus CT scans performed 3-days prior to, during prophylaxis or within seven days from drug cessation. IFD classification adhered to consensus criteria[11] whereby probable/proven cases required fungal pathogen isolation. IFD onset was defined as the first day of suspicious CT abnormality or positive microbiology or pathological test. CT scans were reviewed by a radiologist (JV) blinded to IFD classification, for the presence of accepted IFD-related lesions[11] as distinct from non-specific pulmonary infiltrates.

Prophylactic effectiveness was assessed in patients receiving azoles at standard doses for 7 consecutive days or more (to approximate steady-state). Breakthrough-IFD was defined as occurrence of IFD in patients during azole prophylaxis or seven days or less from drug cessation. Antifungal susceptibility testing of fungal isolates followed reference methods.[12]

Plasma concentrations of itraconazole, voriconazole and posaconazole drawn five days or more after drug commencement (to approximate steady-state) were defined as sub-therapeutic for: itraconazole 0.5 µg/mL or less; voriconazole less than 0.7mg/L and posaconazole less than 500ng/L.[13] Institutional ethics approval was obtained.

Statistical analysis

The primary objective of the study was to evaluate the incidence of breakthrough-IFD. Secondary outcomes were requirement for EAFT and toxicity/ tolerability. Prophylaxis courses in patients who either died or became palliative were excluded from safety analyses. Categorical variables were analyzed using the χ^2 test or Fisher's exact test as appropriate. The Student's t-test or Wilcoxon's rank-sum test was used to compare continuous variables depending on their distribution. Differences in continuous variables between the azole drugs were assessed using the Kruskal-Wallis test. Reported P values were two-tailed and for each analysis $P \leq 0.05$ was considered significant. All analyses used Stata 11.0 software (Stata Corp, College Station, Texas, USA).

Results and Discussion

Patients' characteristics according to azole antifungal prophylaxis

A total of 216 patients (91% with AML) received 573 courses of azole prophylaxis (Table 1). The majority of patients (213 of 216, 99%) underwent chemotherapy for remission-induction/re-induction or relapsed disease. Significant differences in clinical characteristics were noted between fluconazole/itraconazole and voriconazole/posaconazole recipients, respectively: median duration of neutropenia per prophylaxis course [16-days *vs.* 14-days, $P=0.003$], median age (56 *vs.* 51-years, $P<0.001$), male gender (47% *vs.* 56%, $P=0.035$), TPN requirement (39% *vs.* 26%, $P=0.001$) and median duration of prophylaxis (18 days *vs.* 22 days, $P<0.001$). Changes in clinical practice may have accounted for some of these differences. For example, fluconazole early in the study period was started during chemotherapy or at its cessation accounting for its shorter duration of use, a practice that was later abandoned due to the high number of breakthrough-IFDs.

Breakthrough-IFDs

Breakthrough-IFDs occurred in 27 patients (27 of 216, 13%) comprising probable/proven (n=11) and possible (n=16) infections (Table 2). Among the 210 patients who received seven days or more of azole prophylaxis, breakthrough probable/proven-IFD incidence declined over time: fluconazole 6 of 36, 17%; itraconazole 4 of 49, 8.2%; voriconazole one of 58, 1.7%; posaconazole 0 of 67 with a similar trend following inclusion of possible-IFDs: 9 of 36, 25%; 8 of 49, 16%; 8 of 58, 14% and 2 of 67, 3.0% respectively. The incidence of breakthrough possible/probable/proven-IFDs associated with voriconazole/posaconazole was significantly lower than fluconazole/ itraconazole (17 of 85, 20% *vs.* 10 of 125, 8.0%, $P=0.011$).

All probable/proven IFDs were molds, most commonly aspergillosis. The single *A. fumigatius* isolate tested for susceptibility (2001) demonstrated reduced dose-dependent susceptibility to itraconazole in a patient who had consecutive courses of itraconazole prophylaxis lasting 23 and 15 days, 18 days apart and later died of *Aspergillus* pneumonia. IFD complicated remission-induction chemotherapy in 24 of 27 patients (9 of 24 had disease relapse) and consolidation chemotherapy in 3 patients. Breakthrough probable/proven-IFD incidence among patients receiving one day or more of prophylaxis (similar to an intention-to-treat group), with occurrence during or 30 days or less from drug cessation, was: fluconazole 8 of 57, 11%; itraconazole 6 of 59, 10%; voriconazole 2 of 82, 2.4%; and posaconazole 0 of 68.

Plasma levels of itraconazole, voriconazole and posaconazole

A total of 55 patients had 141 plasma levels after five days or more of itraconazole, voriconazole or posacona-

zole. Sub-therapeutic plasma drug levels, regardless of timing (i.e. trough, peak, random), were common for itraconazole (15 of 36, 42%), voriconazole (35 of 92, 38%) and posaconazole (9 of 13, 69%). None of the 5 patients with breakthrough probable/proven-IFDs during itraconazole or voriconazole prophylaxis had TDM performed. There was no significant difference in median drug levels with or without TPN (administered in the seven days prior to plasma level) (*data not shown*).

Discontinuations, use of empiric antifungal therapy and CT scan demand

Table 3 describes secondary outcomes analyzed according to course of prophylaxis. Overall, premature discontinuations, for any reason, were significantly higher among fluconazole/itraconazole compared to the voriconazole/posaconazole groups combined (46% *vs.* 22%, *P*<0.001). Escalation to EAFT lasting four days or more accounted for the majority of fluconazole and itraconazole discontinuations (74% and 62%, respectively) and to a lesser extent voriconazole (51%). Gastrointestinal-related discontinuation rates were similar for itraconazole and posaconazole (19% each) but accounted for the majority of premature discontinuations for posaconazole (71%) compared to 42% for itraconazole. This was not due to differences in severe mucositis reflected by TPN requirement (71% *vs.* 76%, respectively). Hepatotoxicity was low overall but

significantly higher for voriconazole compared to the other drugs combined (5% *vs.* 1.1%, *P*=0.007).

EAFT was higher in the combined fluconazole/itraconazole compared to the voriconazole/ posaconazole groups (31% *vs.* 8.5%, *P*<0.001) as were pulmonary lesions on computed-tomography treated for suspected IFD but not meeting criteria for possible-IFD (10% *vs.* 4.0%, *P*=0.004). Itraconazole offered no advantage over voriconazole/ posaconazole in preventing pulmonary lesions consistent with IFD (8.7% *vs.* 4.0%, *P*=0.047). Demand for CT scans was not diminished with voriconazole/posaconazole compared to fluconazole/itraconazole (42% *vs.* 37%, *P*=0.26) due to the high numbers of voriconazole courses necessitating CT scanning (45%); only posaconazole was associated with a significant reduction compared to fluconazole/itraconazole/voriconazole courses combined (43% *vs.* 26%, *P*<0.001).

Table 1. Clinical characteristics according to azole antifungal prophylaxis.

Characteristic	Fluconazole n (%)	Itraconazole n (%)	Voriconazole n (%)	Posaconazole n (%)
Characteristics of patients, n=216 N. of patients[1]	57	59	82	68
Age at start of chemotherapy, years Median, range	57, 20-79	55, 20-79	51, 17-81	51, 19-78
Male gender	27 (47)	29 (49)	38 (46)	43 (71)
Dates of use	Dec 1998-Sept 2008	May 1999-Jan 2003	Nov 2002-Aug 2008	Sept 2006-Jan 2010
Characteristics per prophylaxis course, n=573 N. of prophylaxis courses	95 (17)	119 (21)	206 (36)	153 (27)
Underlying diagnosis AML[2] (197 patients) Transformed MDS (18 patients)	73 (77) 22 (23)	112 (94) 7 (5.9)	195 (95) 11 (5.3)	145 (95) 8 (5.2)
Phase of treatment Induction/re-induction Relapse Consolidation	55 (58) 10 (11) 30 (32)	63 (53) 16 (13) 40 (34)	83 (43) 26 (13) 97 (47)	67 (44) 15 (9.8) 71 (46)
Duration of neutropenia (≤0.5 cells/L) per chemotherapy cycle, days Median, range	16, 0-54	16, 4-41	13, 0-54	15, 0-48
Receipt of TPN, n (%)	36/95 (38)	48/119 (40)	44/206 (21)	48/153 (31)
Duration of prophylaxis, days Median, range	15, 3-53	20, 1-71	21, 2-79	23, 1-69

[1]*Some patients received more than one antifungal drug as prophylaxis;*[2]*includes one patient with acute undifferentiated leukemia who received 4 courses of posaconazole prophylaxis.*

Table 2. Clinical characteristics of patients with breakthrough invasive fungal disease.

Characteristic	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Probable or proven IFDs[1]	6	4	1	0
Female sex	4	1	1	NA
Age, years Median (range)	50 (40-60)	59.5 (50-70)	71	NA
Year of IFD diagnosis	1999, 2000, 2003/04	2001/02	2003	NA
Underlying disease	AML	AML	AML	NA
Phase of treatment Induction/re-induction Induction for relapse Consolidation	5 1 0	3 0 1	0 1 0	NA
Site of infection Lung Sinus Blood	5 1 0	3 0 1	1 0 0	NA
Organism *A. fumigatus* *A. niger* Fungal hyphae resembling *Aspergillus spp.* Fungal hyphae not specified *Rhizopus spp.* *Scedosporium prolificans*	2 1 2 0 1 0	1 0 1 1 0 1	0 0 0 0 1 0	NA
Receipt of TPN[2]	4/6	3/4	0/1	NA
Outcome at 12 weeks Cure Unfavorable response[3] Death	3 3 3	0 4 2	0 1 0	NA
Possible IFD[4] Lung resection performed Lung biopsy or lavage Any positive PCR	3 0 2 0/1	4 2 4 1/2	7 1 1 0/1	2 2 2 0/2
Probable or proven IFDs by intention-to-treat[5]	8	6	2	0

IFD: invasive fungal disease; AML: acute myeloid leukemia; TPN: total parenteral nutrition; [1]*IFD occurrence in patients receiving ≥7 days of antifungal prophylaxis, during or ≤7 days from cessation of azole prophylaxis;* [2]*Receipt of TPN a surrogate marker for the presence of mucositis;* [3]*Unfavorable response defined as partial response, progressive infection or death;* [4]*Evidence of either halo, nodule(s) or cavitation on computed tomography of the chest. Non-specific pulmonary infiltrates or infiltrates not suggestive of fungal infection were excluded;* [5]*IFD occurrence during or ≤30-days of drug cessation in patients receiving ≥1-days of prophylaxis.*

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Discussion

In our center, adoption of voriconazole/posaconazole in comparison to fluconazole/itraconazole prophylaxis in a high-risk cohort of AML/MDS patients was associated with a significant decrease in the incidence of breakthrough possible/probable/proven-IFD (20% *vs.* 8.0%, *P*=0.011) in addition to reductions in less specific but not insignificant outcomes including escalation to EAFT (31% *vs.* 8.5%, *P*<0.001) and pulmonary lesions on computed-tomography treated for suspected IFD but not meeting consensus criteria for possible-IFD[11] (10% *vs.* 4.0%, *P*=0.004). A declining trend in breakthrough proven/probable-IFDs (fluconazole 17%, itraconazole 8.2%, voriconazole 1.7%) persisted when more stringent criteria similar to an intention-to-treat analysis were applied (fluconazole 11%, itraconazole 10%, voriconazole 2.4%). Notably, the breakthrough-IFD incidence of 3% associated with posaconazole was due to possible IFDs and comparable to the 2% proven/probable-IFD incidence in the randomized trial.[6] Qualifying these findings is the fact that as a non-contemporaneous cohort, host or treatment-related factors (e.g. duration of azole prophylaxis or neutropenia) may have contributed to improvements in effectiveness but further analysis controlling for key variables was not possible due to low numbers of breakthrough-IFDs overall.

Local epidemiology informs the choice and risk-benefit of prophylaxis. Prophylaxis seems warranted in our setting where baseline IFD incidence is likely higher than the 17% observed in our fluconazole cohort, and above the 15% threshold identified in a meta-analysis of non-HSCT neutropenic patients.[14] In our setting, the number-needed-to-treat (NNT) with posaconazole prophylaxis to prevent one probable/proven IFD is 6, which is lower than the posaconazole registration trial (NNT=16)[15] but similar to other real-world experience comparing posaconazole to topical polyene prophylaxis (NNT=7).[10] Breakthrough-IFDs were predominantly IA, in keeping with the decline in invasive candidiasis seen in recent years,[16] but notable in

our setting given the high requirement for TPN and its association with mucositis, both of which are risk factors for invasive candidiasis.[17]

Premature discontinuations were lower with voriconazole/posaconazole compared to fluconazole/itraconazole (46% *vs.* 22%, *P*<0.001). Clinical failure denoted by escalation to EAFT accounted for the majority of discontinuations among the standard azoles (fluconazole 74%, itraconazole 62%). Concern regarding potential incomplete gastrointestinal absorption or intolerance accounted for the majority of posaconazole discontinuations (71%) compared to 42% for itraconazole. This was likely due to a greater propensity for gastrointestinal intolerance with itraconazole and the lack of an iv formulation for posaconazole when mucositis supervened. The Cologne group,[10] in contrast, reported no significant intolerance/toxicities associated with posaconazole, perhaps reflecting a higher degree of clinician confidence in the drug even in the presence of mucositis. Serious adverse events were consistent with the recognized toxicities of azoles[18] but for voriconazole, less frequent than post-marketing reports.[19,20]

The emergence of resistant fungi is a potential drawback of broad-spectrum antifungal prophylaxis. Intrinsically resistant organisms including *A. niger*, *Scedosporium prolificans* and *Rhizopus spp.* were seen but in association with fluconazole, itraconazole, and both fluconazole/voriconazole, respectively, limiting conclusions about causation. Our single case of possible acquired itraconazole resistance echoes the low prevalence of azole resistance in *Aspergillus* isolates (0.85%) reported from a hematology unit where periods of drug exposure were also short.[21]

TDM was performed when absorption was suspected to be inadequate. Therefore, subtherapeutic levels were common and further interpretation was limited by an absence of TDM among the 5 patients who developed probable/proven IFDs.

Our burden of IFD is likely underestimated due to a lack of routine GM testing and, like other transplant centers, falling autopsy rates. Multiple prophylactic azole drugs

Table 3. Reasons for discontinuation of azole prophylaxis courses.[1]

Clinical outcome	Fluconazole, n (%)	Itraconazole, n (%)	Voriconazole, n (%)	Posaconazole, n (%)	*P*[2]
Premature discontinuation, n. of courses (%)[1]	42/93 (45)	53/115 (46)	37/202 (18)	41/149 (28)	<0.001[3]
Reason for discontinuation:					
EAFT (≥4days) for suspected IFD	31/93 (33)	33/115 (29)	19/202 (9.4)	11/149 (7.4)	<0.001[3]
EAFT & pulmonary lesions suggestive of IFD[4]	11/93 (12)	10/115 (8.7)	9/202 (4.5)	5/149 (3.4)	<0.001[3]
Gastrointestinal intolerance/absorption concerns	2/93 (2.2)	22/115 (19)	7/202 (3.5)	29/149 (19)	0.012[5]
Receipt of TPN in subset with GIT absorption/intolerance concerns	0/2	16/22 (73)	4/7 (57)	22/29 (76)	*
Abnormal LFTs[6]	1/93 (1.1)	2/115 (1.7)	10/202 (5)	1/149 (0.7)	0.009[7]
Other[8]	4/93 (4.3)	3/115 (2.6)	4/202 (2.0)	1/149 (0.7)	*
Courses discontinued due to death[2] or palliation of patient	2	4	4	*	

*EAFT: empiric antifungal treatment; TPN: total parenteral nutrition; LFTs: liver function tests; IFD: invasive fungal disease. [1]In some cases patients discontinued drugs for more than one reason. Premature discontinuation excludes courses where patients subsequently died or were palliated; [2]test of difference used the χ^2 test or Fisher's exact test as appropriate; [3]comparing discontinuation in the standard azole (fluconazole, itraconazole) vs. voriconazole+posaconazole groups combined; [4]Pulmonary lesions treated for suspected invasive fungal infection but not meeting consensus criteria.[11] [5]Comparing discontinuation in the itraconazole vs. voriconazole+posaconazole groups combined. [6]Abnormal LFTs according to clinician judgment as documented in medical chart. [7]Comparing discontinuation in voriconazole vs. fluconazole/itraconazole/posaconazole groups combined. [8]Includes discontinuations due to photopsia and rash (voriconazole, n=2); avoidance of drug-drug interactions with voriconazole (all-trans retinoic acid and arsenic in one patient and amiodarone in another patient); ventricular fibrillation associated with a prolonged QT interval with posaconazole (n=1); reasons for discontinuation were unclear for fluconazole and itraconazole. *No test of comparison performed.*

were administered to 52 patients (*data not shown*) during their entire treatment schedule due to toxicities/intolerance, changes in unit policy, or following long intervals between treatment, e.g. disease relapse. Therefore, we analyzed courses rather than patients assuming that episodes of chemotherapy-induced neutropenia were discrete, temporally separate and, therefore, independent periods of risk. The choice of fluconazole/itraconazole as comparators to voriconazole/posaconazole was based on clinical trial experience.[6] That consolidation chemotherapy is low risk for IFD (affecting 3 of 27 patients) compared to post-induction aplasia[1,16,22] suggests review of our universal policy of broad-spectrum prophylaxis may be warranted.

Concordance of real-world effectiveness of posaconazole prophylaxis with trial experience is reassuring but we welcome advances in risk-stratification tools to better direct prophylaxis to those at highest risk. However, unless persuasive evidence emerges that approaches alternative to broad-spectrum prophylaxis[23] do not threaten longer term outcomes, i.e. the completion and intensity of leukemia treatment, due to the development of IFD,[5] then it is not a strategy we are likely to abandon but would prefer to refine.

Authorship and Disclosures

References

1. Pagano L, Caira M, Candoni A, Offidani M, Martino B, Specchia G, et al. Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study. Haematologica. 2010;95(4):644-50.
2. Bow EJ, Loewen R, Cheang MS, Schacter B. Invasive fungal disease in adults undergoing remission-induction therapy for acute myeloid leukemia: the pathogenetic role of the antileukemic regimen. Clin Infect Dis. 1995;21(2):361-9.
3. Neofytos D, Horn D, Anaissie E, Steinbach W, Olyaei A, Fishman J, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis. 2009; 48(3):265-73.
4. Perkhofer S, Lass-Florl C, Hell M, Russ G, Krause R, Honigl M, et al. The Nationwide Austrian Aspergillus Registry: a prospective data collection on epidemiology, therapy and outcome of invasive mould infections in immunocompromised and/or immunosuppressed patients. Int J Antimicrob Agents. 2010;36(6):531-6.
5. Even C, Bastuji-Garin S, Hicheri Y, Pautas C, Botterel F, Maury S, et al. Impact of invasive fungal disease on the chemotherapy schedule and event-free survival in acute leukemia patients who survived to fungal disease. A case-control study. Haematologica. 2010;96(2):337-41.
6. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356(4):348-59.
7. Ananda-Rajah MR, Cheng A, Morrissey CO, Spelman T, Dooley M, Neville AM, et al. Attributable hospital cost and antifungal treatment of invasive fungal diseases in high-risk hematology patients: an econom-

ic modeling approach. Antimicrob Agents Chemother. 2011;55(5):1953-60.
8. De Pauw BE, Donnelly JP. Prophylaxis and aspergillosis--has the principle been proven? N Engl J Med. 2007;356(4):409-11.
9. Caira M, Girmenia C, Padda RM, Mitra ME, Picardi M, Van Lint MT, et al. Invasive fungal infections in patients with acute myeloid leukemia and in those submitted to allogeneic hemopoietic stem cell transplant: who is at highest risk? Eur J Haematol. 2008;81(3):242-3.
10. Vehreschild JJ, Ruping MJ, Wisplinghoff H, Farowski F, Steinbach A, Sims R, et al. Clinical effectiveness of posaconazole prophylaxis in patients with acute myelogenous leukaemia (AML): a 6 year experience of the Cologne AML cohort. J Antimicrob Chemother. 2010;65(7):1466-77.
11. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46(12):1813-21.
12. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi: approved standard, 2nd 144 ed. M38-A2. Clinical and Laboratory 145 Standards Institute, Wayne, PA 2008.
13. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother. 2009; 53(1):24-34.
14. Kanda Y, Yamamoto R, Chizuka A, Hamaki T, Suguro M, Arai C, et al. Prophylactic action of oral fluconazole against fungal infection in neutropenic patients. A meta-analysis of 16 randomized, controlled trials. Cancer. 2000;89(7):1611-25.
15. Cornely OA, Ullmann AJ. Numbers needed to treat with posaconazole prophylaxis to

prevent invasive fungal infection and death. Clin Infect Dis. 2008;46(10):1626-7; author reply 7-8.
16. Pagano L, Caira M, Candoni A, Offidani M, Fianchi L, Martino B, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica. 2006;91(8):1068-75.
17. Leon C, Ruiz-Santana S, Saavedra P, Galvan B, Blanco A, Castro C, et al. Usefulness of the "Candida score" for discriminating between Candida colonization and invasive candidiasis in non-neutropenic critically ill patients: a prospective multicenter study. Crit Care Med. 2009;37(5):1624-33.
18. Cronin S, Chandrasekar PH. Safety of triazole antifungal drugs in patients with cancer. J Antimicrob Chemother. 2010;65(3):410-6.
19. Eiden C, Peyriere H, Cociglio M, Djezzar S, Hansel S, Blayac JP, et al. Adverse effects of voriconazole: analysis of the French Pharmacovigilance Database. Ann Pharmacother. 2007;41(5):755-63.
20. Riedel A, Choe L, Inciardi J, Yuen C, Martin T, Guglielmo BJ. Antifungal prophylaxis in chemotherapy-associated neutropenia: a retrospective, observational study. BMC Infect Dis. 2007;7:70.
21. Alanio A, Sitterle E, Liance M, Farrugia C, Poulet F, Botterel F, et al. Low prevalence of resistance to azoles in Aspergillus fumigatus in a French cohort of patients treated for haematological malignancies. J Antimicrob Chemother. 2011;66(2):371-4.
22. Lewis G, Hall P, Eisa N, Deremer D, Dobbins R, El-Geneidy M, et al. Acute Myelogenous Leukemia Patients Are at Low Risk for Invasive Fungal Infections after High-Dose Cytarabine Consolidations and Thus Do Not Require Prophylaxis. Acta Haematol. 2010;124(4):206-13.
23. Cordonnier C, Pautas C, Maury S, Vekhoff A, Farhat H, Suarez F, et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. Clin Infect Dis. 2009;48(8):1042-51.

Attributable Hospital Cost and Antifungal Treatment of Invasive Fungal Diseases in High-Risk Hematology Patients: an Economic Modeling Approach[▽]

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Studies using patient-level data to determine the attributable cost of invasive fungal diseases (IFDs) are few. Using a case-control study with activity-based costing of patients admitted to a quaternary hospital from 2002 to 2007, we determined attributable hospitalization cost (and 12 weeks thereafter), length of stay (LOS), and costly antifungal treatment (C-AT; liposomal amphotericin B, voriconazole, posaconazole, caspofungin), expressed as defined daily doses (DDDs) per IFD episode, in patients with hematological malignancies and hematopoietic stem cell recipients. Matching criteria and median regression modeling controlled for confounding variables, including LOS prior to IFD onset. Multiple mycoses were identified in 43 matched case-control pairs ($n = 86$). A separate sensitivity analysis included 22 unmatched patients. IFD status was associated with a median excess cost of AU\$30,957 (95% confidence interval [CI] = AU\$2,368 to AU\$59,546; $P = 0.034$), approximating at purchasing power parity US\$21,203 (95% CI = US\$1,622 to US\$40,784) and €15,788 (95% CI = €1,208 to €30,368), increasing to AU\$80,291 (95% CI = AU\$33,636 to AU\$126,946; $P = 0.001$), i.e., US\$54,993 (95% CI = US\$23,038 to US\$86,948) and €40,948 (95% CI = €17,154 to €64,742), with intensive care unit (ICU) requirement. Cost determinants were pharmacy costs (64%; $P < 0.001$) inclusive of antifungal treatment (27%; $P < 0.001$) and ward costs (27%; $P = 0.091$), with proportions persisting through 12 weeks for 25 surviving matched pairs (pharmacy, 60% [$P = 0.12$]; ward, 31% [$P = 0.21$]). Median LOS was not significantly increased unless unmatched patients were included (8 days, 95% CI = 1.8 to 14 days; $P = 0.012$). Excess C-ATs were 17 DDDs (95% CI = 15 to 19 DDDs; $P < 0.001$) per case patient and 19 DDDs (95% CI = 16 to 22 DDDs; $P < 0.001$) per ICU patient. The sensitivity analysis was confirmatory (for median cost, AU\$29,441, 95% CI = AU\$5,571 to AU\$53,310, $P = 0.016$; for C-AT, 17 DDDs, 95% CI = 16 to 18 DDDs, $P < 0.001$). IFD results in increased hospital and ICU costs, with pharmacy costs, including antifungal treatment, being major determinants. Consumption of costly antifungal drugs may be a novel resource metric with wider generalizability than cost alone.

Improvement in the short-term survival of patients with invasive aspergillosis (IA) (22, 24) is encouraging, but crude mortality rates remain high at >30% in patients with acute myeloid leukemia (AML) (24) and 57% in hematopoietic stem cell (HSCT) recipients (1). As a result, interest in prevention continues, with efficacy demonstrated for posaconazole in patients receiving induction-remission chemotherapy for AML/myelodysplastic syndromes (MDSs) and high-risk allogeneic HSCT (allo-HSCT) recipients (7, 32). However, given incidence rates of invasive fungal diseases (IFDs) of 10 to 15%

among patients with AML and HSCT recipients (5, 17, 23), nonselective prophylaxis has raised concerns regarding overtreatment and expenditure (9, 25) because the numbers of eligible patients are high and the duration of prophylaxis is potentially lengthy.

Increasingly, the economic impact of IFDs has been considered in the clinical debate. One center, after determining the attributable mean IA-associated medical cost in AML/MDS patients to be €15,280 in association with a 30% institutional incidence, concluded that antimold prophylaxis was likely cost-beneficial from the patient and hospital perspectives (29). Cost determination methods for IFDs have included gross costs (16, 31), expert opinion (33), and clinical trial data (34, 36); but studies reporting attributable cost, a key component of cost-effectiveness analyses, are few (19–21, 29, 35), and those using patient-level data are even rarer (29). Importantly, sound es-

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timates of attributable cost are dependent on the appropriate selection of case and reference groups in order to disentangle the confounding effect of underlying illness. In addition, measures of resource use alternative to cost which are independent of country and inflation are needed if health economic studies are to have improved generalizability. Thus, our goal was to determine the median hospitalization cost, length of stay (LOS), and consumption of costly antifungal treatment (C-AT: liposomal amphotericin B [L-AMB], voriconazole, posaconazole, caspofungin) attributable to IFD from a hospital perspective in high-risk hematology patients using actual hospital costs, preliminary results of which were used for the listing of posaconazole on Australia's national formulary.

(Preliminary results of this study were presented at the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy-Infectious Diseases Society of America 46th Annual Meeting, Washington, DC, 2008, absr. M-727.)

MATERIALS AND METHODS

Study design and setting. We undertook a retrospective case-control study of patients with acute leukemia or HSCT from 2002 to 2007 at Alfred Health, a 750-bed adult quaternary university-affiliated hospital network with heart/lung and HSCT units, the latter performing approximately 50 allo-HSCTs per year. Patients were identified from the International Classification of Diseases, 10th revision, Australian Modification, diagnostic codes and underwent manual chart review. Hospitalization costs 12 weeks subsequent to the index admission were also examined. Institutional ethics approval was obtained.

Matching criteria. Control patients were matched 1:1 with case patients using the following criteria: age within 10 years of a case patient, same underlying hematological disease or year of transplantation, and LOS at least as long as that of case patients prior to IFD, whose date of onset was determined by investigators (M.R.A.-R., M.S.) following manual chart review. The LOS criterion meant that selection of control patients began after chart review of case patients. Exclusion criteria were death at ≤48 h of admission, LOS of <3 days, HIV infection, or key data missing from the chart. If suitable controls were not found, the matching criteria were relaxed sequentially: the age criterion was dropped, alternative hematological conditions were considered, and for HSCT recipients, the year of transplantation within 2 years of the case patient was accepted. The LOS criterion was not relaxed, as this was regarded a key component of cost.

Clinical data and definitions. Collected information included demographics; antifungal drug indications and usage, expressed as defined daily doses (DDDs; WHO Collaborating Centre for Drug Statistics Methodology [http://www.whocc.no]), with prescribed daily doses of 250 mg/day used for L-AMB [11]); type/usage of chemotherapy; duration of neutropenia (absolute neutrophil count < 500 cells/mm³); status of underlying disease; HSCT type; graft-versus-host disease (GVHD); Charlson comorbidity index (CCI); intensive care unit (ICU) admission; IFD classification according to accepted criteria [10]; and in-hospital mortality and all-cause mortality 12 weeks after IFD diagnosis, as recorded in the medical chart. Date of IFD onset was defined as the first day of suspicious radiological abnormality or positive microbiology result. Although the galactomannan assay became available in 2005, it is not widely used and results of that assay were not used in this study.

Costing data. Hospitalization costs were obtained from an activity-based costing (ABC) system (Power Business Analytics) in use since 1994. It captures direct (i.e., patient-related) and indirect (e.g., overhead/capital outlay) medical costs reflecting fixed (e.g., salaries) and variable (e.g., investigations and medication costs) costs, ascribing 130 categories per patient which were collated into diagnostics, procedures, operating theater, pharmacy, ICU, and ward costs using mapping tables. Variable costs are patient specific and itemized, with fixed costs apportioned across all inpatients. Collection of detailed resource utilization data was restricted to antifungal treatment after preliminary analysis indicated that antifungal drugs were a major contributor to cost. Antifungal drug acquisition costs are primarily the list price or the Victorian Health Purchasing state contract price (Health Purchasing Victoria tender 2007 to 2009 [http://www.hpv.org.au]). Costs of antifungal drugs available on impress (only fluconazole) are apportioned across all ward patients. Indirect nonmedical (e.g., loss of productivity) and

intangible costs were not evaluated. The short time horizon obviated discounting of future costs or benefits. Costs are reported in Australian dollars inflated to 2009 using the health care component of the Australian consumer price index (Australian Institute of Health and Welfare [http://www.aihw.gov.au/publications/index.cfm/title/10954]), and final costs were converted to 2009 US$/€ using purchasing power parity (PPP) measures (Organisation for Economic Co-Operation and Development Stat Extracts [http://stats.oecd.org/index.aspx?datasetcode=SNA_TABLE4]).

Statistical analysis. The highly skewed nature of health outcomes (cost, LOS, antifungal treatment) motivated the choice of median (quantile) regression for data analysis. The median is a more reliable measure of central tendency than the mean or geometric mean, as it is more resistant to outlier influence and median regression models are less sensitive to assumptions that are made in generalized linear models (GLMs), particularly heteroscedasticity and error normality. In this technique, the coefficient represents the incremental median cost associated with a unit change in the explanatory variable; for dummy-coded categorical variables, this was the cost associated with the presence of the factor. We considered dependent variables in a univariable analysis against each outcome variable; all explanatory variables associated with each outcome variable with a P value of <0.1 and eliminated by backwards stepwise selection were selected for three multivariable models. We forced inclusion of case-control status (as the primary dependent variable of interest) and ICU admission (a factor known to be strongly associated with increased cost) into all multivariable models. Model fit was assessed using the link test. Reported P values were two-tailed, and for each analysis a P value of <0.05 was considered significant. All analyses used the Stata (version 11.0) statistical package (Stata Corp., College Station, TX).

RESULTS

Patient characteristics. A total of 110,744 admissions were screened from coding data, and 43 matched pairs were identified after manual chart review. Study groups were similar with regard to prespecified characteristics (Table 1) and additional clinical features, including prolonged neutropenia (≥10 days; 74% versus 70% for case and control patients, respectively) and baseline neutropenia (35% versus 33% for case and control patients, respectively) and poor-risk hematological disease (86% versus 84% for case and control patients, respectively). More case patients (21%) than control patients (9.3%) required ICU admission (P = 0.23), which occurred after IFD diagnosis in 8 of 9 case patients.

IFD complicated chemotherapy-induced aplasia in 24/43 (56%) patients, with induction (n = 21) regimens predominating. Hematological disease progression or leukemic relapse was a factor in 6/43 (14%) patients. Times of IFD onset from allo-HSCT were ≤30 days (n = 4), 30 to 100 days (n = 2), and late (>100 days) in 2 patients (who had GVHD and leukemic relapse, respectively); IFD preceded allo-HSCT in 2 patients.

Antifungal prophylaxis was administered to 60% (n = 26) of the patients in each study group, with fluconazole and itraconazole being the most common and voriconazole used off-label as prophylaxis after 2004 in small numbers. Antifungal prophylaxis was not administered to 11 case patients with IFD complicating postinduction aplasia (n = 2 in 2004, n = 2 in 2005, n = 4 in 2006, n = 3 in 2007).

Characteristics of case patients and clinical outcomes. The most common infection was sinopulmonary (70%), followed by fungemia (19%). A total of 21 fungal isolates (13 molds, 8 Candida species) were recovered from 20 patients with probable/proven IFDs. Aspergillus species were the most frequently isolated (10/21, 48%), with Aspergillus fumigatus recovered from 9/13 patients. Opportunistic molds (Scedosporium and Rhizopus species) were uncommon (n = 3). Non-Candida al-

TABLE 1. Characteristics of patients with and without invasive fungal infections[a]

Variable	IFD group (n = 43)	Control group (n = 43)	Variable	IFD group (n = 43)	Control group (n = 43)
Age (yr)			CCI		
Median	50	54	<4	41/43 (95)	38/43 (88)
Mean	44	52	≥4	2/43 (4.7)	5/43 (12)
range	26–76	20–83			
			Inpatient death	6/43 (14)	5/43 (12)
Male sex	23/43 (53)	22/43 (51)	Inpatient death at ≥14 days	6/43 (14)	3/43 (7.0)
Length of stay (days)					
Median	39	31	All-cause mortality at 12 wk for	11/42 (26)	8/36 (22)
Mean	44	29	evaluable patients		
Range	7–193	3–54			
			Infection[c]		NA[d]
Hematological malignancy			Sinopulmonary	30/43 (70)	
Leukemia	35/43 (81)	36/43 (84)	Fungemia	8/43 (19)	
Leukemia newly diagnosed	16/43 (37)	21/43 (49)	Hepatic	4/43 (9.3)	
Relapsed leukemia	8/43 (19)	3/43 (7.0)	Other[e]	2/43 (4.7)	
Stem cell transplantation	13/43 (30)	12/43 (28)	Disseminated	10/43 (23)	
Allogeneic	11/43 (26)	11/43 (26)	Localized	33/43 (77)	
Transformed MDS	2/43 (4.7)	2/43 (4.7)			
Lymphoma	4/43 (9.3)	4/43 (9.3)	Antifungal drug consumption (DDD)[f]		
Other	2/43 (4.7)	1/43 (2.3)	Total		
Poor-risk hematological disease[b]	37/43 (86)	36/43 (84)	Median	52	32
			Mean	70	33
Receipt of myelotoxic chemotherapy	32/43 (74)	33/43 (77)	Range	1.5–287	0–113
ICU admission	9/43 (21)	4/43 (9.3)			
			Costly antifungal treatment[g]		
Time of neutropenia < 500 cells/μl			Median	19	0
(days)			Mean	34	5.5
Median	24	19	Range	0–122	0–32
Range	5–53	1–47			
			Receipt of systemic antifungal	26/43 (60)	26/43 (60)
Neutropenia for ≥10 days	32/43 (74)	30/43 (70)	prophylaxis		
Neutropenia at baseline	15/43 (35)	14/43 (33)			
			No. of courses[h] of antifungal		
Date of index admission			prophylaxis		
2003	0/43 (0)	3/43 (7.0)	Fluconazole	13/31 (42)	11/37 (30)
2004	11/43 (26)	7/43 (16)	Itraconazole	14/31 (45)	19/37 (51)
2005	13/43 (30)	12/43 (28)	Voriconazole	4/31 (13)	4/37 (11)
2006	15/43 (35)	15/43 (35)	Posaconazole	0	1/37 (2.7)
2007	4/43 (9.3)	6/43 (14)	Caspofungin	0	2/37 (5.4)

[a] Unless indicated otherwise, data represent number of patients with the characteristic/total number of patients tested (percent).
[b] Poor-risk disease includes relapse, progressive disease, partial remission, induction, and failed induction.
[c] Some patients had one or more sites involved.
[d] NA, not applicable.
[e] One each central nervous system and hepatosplenic.
[f] DDD, defined daily dose.
[g] Denoted by liposomal amphotericin B, voriconazole, posaconazole, and caspofungin.
[h] Course denotes antifungal drug administered for any duration.

bicans Candida species accounted for 6 of 8 Candida isolates. Overall mortality at 12 weeks for 42 evaluable case patients was 26%. The high number of control patients (n = 7) unevaluable at 12 weeks limited outcome comparisons.

Characteristics of unmatched case patients. Our anticipated goal of 50 matched pairs (on the basis of feasibility considerations) was undermined by insufficient control patients, complicated by the loss of 24 potential candidates due to previous (n = 11) or possible (n = 13) IFD. Thus, our case target was easily met but 13 case patients (10 with probable/proven IFD) lacked suitable controls. Unmatched case patients had a mean age of 44 years (range, 25 to 67 years), median LOS of 36 days (range, 10 days to 133 days), and median hospitalization costs of AU$76,456 (mean, AU$160,854; range, AU$34,548 to AU$820,452). There were 7 HSCT recipients (5 allo-HSCT), and all had poor-risk hematological disease.

Cost, length of stay, and antifungal drug consumption adjusted for additional clinical characteristics. Differences between groups resulted in a crude median IFD-attributable cost of AU$28,309 (mean, AU$79,129) (Table 2) and LOS of 8 days (mean, 15 days). Median regression analyses adjusted for additional clinical characteristics not accounted for by matching criteria (Table 3). Of several candidate variables (P < 0.1), only receipt of chemotherapy and late (≥14 days) in-hospital mortality (in addition to case status and ICU admission) were included in the final model, on the basis of their consistent association on univariable analyses with all outcome variables.

On multivariable analysis, IFD status was associated with an excess median cost over that for the baseline patient of AU$30,957 (95% confidence interval [CI] = AU$2,368 to AU$59,546; P = 0.034) and 17 DDDs of C-AT. If ICU admis-

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TABLE 2. Hospitalization costs inflated to 2009 AU$ per patient for index hospitalization and hospitalizations 12 weeks after index admission, outpatient care excluded[a]

Cost category	Index hospitalization				Hospitalization up to 12 wk from index hospitalization[b]			
	Cost (2009 AU$)			P[c]	Cost (2009 AU$)			P[c]
	IFD group (n = 43)	Control group (n = 43)	Difference between groups		IFD group (n = 25)	Control group (n = 25)	Difference between groups	
Hospital stay								
Ward[d]	49,947	33,292	16,655 (21)[e]		26,512	10,927	15,585 (30)	
ICU	7,609	2,655	4,954 (6.3)		847	196	651 (1.2)	
Total	57,556	35,947	21,609 (27)	0.091	27,359	11,123	16,235 (31)	0.21
Pharmacy (total)[f]	72,529	22,130	50,399 (64)	<0.001	40,358	8,731	31,627 (60)	0.12
Antifungal drugs	26,219	4,775	21,444 (27)	<0.001	—[g]	—	—	—
Diagnostics								
Pathology	10,563	7,066	3,497 (4.4)		5,307	2,918	2,389 (4.5)	
Radiology	4,567	2,322	2,245 (2.8)		1,820	982	838 (1.6)	
Total	15,130	9,388	5,742 (7.3)	0.072	7,127	3,900	3,227 (6.1)	0.15
Procedures[h]	2,082	1,179	903 (1.1)	0.32	1,131	348	783 (1.5)	0.20
Operating theater	1,008	532	476 (0.6)	0.14	1,020	201	819 (1.6)	0.043
Total costs								
Mean	148,305	69,176	79,129[i]		76,995	24,303	52,692	
Median	81,691	53,382	28,309[j]	0.0099	37,815	11,237	26,578	0.098
Range	10,518–687,574	3,468–233,020			0–425,631	0–148,886		

[a] Values are reported as means (unless otherwise stated).
[b] For surviving matched pairs at 12 weeks.
[c] Test of difference between IFD and control groups used the Mann-Whitney U test.
[d] Ward costs include emergency and inpatient care.
[e] Values in parentheses represent percent difference.
[f] Pharmacy expenditure includes staff salaries as well as medications.
[g] —, data not available.
[h] Therapeutic or diagnostic procedures, e.g., bronchoscopy.
[i] Mean cost at purchasing power parity (2009): US$54,198 and €40,356.
[j] Median cost at purchasing power parity (2009): US$19,390 and €14,438.

sion was also required, then the excess median cost increased to AU$80,291 (95% CI = AU$33,636 to AU$126,946; P = 0.001) and an additional 19 DDDs of C-AT were required (P < 0.001). Late in-hospital mortality was strongly associated with prolonged excess median LOS (33 days; P < 0.001) and 13 DDDs of C-AT (P < 0.001) but not cost (P = 0.39), unless ICU admission was omitted from the multivariable model (AU$105,115; 95% CI = AU$60,437 to AU$149,792; P < 0.001). Case status was not associated with increased median LOS (P = 0.83), but following inclusion of 22 unmatched patients (13 case patients, 9 control patients) in a sensitivity analysis akin to that of Dubberke et al. (12), a significant association (LOS, 8 days; 95% CI = 1.8 to 14 days; P = 0.012) emerged, while median cost (AU$29,441; 95% CI = AU$5,571 to AU$53,310; P = 0.016) and C-AT (17 DDDs; 95% CI = 16 to 18; P < 0.001) remained largely unchanged.

Distribution of costs is shown in Table 2. Main determinants of the difference in mean cost were pharmacy costs (64%; P < 0.001), of which antifungal drugs comprised 27% (P < 0.001), followed by ward costs (27%; P = 0.091). Proportionate differences in mean hospitalization cost were maintained 12 weeks from the index hospitalization for the 25 surviving matched pairs (pharmacy costs, 60%; ward costs, 31%) but were not statistically significant.

Antifungal drug consumption according to treatment indication is presented in Fig. 1. Mean drug consumption was higher among case patients, with the exception of amphotericin B deoxycholate (AMB-d), but significant differences were observed for voriconazole (P < 0.001), L-AMB (P < 0.001), and caspofungin (P = 0.048). The small numbers (n = 3) using posaconazole (prior to its licensure) limited its interpretation. In case patients, median drug administrations were as follows: L-AMB 240 mg/day (mean, 266 mg/day) for 7.5 days (mean, 11 days); voriconazole, 400 mg/day (mean, 464 mg/day) for 6 days (mean, 10 days); and caspofungin, 50 mg/day (mean, 52 mg/day) for 6 days (mean, 10 days).

DISCUSSION

Determining disease attribution and broadening the generalizability of economic analyses are challenges we attempted to overcome in this study. A comparative attribution approach using a case-control method, followed by regression modeling to adjust for clinical characteristics not accounted for by matching criteria, was used to separate the confounding effect of underlying illness from IFD-related outcomes. Informed by Graves et al.'s caution against overestimating the cost of hospital-acquired infections (14), we therefore reported median outcomes to describe the typical value for most patients rather than the arithmetic mean, which, while relevant to payers, e.g., the hospital, is highly sensitive to outliers, thus limiting its generalizability while potentially overstating cost. Commonly

TABLE 3. Median regression model for hospitalization costs, LOS, and antifungal treatment per patient

Variable	Result by outcome[a]					
	Hospitalization cost[b] (AU$)		LOS (days)		Costly antifungal treatment[c] (DDD)	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P
Univariable analysis						
IFD patient	28,309 (568 to 56,049)	0.046	8.0 (0.57 to 15)	0.035	19 (18 to 20)	<0.001
LOS	1,961 (1,518 to 2,405)	<0.001	—[d]	—	0.45 (0.33 to 0.56)	<0.001
ICU admission	65,470 (19,224 to 111,716)	0.006	13 (0.99 to 25)	0.034	25 (5.6 to 44)	0.012
HSCT	53,549 (24,576 to 82,521)	<0.001	−2.0 (−13 to 9)	0.71	11 (−2.6 to 25)	0.11
Allo-HSCT	57,681 (27,602 to 87,760)	<0.001	5.0 (−6 to 16)	0.37	12 (−1.4 to 25)	0.078
Receipt of chemotherapy	49,268 (13,047 to 85,489)	0.008	25 (15 to 35)	<0.001	12 (3.2 to 20)	0.008
Inpatient death ≥ 14 days[e]	104,164 (51,646 to 156,681)	<0.001	45 (31 to 59)	<0.001	41 (17 to 65)	0.001
Inpatient death	52,502 (5,555 to 99,449)	0.029	10 (−3.24 to 23)	0.14	25 (5.6 to 44)	0.012
Age (yr)	−1,392 (−2,377 to −407)	0.006	−0.29 (−0.60 to 0.02)	0.066	−0.34 (−0.63 to −0.06)	0.018
Receipt of costly antifungal treatment[c]	426 (−162 to 1,014)	0.15	0.39 (0.23 to 0.54)	<0.001	—	—
Neutropenia ≥ 10 days	19,529 (−22,524 to 61,581)	0.36	19 (11 to 27)	<0.001	11 (2.5 to 20)	0.012
Neutropenia at baseline	−12,252 (−52,628 to 28,124)	0.55	−1.0 (−11 to 9.3)	0.85	−1.05 (−17 to 14)	0.89
Poor-risk hematological disease[f]	−40,267 (−85,936 to 5,402)	0.083	1.0 (−11 to 13)	0.87	1.4 (−20 to 23)	0.90
Newly diagnosed leukemia	−10,048 (−44,615 to 24,520)	0.57	7.0 (−1.81 to 16)	0.12	−5.3 (−20 to 9.2)	0.47
Multivariable analysis[g]						
Base case[h]	23,964 (−8,819 to 56,747)	0.15	12 (2.8 to 21)	0.011	0 (−1.5 to 1.5)	1.0
IFD patient[i]	30,957 (2,368 to 59,546)	0.034	7.0 (−0.95 to 15)	0.083	17 (15 to 19)	<0.001
ICU admission[i]	80,291 (33,636 to 126,946)	0.001	6.0 (−7.23 to 19.23)	0.37	19 (16 to 22)	<0.001
Receipt of chemotherapy	29,418 (−4,695 to 63,531)	0.09	20 (11 to 29)	<0.001	0 (−1.9 to 1.9)	1.0
Inpatient death ≥ 14 days[e]	24,824 (−32,713 to 82,360)	0.39	33 (17 to 49)	<0.001	13 (9.0 to 17)	<0.001

[a] Values are reported as medians.
[b] Cost inflated to 2009 AU$.
[c] For liposomal amphotericin B, 250 mg intravenously was regarded to be equivalent to 1 DDD (11), denoted by liposomal amphotericin B, voriconazole, posaconazole, and caspofungin.
[d] —, variables not included in the model.
[e] The reference group comprised surviving patients and 2 control patients who died early in their admission, i.e., within the first 7 days.
[f] Poor-risk disease includes relapse, progressive disease, partial remission, induction, and failed induction.
[g] Multivariable analysis included forced inclusion of case status and ICU admission and variables significant on univariable analysis (P < 0.1).
[h] The baseline patient who did not develop an IFD received chemotherapy and survived a minimum of 14 days in hospital. All values for each variable in the multivariable analysis refer to the excess cost, LOS, or antifungal drug consumption attributable to an IFD and added to the base case.
[i] Median excess cost for an IFD patient at purchasing power parity (2009): US$21,203 (95% CI = US$1,622 to US$40,784)/€15,788 (95% CI = €1,208 to €30,368) increasing to US$54,993 (95% CI = US$23,038 to US$86,948)/€40,948 (95% CI = €17,154 to €64,742) with intensive care unit admission.

used approaches for adjustment of highly skewed data include linear regression models for log-transformed dependent variables and GLMs with a logarithmic link function (26); however, normalization of data is not always successful (13), and for linear regression models, retransformation of predicted results may be misleading (26). Quantile regression models, in contrast, make no assumptions about distribution of errors or outcomes and can accommodate different quantiles, depending on the focus of interest, i.e., the median to describe the general population or higher quantiles for outliers (2). Predictably, the crude hospitalization cost in our matched-pairs analysis was right skewed, with median and mean IFD-attributable costs being AU$28,309 and AU$79,129 per patient, respectively. By median regression analysis adjusted for ICU requirement, receipt of chemotherapy and late (≥14 days) in-hospital mortality, the IFD cost was AU$30,957 (95% CI = AU$2,368 to AU$59,546; P = 0.034; approximating at a PPP of US$21,203/€15,788) over that for the baseline patient and consistent with the crude estimate, differing by <10%. Median excess cost increased to AU$80,291 (95% CI = AU$33,636 to AU$126,946; P = 0.001) if intensive care was also required, which occurred in 21% of case patients.

Antifungal drugs being a substantial component of our IFD-attributable cost is contrary to the findings of previous studies

(8, 27), which have found LOS to be the main determinant of hospitalization cost. This result was not unexpected due to the high acquisition costs of drugs we commonly use for treatment, namely, L-AMB, voriconazole, caspofungin, and, to a lesser extent, posaconazole.

Driving the difference in mean cost per patient was overwhelmingly pharmacy (64%; P < 0.001), of which antifungal drugs accounted for 43% of pharmacy expenditure or 27% of the overall difference (P < 0.001), with no significant difference in ward costs seen (27%; P = 0.091). The robustness of these results was confirmed in the 12-week analysis of subsequent inpatient care (pharmacy costs, 60%; ward costs, 31%), which was not significant, probably due to fewer surviving matched pairs (n = 25). Historically, antifungal drugs have accounted for 7 to 15% of total treatment costs (4, 27, 35), a finding supported by a recent U.S. study where intravenous antifungal drugs accounted for 7.2% of IA-associated hospitalization costs (16), but differences in case mix and clinical care are likely responsible.

Slobbe et al. (29), in a cohort similar to ours (2002 to 2007), used fluconazole prophylaxis and AMB-d (pre-2003) or voriconazole (typically, the less costly oral form) for treatment of IA. In contrast, our practice is characterized by antimold prophylaxis (58% of case patients, 70% of control patients) and
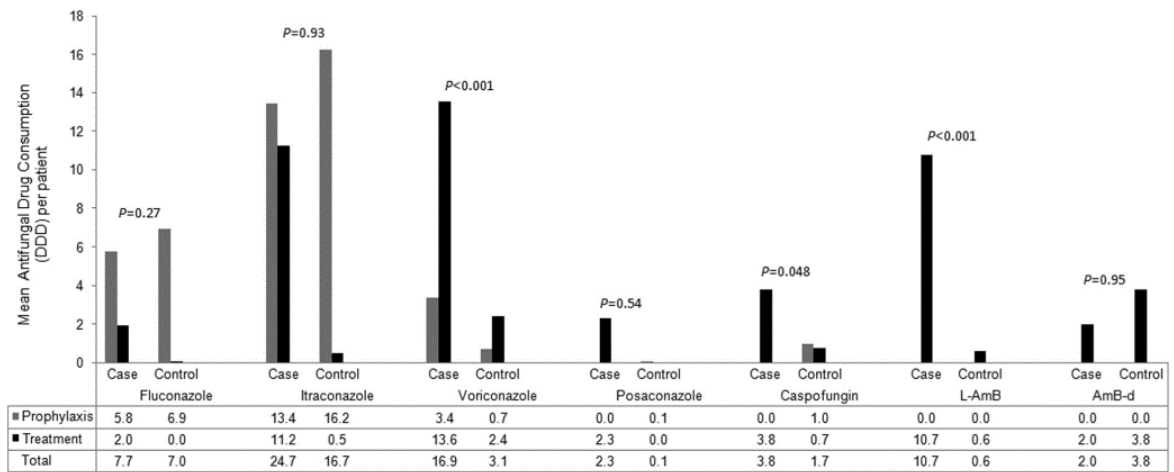
	Case Fluconazole	Control	Case Itraconazole	Control	Case Voriconazole	Control	Case Posaconazole	Control	Case Caspofungin	Control	Case L-AmB	Control	Case AmB-d	Control
■ Prophylaxis	5.8	6.9	13.4	16.2	3.4	0.7	0.0	0.1	0.0	1.0	0.0	0.0	0.0	0.0
■ Treatment	2.0	0.0	11.2	0.5	13.6	2.4	2.3	0.0	3.8	0.7	10.7	0.6	2.0	3.8
Total	7.7	7.0	24.7	16.7	16.9	3.1	2.3	0.1	3.8	1.7	10.7	0.6	2.0	3.8

FIG. 1. Mean antifungal drug consumption (in DDDs) for patients with and without invasive fungal diseases. For liposomal amphotericin B, 250 mg intravenously was regarded equivalent to 1 DDD (11). Differences in total drug consumption between case and control patients were determined using the Mann-Whitney U test.

C-AT (i.e., voriconazole, posaconazole, caspofungin, L-AMB), with voriconazole (means, 16.9 DDDs/case patient and 3.1 DDDs/control patient; $P < 0.001$) and L-AMB (means, 10.7 DDDs/case patient and 0.6 DDDs/control patient; $P < 0.001$) predominating principally for empiric or definitive treatment of IFD with AMB-d rarely used due to its recognized toxicities. The high contribution of antifungal treatment to hospitalization costs is also recognized in the ICU, where it is regarded a costly intervention, along with hemodialysis and blood product administration (18).

Alternatives to cost as a descriptor of resource utilization were sought in order to enhance generalizability. IFD status was associated with an excess crude median LOS of 8 days (mean, 15 days; $P = 0.083$) which reached significance after inclusion of 22 unmatched patients into the model (median, 8 days; 95% CI = 1.7 days to 14 days; $P = 0.012$), suggesting a sample size effect. Thus, a conservative estimate of the opportunity cost per IFD episode includes the loss of 8 ward-bed days at AU$700/day and a crude mean difference in antifungal treatment of AU$21,444, approximating AU$27,044 in total, notwithstanding other marginal costs, e.g., diagnostics and potential loss of ICU-bed days at AU$3,200/day.

C-AT represented another measure not previously described in the economic literature but proved useful in comparing subgroups, including case patients (17 DDDs; 95% CI = 15 to 19 DDDs; $P < 0.001$), ICU patients (19 DDDs; 95% CI = 16 to 22 DDDs; $P < 0.001$), and patients with late in-hospital mortality (13 DDDs; 95% CI = 9.0 to 17 DDDs; $P < 0.001$). In case patients, 17 DDDs approximates L-AMB at 250 mg/day for 7 to 10 days, followed by voriconazole at 400 mg/days for 7 days, and is consistent with documented prescribing, thus validating the model. Late in-hospital mortality, i.e., nonsurvivor care, was not more costly (compared to the reference group, comprising survivors and 2 control patients who died early in hospital), despite a strong association with

C-AT and prolonged LOS (33 days; $P < 0.001$), perhaps due to the competing effect of intensive care, which was required by some nonsurvivors (6 of 10; data not shown) but by more patients overall ($n = 13$). Indeed, with omission of ICU admission from the final model, nonsurvivor care was substantial (AU$105,115; $P < 0.001$), suggesting that IFD could prolong hospitalization and increase cost before death supervenes.

The economic burden of IFDs on hospitals is recognized (16, 20), but methodological differences between our study and others limit comparisons. Kim et al. (16), using actual costs reported median gross hospitalization costs of US$72,029 for a subset of hematology patients with IA (2000 to 2006), while Tong et al. (31), using cost-to-charge ratios (2003), reported a median gross cost of US$47,949 for non-HSCT hematology patients. Menzin et al. (20) estimated the mean IFD-attributable cost in patients with hematological malignancies and HSCT recipients to be US$37,046 ($P < 0.001$) and US$60,190 ($P < 0.001$), respectively, a range which includes our crude mean estimate approximating at a PPP of US$54,198. These studies (16, 20, 31), like others now ≥10 years old (8, 27, 28, 35), used administrative data sets, which have poor case detection (6); in our case, an administrative IFD diagnosis was absent for 13 possible case patients.

Study limitations include the small sample size, reflecting the epidemiology of a disease with a low institutional incidence (17), compounded by difficulties in finding suitable controls. Inpatient care underestimates the true burden of IFDs, which have outpatient and societal costs, but previous studies have suggested that >50% of costs are incurred in hospital (35). Generalizability, a concern of single-center studies, was mitigated by median regression modeling and C-AT as a resource metric. Use of retrospective data in combination with ABC is a valid approach (15), with ABC being a highly regarded cost-capturing tool (3); however,

studies utilizing bottom-up methods are few (29), with proxies such as cost-to-charge ratios popular in the United States, despite their recognized shortcomings as billing parameters rather than actual expenses (15).

Gross hospitalization costs are of interest, but attributable estimates are preferred for pharmacoeconomic analyses. To this extent, our case and reference groups were well-defined, and chart review ensured that only patients truly with or without IFD were included. Time-dependent bias was addressed by controlling for LOS prior to IFD onset, thus separating preinfection from postinfection costs (14). Inclusion of parameters (e.g., receipt of chemotherapy) predictive of treatment-related complications not controlled for (e.g., mucositis) minimized residual confounding. A sensitivity analysis addressed omitted variables and selection biases inherent in matched-cohort studies (14) by including all unmatched patients and showed similar results. The CCI was poorly discriminatory in our cohort, as in HSCT recipients (30), because many comorbidities are exclusion criteria for chemotherapy, and therefore, no adjustment for comorbidities was made. Strategies such as prophylaxis as part of a stewardship program may reduce costs, as highlighted by the few patients (2 to 3/year, 2004 to 2007) who failed to receive antifungal prophylaxis and developed IFD during postinduction aplasia.

Ameliorating the economic burden of IFDs while optimizing the return from finite health care resources is possible with better diagnostics, improved antifungal stewardship, and individualized prophylaxis. In our setting, the attributable cost of an IFD is driven by pharmacy expenditure, of which antifungal drugs are a major contributor, with supportive care, i.e., ICU admission, also being substantial. Our methods are applicable to other settings, and the results provided can inform future studies assessing the cost-effectiveness of IFD interventions.

ACKNOWLEDGMENTS

REFERENCES

1. Baddley, J. W., et al. 2010. Factors associated with mortality in transplant patients with invasive aspergillosis. Clin. Infect. Dis. 50:1559–1567.
2. Bang, H., and A. A. Tsiatis. 2002. Median regression with censored cost data. Biometrics 58:643–649.
3. Barnett, P. G. 2009. An improved set of standards for finding cost for cost-effectiveness analysis. Med. Care 47:S82–S88.
4. Cagnoni, P. J., et al. 2000. Pharmacoeconomic analysis of liposomal amphotericin B versus conventional amphotericin B in the empirical treatment of persistently febrile neutropenic patients. J. Clin. Oncol. 18:2476–2483.
5. Caira, M., et al. 2008. Invasive fungal infections in patients with acute myeloid leukemia and in those submitted to allogeneic hemopoietic stem cell transplant: who is at highest risk? Eur. J. Haematol. 81:242–243.
6. Chang, D. C., et al. 2008. Comparison of the use of administrative data and an active system for surveillance of invasive aspergillosis. Infect. Control Hosp. Epidemiol. 29:25–30.
7. Cornely, O. A., et al. 2007. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N. Engl. J. Med. 356:348–359.
8. Dasbach, E. J., G. M. Davies, and S. M. Teutsch. 2000. Burden of aspergillosis-related hospitalizations in the United States. Clin. Infect. Dis. 31:1524–1528.
9. De Pauw, B., and J. P. Donnelly. 2007. Prophylaxis and aspergillosis—has the principle been proven? N. Engl. J. Med. 356:409–411.
10. De Pauw, B., et al. 2008. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin. Infect. Dis. 46:1813–1821.
11. de With, K., et al. 2005. Hospital use of systemic antifungal drugs. BMC Clin. Pharmacol. 5:1.
12. Dubberke, E. R., K. A. Reske, M. A. Olsen, L. C. McDonald, and V. J. Fraser. 2008. Short- and long-term attributable costs of Clostridium difficile-associated disease in nonsurgical inpatients. Clin. Infect. Dis. 46:497–504.
13. Graves, N., F. Birrell, and M. Whitby. 2005. Effect of pressure ulcers on length of hospital stay. Infect. Control Hosp. Epidemiol. 26:293–297.
14. Graves, N., et al. 2010. Estimating the cost of health care-associated infections: mind your p's and q's. Clin. Infect. Dis. 50:1017–1021.
15. Jegers, M., D. L. Edbrooke, C. L. Hibbert, D. R. Chalfin, and H. Burchardi. 2002. Definitions and methods of cost assessment: an intensivist's guide. ESICM Section on Health Research and Outcome Working Group on Cost Effectiveness. Intensive Care Med. 28:680–685.
16. Kim, A., D. P. Nicolau, and J. L. Kuti. 14 June 2010. Hospital costs and outcomes among intravenous antifungal therapies for patients with invasive aspergillosis in the United States. Mycoses. [Epub ahead of print.]
17. Kontoyiannis, D. P., et al. 2010. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin. Infect. Dis. 50:1091–1100.
18. McLaughlin, A. M., J. Hardt, J. R. Canavan, and M. B. Donnelly. 2009. Determining the economic cost of ICU treatment: a prospective "microcosting" study. Intensive Care Med. 35:2135–2140.
19. Menzin, J., et al. 2005. Excess mortality, length of stay, and costs associated with serious fungal infections among elderly cancer patients: findings from linked SEER-Medicare data. Value Health 8:140–148.
20. Menzin, J., et al. 2009. Mortality, length of hospitalization, and costs associated with invasive fungal infections in high-risk patients. Am. J. Health Syst. Pharm. 66:1711–1717.
21. Morgan, J., et al. 2005. Excess mortality, hospital stay, and cost due to candidemia: a case-control study using data from population-based candidemia surveillance. Infect. Control Hosp. Epidemiol. 26:540–547.
22. Neofytos, D., et al. 2009. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance Registry. Clin. Infect. Dis. 48:265–273.
23. Pagano, L., et al. 2006. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica 91:1068–1075.
24. Pagano, L., et al. 2010. Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study. Haematologica 95:644–650.
25. Pagano, L., L. Fianchi, and M. Caira. 2008. Pulmonary aspergillosis in hematologic malignancies: lights and shadows. Haematologica 93:1611–1616.
26. Polsky, D., and H. Glick. 2009. Costing and cost analysis in randomized controlled trials: caveat emptor. Pharmacoeconomics 27:179–188.
27. Rentz, A. M., M. T. Halpern, and R. Bowden. 1998. The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. Clin. Infect. Dis. 27:781–788.
28. Slavin, M., et al. 2004. Burden of hospitalization of patients with Candida and Aspergillus infections in Australia. Int. J. Infect. Dis. 8:111–120.
29. Slobbe, L., et al. 2008. Outcome and medical costs of patients with invasive aspergillosis and acute myelogenous leukemia-myelodysplastic syndrome treated with intensive chemotherapy: an observational study. Clin. Infect. Dis. 47:1507–1512.
30. Sorror, M. L., et al. 2005. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 106:2912–2919.
31. Tong, K. B., C. J. Lau, K. Murtagh, A. J. Layton, and R. Seifeldin. 2009. The

economic impact of aspergillosis: analysis of hospital expenditures across patient subgroups. Int. J. Infect. Dis. 13:24–36.

32. **Ullmann, A. J., et al.** 2007. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N. Engl. J. Med. 356:335–347.

33. **Van Campenhout, H., S. Marbaix, M. P. Derde, and L. Annemans.** 2008. Voriconazole treatment of invasive aspergillosis: real-world versus health-economic model results. Clin. Drug Invest. 28:509–521.

34. **Wenzel, R., et al.** 2005. Economic evaluation of voriconazole compared with conventional amphotericin B for the primary treatment of aspergillosis in immunocompromised patients. J. Antimicrob. Chemother. 55:352–361.

35. **Wilson, L. S., et al.** 2002. The direct cost and incidence of systemic fungal infections. Value Health 5:26–34.

36. **Wingard, J. R., et al.** 2007. Resource use and cost of treatment with voriconazole or conventional amphotericin B for invasive aspergillosis. Transpl. Infect. Dis. 9:182–188.

Automated detection of invasive mold diseases using natural language processing of CT scan reports in haematology-oncology patients: making real-time surveillance a reality

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Background

Methods

Results

Discussion

References

Appendix 5

Intermittent liposomal amphotericin prophylaxis in high-risk haematology-oncology and SCT patients from an Australian Transplant Centre

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Background

Methods

Results

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References

Appendix 6

Automatic detection of patients with invasive fungal infection from free-text computed tomography (CT) scans

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Abstract

Background: Invasive fungal infections are associated with considerable health and economic costs. Surveillance of the more diagnostically challenging invasive fungal diseases (IFDs), specifically of the sino-pulmonary system, is not feasible for many hospitals because case finding is a costly and labour intensive exercise. We developed text classifiers for detecting such IFDs from free-text radiology (CT) reports, using machine-learning techniques.

Method: We obtained free-text reports of CT scans performed over a specific hospitalisation period (2003 to 2011), for 264 IFD and 289 control patients from three tertiary hospitals. We analysed IFD evidence at patient, report, and sentence levels. Three infectious disease experts annotated the reports of 73 IFD-positive patients at sentence level, and graded the sentences as to whether they suggested or excluded the presence of IFD. Reliable agreement between annotators was obtained and this was used as training data for our classifiers. We tested a variety of Machine Learning (ML), rule based, and hybrid systems, with feature types including *bags of words*, *bags of phrases*, and *bags of concepts*, as well as report-level *structured* features. Evaluation was carried out over a robust framework with separate Development and Held-Out datasets.

Results: We achieved very high recall at report- and patient-levels over unseen data: 95 and 100% respectively. Precision at report-level over held-out data was 71%, however, most of the associated false-positive reports

(53%) belonged to patients that had a previous positive report appropriately flagged by the classifier, reducing any negative impact in practice.

Conclusions: Our machine learning application holds the potential for developing systematic IFD surveillance systems for hospital populations.

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1 Introduction

Invasive fungal diseases (*IFDs*) are associated with considerable health [1,2] and economic costs [3,4]. Among the immunocompromised host population, patients with haematological malignancies and haematopoeitic stem cell transplant recipients (HSCTs) carry the greatest burden of IFDs [1,2]. The incidence of IFDs is highly variable ranging from 8% to 48% in patients with acute myeloid leukaemia and HSCT patients [1,5]. IFDs of the sino-pulmonary system, of which invasive *aspergillosis* (IA) is most common, now comprise the majority of IFDs [1,2]—focus in this paper is exclusively on this class of IFDs. The short-term mortality of invasive pulmonary *aspergillosis* remains unacceptably high at 34-43% in more recent reports among HSCT recipients and patients with a variety of haematological malignancies [5–7]. Several authorities and professional societies advocate that *surveillance* of IFDs should be the standard of care [8–10].

Surveillance is a necessary step towards defining the burden of IFDs, informing and evaluating choice of preventative strategies, tracking epidemiological data in response to changing therapeutic advances, host or environmental factors [11], and recognizing sporadic but catastrophic healthcare related outbreaks [12]. At present, surveillance of IFDs is not routinely performed in most hospitals for a variety of reasons, including cost and the absence of an easily identifiable laboratory trigger. Laboratory-based surveillance for IFDs is not suitable because isolation of infection-causing molds occurs in less than 50% of cases [13] and/or patients may be too unwell to undergo invasive diagnostic procedures. Further, non-culture based tests are not widely available in hospitals, or may be associated with a delayed turn-around. Clinical review is challenging, requiring multiple data sources (radiology, clinical, laboratory) and multi-disciplinary teams, followed by the application of complicated definitions [1,14,15]. Thus, traditional methods of surveillance using either clinical review, laboratory-based methods, or less commonly administrative data are costly,

labour intensive, error prone, and subject to incomplete case findings [1,16].

The optimal screening method for IFD surveillance is undefined but the choice of screening method is critically important to minimise effort while maximising case capture. Computed tomography (CT) is appealing as a screening method for IFD surveillance. CT is a key diagnostic test for IFDs stipulated in internationally recognised guidelines [14], and lung involvement is present in the overwhelming majority (90% to 100%) of patients with IFDs [1,2,15]. CT is a non-invasive test uniformly performed when IFD is suspected and it is widely available in hospitals with results reported within hours rather than days. Although the radiologic features of IFDs are not specific for IFD [17], CT remains a valuable diagnostic adjunct [14].

In this paper, we address the challenge of surveillance of sino-pulmonary IFDs using the technique of directly processing free-text radiology reports, specifically CT scans, as a means of screening patients for features supportive of IFD. Text Mining techniques over scans have been previously proposed to support detection and surveillance, including for infectious diseases and their symptoms (e.g., fever) [18–24], but not previously to the challenge of detecting IFDs. The approach has the potential to identify patients with suspected IFDs in real-time, delivering to hospitals a feasible, sustainable and cost-effective solution to the task of IFD surveillance with minimal interruption to routine clinical workflow.

Text classifiers were developed for CT scan reports at the sentence, individual report, and patient level. Classification at the report level enables the potential for real-time detection and monitoring of incidence of IFDs, while patient-level classification enables a surveillance and reporting mechanism for IFD. Sentence-level classification is shown to facilitate improved classification performance at the report- and patient-levels, and has the added benefit of indicating "supporting evidence" for a positively-classified report. While both report- and patient-level classification could facilitate detection and monitoring of patients with IFD, report level classification further enables the possibility of real-time detection. The collection of scan reports used was drawn from three major Melbourne hospitals. A subset of these reports was manually annotated by infectious disease physicians with domain expertise in the area of IFDs. Manual annotation was performed *at the sentence level*, where the physicians arbitrated over several categories according to pre-specified annotation guidelines, of which presence or absence of language supportive of the presence of an IFD was most discriminatory. Note that we use a light annotation schema, requiring much less annotation effort than is generally required for machine-learning approaches to biomedical text mining tasks (which may require annotation of phrases and relationships between entities). Moreover, we ensured that the machine-learning classifiers have no hand-coded intervention: i.e., they were

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constructed in a fully automated fashion. This makes the techniques more transferable to other problem tasks, and means even better performance could potentially be achieved on deployment in specific contexts, via hand-crafted tuning.

Evaluation showed high Recall at the report- and patient-levels: 95% and 100% respectively. Precision was lower than this for both tasks, especially for report classification; however, many of the false-positives were found to be "early" indicators for patients later classified as positive for IFD, as well as redundant alerts over patients earlier tagged as positive by the system. The former cases could be beneficial to a surveillance system through earlier identification of potential cases; the latter alerts could be handled differently to first-time alerts to reduce overhead. Importantly, the number of false negatives or missed cases was few over reports annotated as supportive of IFD. Hence we consider the systems developed to be a strong basis for automated surveillance of IFDs.

Our ultimate aim is to develop an automated biosurveillance system that can be trained to detect a new condition by having an expert in that condition analyse and annotate data directly. In particular, other than data-annotation, the models require no human input during training. We intend the text mining component will ultimately be part of a pervasive biosurveillance system which integrates other types of electronic data routinely available in hospitals, such as pathology results and pharmacy drug-dispensing information, to enhance accuracy above the use of text-mining alone.

2   Related Work

As noted by Demner-Fushman et al. [25], radiology reports are a rich source of knowledge and were used in early applications of still-influential clinical NLP systems (e.g., [26,27]). The types of reports examined have varied (e.g., X-ray, CT), and tasks have ranged from specific classification tasks to more general named entity recognition (e.g., [28]), coding, and information extraction (e.g., [29,30]), across a broad range of challenges. Applications have included disease/infection detection and surveillance from radiology reports, with pneumonia being the disease of greatest focus. A number of authors have demonstrated favourable performance of more sophisticated NLP techniques for identifying/classifying radiology reports for specific purposes, in comparison to simpler techniques: for example, Solti et al. [31] demonstrate the efficacy of machine-learning NLP over keyword search for identifying X-ray reports of cases of acute lung injury; Womack et al. [32] show that the NegEx system [33] compares favourably to keyword search for identifying cases of acute fracture.

Work associated with LDS Hospital from Salt Lake City (Utah, US), has resulted in a series of systems for

coding concepts and performing disease and infection surveillance, particularly the identification of pneumonia cases from X-ray reports. Haug *et al.* [26] used Augmented Transition Networks (ATNs) for syntactic-level processing of X-ray reports and a Bayesian Network model for semantic-level representation and constraining the interpretation of concept terms. The system was evaluated on the task of identifying (three) pneumonia-related concepts and inferring the presence (or absence) of acute bacterial pneumonia from X-ray reports, and was found to perform to a level comparable to physicians: 0.95 / 0.78 / 0.85 recall/precision/specificity respectively for the system versus 0.94 / 0.87 / 0.91 for the team of three physicians employing majority vote.

More recently, Tinoco *et al.* [34] compared the effectiveness of a more general version of LDS Hospital's computerized surveillance system (CSS), against manual methods (i.e., chart review) on the tasks of detecting reportable adverse drug effects (ADE) and hospital-acquired infections (HAIs). They found that the automated system detected substantially more HAIs than did manual review (92% vs 34%) while the two methods did not differ substantially on detecting ADEs, demonstrating the value of automated surveillance techniques for HAIs in general. One significant source of HAIs *missed* by the CSS was information in physician's narratives—58% of the HAIs missed by the CSS were explicitly described in the narratives: i.e., adding text mining capabilities would have improved performance of HAI-detection up to approximately 97%.

The general clinical NLP system MEDLEE has been used for a number of tasks involving processing radiology reports, including in early work by its authors [27]. Of specific relevance to our context, Mendonça *et al.* [35] describe the application of MEDLEE to detecting pneumonia in newborns, from a range of text sources, including radiology, pathology and microbiology reports. They demonstrate strong performance, compared to judgements made by clinicians: 71% sensitivity and 95% specificity.

Travers *et al.* [36] describe a search system for identifying patients with acute respiratory illness, such as influenza, SARS, and anthrax. The system pre-processes text (e.g., replacing acronyms, abbreviations, and common misspellings), and clinician-designed queries are used to identify records indicating such cases. Specificity was high (0.99) but sensitivity was low (0.24).

Jones *et al.* [37] describe a surveillance approach using a simple NLP pipeline to detect methicillin-resistant *Staphylococcus aureus* within US Veterans' Affairs (VA) medical centers. Their NLP pipeline maps concepts to SNOMED-CT and uses rules based on matching against relevant keywords. With the benefit of a large data-collection (more than 65,000 records) available for training, they obtain 99% sensitivity and specificity. Matheny et al. [24] also tackle the task of detecting infectious symptoms from VA patient

records. Their NLP approach also extracts concepts (against UMLS, HL-7, and SNOMED-CT) and also uses rules based on concept- and keyword-matching.

Elkin *et al.* [38] use an NLP pipeline to identify cases of pneumonia, and related pulmonary diseases, by processing radiology reports (chest x-rays and CT scans), in a task closely related to ours. Their rule-based approach, however, is very different to our machine-learning approach. Elkin *et al.* use an NLP pipeline that identifies clinical concepts in the text reports and maps them into SNOMED-CT concepts. They then hand-author rules operating over the SNOMED-CT concepts to attempt to identify positive (or uncertain) assertions of pneumonia (or positive assertions of infiltrates or consolidations when pneumonia assertions are not identified) in various sections of each radiology report. The rule-set for classifying "uncertain" cases (as well as "positive") leads to high performance: 1.0 sensitivity and 0.98 specificity. The risk with their approach is whether the rules were overfit to the data, since only 400 reports were used and testing occurs over the same dataset used to construct the rules.

Recently, Bejan *et al.* [39] tackled the problem of identifying intensive care patients with pneumonia from narrative reports, using techniques with some commonalities to those we describe below. In particular, they combine the use of n-grams with use of UMLS concepts as features. They use a feature-selection technique based on statistical significance testing to rank features, which results in large performance improvements over their baseline.

Finally, another recent work has explored the detection of HAIs from text, in this case over Swedish patient records [40]. The annotation for this article was performed at patient level over 213 records, and also aimed at achieving high recall. They obtained close to 90% recall for 67% precision at patient level, and highlighted feature selection as a crucial step for raising recall.

3   Methods I: Data Collection and Annotation

This section describes the corpus of reports and annotation process used for training (and evaluating) the various classifiers for identifying scan-reports and patients considered to be positive for IFD. Supervised machine learning techniques were used for the report classification task. A *gold standard* dataset of reports was constructed from a collection of CT reports sourced from three different hospitals (listed below) and annotated by experts in Invasive Fungal Disease.

3.1 Data collection

CT reports were collected for patients known to have contracted an *Invasive Fungal Disease (IFD)* along with those for control patients, from three different hospitals in Melbourne (Australia): the Alfred Hospital (AH), the Royal Melbourne Hospital (RMH), and the Peter MacCallum Cancer Centre (PM). IFD and uninfected patients from 2003 to 2011 inclusive were identified from previously completed observational and controlled clinical mycology studies [3, 41–44]. Additional cases were identified by interrogating HSCT (RMH), infectious diseases consultation (PM) databases and microbiology records (AH, RMH). Patients lacking CT reports were excluded.

CT reports were obtained from each hospital information system as text files and de-identified. CT reports of any anatomical site were included; however, in order to focus on sino-pulmonary involvement, brain reports were later excluded from analysis due to few patients with brain infection, except for brain scan reports performed in combination with another site e.g. chest and/or sinus. All scans were performed during the clinical encounter; an encounter was defined as being from admission to either discharge, death or transfer; or for those few outpatients, from performance of the diagnostic scan and for 12 weeks thereafter were included. A follow up duration of 12 weeks was chosen since clinical practice guidelines recommend 12 weeks of treatment for IFDs [45]; evaluating radiological response over this period was therefore important.

For each report, we used the free-text section, which contains the radiologist's interpretation of the scan and (with the exception of reports from one hospital) the reason for the requested scan as written by clinicians. We obtained data for 553 patients of the hospitals over the given period, i.e., over the total pool including IFD-positive and control patients. Each report was annotated independently of whether the patient had an IFD or not; therefore, in some cases a report from an IFD-positive may not be suggestive of IFD and would therefore be annotated as negative for such. Our goal for this work was to build and evaluate classifiers according to physicians' interpretation using *only the text in the scan reports*, regardless of how other evidence (e.g., from pathology reports) may have impacted diagnosis of patients.

3.2 Data annotation

Manual annotation of the text reports was guided by annotation guidelines developed at the start of the process and subsequently refined through consultation. From the dataset of 553 patients, an initial sample of 73 IFD-positive patients was extracted in order to develop the annotation schema and to measure inter-annotator agreement.

Annotation categories agreed on by the clinician experts are shown in Table 1. Categories include both positive and negative presence of evidence of fungal infection, as well as indicators that may be appropriate to related tasks (e.g., 1n: *positive but not specific to IFD*). Sentence-level annotations were used to train and evaluate sentence classification systems, while report-level annotations were applied for evaluating over the main task of report-level classification. Note that annotation at the *concept-mention* level was avoided in order to keep the annotation process relatively lightweight so as to make the process more easily transferable to other similar tasks.

Annotation-level	Code	Description
Sentence	1s	Positive but specific to IFD e.g. halo, nodule, cavity, focal mass; for sinus reports consider bony erosion as 1s (with all other abnormalities 1n)
	1n	Positive but not specific to IFD i.e. may denote pneumonia e.g. infiltrate, consolidation, ground glass, effusions; all abnormalities in sinus reports other than bony erosion should be regarded as 1n
	2	Speculative comment eg clinical query such as "query IFD"
	3	Important negatives; either no pathology specifically related to an IFD e.g. No cavity seen, no evidence of invasive aspergillosis, no necrosis, orbit unremarkable
	4	Equivocal e.g. radiologist hedging their bets regarding the final diagnosis
	5	Other process e.g. pulmonary embolism, pulmonary oedema, BOOP
	6	Clinical alert e.g. treating doctor directly contacted by radiologist, or followup test advised
	7	Other valuable data e.g. for a registry such as outcome of IFD such as disease progression or resolution
Report	1	Suggestive of IFD
	2	Equivocal or indeterminate for IFD
	3	Negative for IFD

Table 1: Set of labels for the initial annotation of 73 patients. We highlight in bold the categories that were selected to build classifiers.

For the first iteration of annotation, the annotation targets were the reports associated with the aforementioned 73 patients. Annotation was performed at both sentence and report levels: i.e., the annotators marked (entire) sentences as per the sentence-level annotation labels in Table 1, while reports were annotated as per the report-level categories in the table. Note that each sentence could have multiple labels, but reports had only one. Examples of annotated sentences are provided in Table 2.

Code	Description
1s	Findings: There are several areas of parenchymal opacification scatted throughout both lungs with a few smaller nodules seen in the lower lobes.
1n	These have a peripheral predominance and there are areas of surrounding ground-glass opacification.
2	? Chest infection
3	The upper abdomen is unremarkable.
4	Patchy changes within the left base may indicate underlying infection including atypical airways invasive fungal and gram-negative bacteria, (however it is difficult to determine the degree of atelectasis vs. infection).
5	PR bleed + diabetic.
6	Referring doctor alerted at 5 p.m.
7	Conclusion: Almost complete resolution of the left pleural effusion.

Table 2: Annotated examples for each of the labels. Note that each sentence can have multiple tags, e.g. "Air bronchograms are seen in some of these areas but no central cavitation present." (tags *1n* and *3*)

Annotation was performed by the three infectious diseases physicians (authors MAR, MS, KT). The complete dataset was annotated by the primary annotator (MAR), with the other two annotators (MS,

KT) annotating half the collection each, ensuring that all items were annotated by two experts. Inter-annotator agreement was measured using Cohen's Kappa metric [46], the accepted standard for measuring agreement in linguistic annotation. *Kappa* scores were calculated by comparing the results of the primary annotator to those of the other annotators. This was performed separately for each label. Final *kappa* scores are shown in Table 3. Note that since labels 2 and 4 are strongly related, we also measured agreement of their joint occurrence on sentence instances.

Annotation-level	Label	Kappa
Sentence	1s	0.64
	1n	0.44
	2,4	0.18
	3	0.58
	5	0.22
	6	0.49
	7	0.31
Scan Report	1	0.49
	2	0.06
	3	0.83

Table 3: Kappa scores when comparing annotator 1 vs joint 2 and 3; each row represents one (or two) categories separately.

Kappa values in the vicinity of 0.60 and higher are considered indicative of at least moderate agreement [47]. For our annotation task, only labels 1s ("positive and specific to IFD") and 3 ("important negative") surpassed or approximated this value for sentence-level annotation. This showed that these categories were best suited for building reliable automatic classifiers. At report level, Category 2 ("equivocal or indeterminate for IFD") obtained very low agreement score; this adversely impacted the agreement score for Category 1 ("Suggestive of fungal infection"). These scores indicated that there was no clear boundary between reports that were interpreted as "equivocal" and those interpreted as "positive" for IFD. In practice, a binary classifier that alerted on "equivocal" reports would improve recall by minimising missed cases. By merging Categories 1 and 2, i.e., treating report-level classification as binary, high inter-annotator agreement was achieved (*kappa*=0.83).

We thus developed and evaluated binary sentence classifiers to distinguish two categories: "positive and specific to IFD" and "important negative for IFD". Sentences were thereby classified into three mutually-exclusive categories: *positive, important negative,* or *neutral* with respect to IFD. At report level, we developed binary classifiers to discriminate *negative* reports from those that were *positive or equivocal* for IFD.

3.3 Gold Standard and Evaluation Datasets

For classifier training and evaluation purposes, we partitioned our entire data collection into the following subsets, variously used for training sentence-level classifiers, and evaluating classifiers for the sentence-, report-, and patient-level classification task. Table 4 summarises these partitions and their purposes.

Dataset	Contents	Purpose
Development Dataset (annotated at sentence level)	reports from 120 patients (60 IFD-positive, 60 control)	• Training sentence classifiers • Evaluation at all levels (using cross-fold validation)
Held-Out-Verified Dataset (annotated for IFD at report-level)	reports from 40 patients (20 IFD-positive, 20 control)	• Training report-level classifiers • report- and patient-level Evaluation
Held-Out-Unverified Dataset (held out; unexamined)	reports from 393 patients	• Patient-level Evaluation
Complete Dataset	553 patients 1716 scan reports	

Table 4: Subdivisions of the dataset and their purpose.

3.3.1 Development Dataset

After finalising the annotation schema, we proceeded to annotate our gold standard data. From the initial collection of 73 patients, 13 patients were removed as they did not satisfy the inclusion criteria. Specifically excluded were patients that had brain scans only, not performed in combination with a lung or sinus scan. (Note: these patients were moved to the set of un-annotated patients used as held-out testing data, as described below). For cases where there was inter-annotator disagreement, annotations from the primary annotator (MAR) were used as gold standard, and the annotated dataset was subsequently extended by employing this annotator only. Similarly, reports from 60 control patients were annotated as per the process described above, resulting in a dataset of 120 patients annotated at both sentence- and report-levels. We henceforth refer to this as the *Development Dataset*: this corpus was used for developing the sentence-level classification models and for cross-validation evaluations. During the annotation process, we observed that some (8 in total) of the patients in the control set had reports that were annotated as IFD-positive by the medical expert; these patients were moved to the IFD-positive group. Conversely, there were two cases where IFD-positive patients did not have any positive evidence *in the text*, and these were moved to the control set[1]. There was a total of 13 reports associated with these 10 patients. Table 5[2]

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[1]These patients may have been diagnosed as IFD-positive using other tests; however, the scope of this paper is limited to the evidence in the scan reports themselves.

[2]From now on, the refered Tables will be found in the Appendix.

shows characteristics of the Development Dataset; We see that control patients tend to receive fewer scans, and that there are clear differences across hospitals in the ratio of scans per patient.

3.3.2 Held-Out Verified Dataset

An additional 40 patients (20 controls and 20 positives) were annotated at report level (not at sentence level), in order to create a held-out dataset for more reliable evaluation of our systems at report and patient level. It was found that 5 patients originally categorised as IFD-positive actually had no IFD-positive reports, and 2 control patients actually had reports labelled as IFD-positive by the medical experts; these patients (with 22 associated reports) were redistributed accordingly. Characteristics for this test set are also shown in Table 5. We henceforth refer to this dataset as *Held-Out-Verified*.

3.3.3 Unverified Data

The remaining reports were not manually labelled by the medical experts, neither at sentence nor report level: i.e., these remained were attributed to positive or control patients as determined by the treating hospital. These unlabelled reports were used for a final patient-level evaluation of our systems. The distribution across hospitals of this dataset is also shown in Table 5. In this case, it is possible that information used to classify patients as positive came from a source other than the reports themselves (e.g., pathology results), making it a less reliable gold-standard for purely text classification evaluation. This corpus is henceforth referred to as *Held-Out-Unverified*.

4 Methods II: Constructing the Classifiers

Following is a description of construction of the Text Classifiers, at each of sentence-, report-, and patient-levels.

4.1 Feature Representations

For the implementation of our machine-learning approach to text classification, we identified a number of useful features, all of which were computed fully automatically. Two main types of features were explored: "Bag", and "Structural". Bag features can be applied to both sentence and report-level prediction, while Structural features can only be applied at the report level.

In order to represent the instances of the "Bag" features as feature vectors, lexical and semantic information within sentence boundaries was extracted. Documents were segmented into sentences using the

JulieLab automatic sentence segmentor [48]; semantic information was obtained by applying the MetaMap parser [49], which maps phrases in text into medical concepts from the Metathesaurus of the Unified Medical Language System (UMLS) from the US National Library of Medicine (NLM).

Three subtypes of Bag features were tested: BOW is the basic *bag-of-words* model; the other two subtypes were constructed by adding semantic features:

- **Bag-of-Words (BOW)**: The Genia Tagger [50] was used to tokenise text and remove punctuation. Dates were normalised into a "DATE" feature and numbers into a "NUMBER" feature. Finally, the position of question marks—beginning, inside, or end of the sentence—were marked to help identify speculative sentences.

- **Bag-of-Phrases (BOP)**: Phrases mapped into UMLS medical concepts by MetaMap were collected for each sentence. Negated concepts were identified using Negex [33], and automatic disambiguation of concepts was performed using the module within MetaMap designed for this purpose. The identified phrases were marked with whether the concepts were found in positive or negative context.

- **Bag-of-Concepts (BOC)**: Use of MetaMap, which links identified phrases to concept identifiers from the UMLS Metathesaurus, enabled generalisation by linking phrases with shared meaning: e.g., the terms "mycosis" and "fungal infection" are both linked to the concept "C0026946". Bag of concept ids detected in each sentence were identified, and again marked with whether the concepts were found in positive or negative context.

Structural features operate on the output of sentence classification and were used for classification of scan reports. There were two main types of Structural features, which were integrated into a single feature vector representation:

- **Scan type**: the anatomic site(s) of the target scan (e.g. "Chest scan") were identified using regular expressions over the text of the reports. An additional feature was introduced for each scan-type to measure how many scans of the given type preceded the current one (e.g. "Number of previous chest-scan reports").

- **Sentence-level classifications** (over previous and current reports): these features indicated the number of sentences that had been scored with positive / negative labels in the current report, and accumulatively over previous reports for that patient. This set of features included a feature type

indicating the most recent positive/negative prediction made by the sentence classifier over the current document.

4.2 Classification Techniques

Different types of systems were developed to classify sentences and scan reports, mainly using Machine Learning (ML) techniques. Also evaluated were the use of rules (both hand-crafted and automatically derived), hybrid systems (combining ML and rules), and the use of simple heuristics.

4.2.1 Sentence-Level Classification

For sentence-level classification, the task was to perform 3-way classification, i.e., to determine whether each sentence in a report provided positive, negative, or neutral evidence for IFD. This task was modeled as two separate binary classification problems: i.e., discrimination between IFD-positive sentences and others, and between IFD-negative sentences and others. Keyword-matching classifiers and ML approaches were used at this level; these approaches were evaluated separately.

Keyword-Matching Approach: As a **baseline** approach, we devised a simple method to classify sentences as positive for IFD using a set of keywords compiled as described below. Another list of terms was used to identify when a given sentence contained negation: in that case, or when the keyword is followed by a question mark, the sentence was marked as **neutral**.

We first created a list of positive-indicator terms compiled by medical experts from the literature [51]; these terms were mapped to UMLS concepts. The final list of manually curated terms is shown in Table 6. As a variation to the above, we explored *automatic identification* of a list of terms to be used for keyword-matching, leveraging the feature set defined in Section 4.1; in particular, features scored according to their log-likelihood of appearance in the collection. For a given term, log-likelihood was calculated as per Equation 1, with additive smoothing applied, and $\epsilon = 0.1$:

$$Loglikelihood(feat) = log\frac{Pr(IFD|feat) + \epsilon}{Pr(NEG|feat) + \epsilon} \tag{1}$$

Different thresholds for this system were tested empirically, and cross-validation was used to avoid overfitting the data. Table 7 shows the top-scoring terms with log-likelihood value (over the full dataset) greater than 2.6.

Machine Learning Approach: The second set of classifiers used standard ML techniques. A number of characteristics of the training data led us to experiment with a variety of ML algorithms. Due to "Bag"

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features being used for sentences, these techniques were required to cope with large and sparse feature vectors. The fact that most sentences in the training data were neutral—i.e., neither negative or positive—also contributed to the sparseness. Moreover, the cost of failing to identify positive sentences is higher than missing neutral or negative sentences, leading us to bias towards high Recall over Precision. The following are the main types of approaches explored:

- **Kernel methods** are able to deal with high dimensional feature sets, and have been widely applied to NLP tasks, in particular Support Vector Machine (SVM) classifiers.

- **Graphical models** are probabilistic methods used to learn conditional dependence structure between random variables via a directed acyclic graph. In our setting there were strong inter-dependencies among the random variables (feature representations of sentences), and these models could be helpful to identify such relations. A disadvantage of these methods is the difficulty of dealing with high-dimensional spaces, and we combined this technique with feature selection (described below). We used Bayesian Network models from this type of method.

- **Independent feature models**: when dealing with thousands of sparse features, with few positive instances, it may be useful to assume independence among features and combine scores using a simple model, such as Naive Bayes. These models could help to better characterise a label that has fewer instances in training data, and avoid false negatives in testing (at a cost of more false positives).

- **Ensemble classifiers** combine predictions from multiple classifiers. We tested *Random Forests*, an ensemble approach that learns different decision trees from random subsets of features, and outputs the class that is the mode of the outputs of the underlying decision tree classifiers. We combine this technique with feature selection, due to the cost of dealing with the full feature space.

- **Feature selection**: For some of our experiments, we applied a correlation-based feature subset selection method, which considers individual predictive ability of each feature and the redundancy of each subset [52]. Our configuration used Best-First search, with a cache-size of one element, and five levels of backtracking.

The Weka Machine Learning toolkit [53] was used for the implementation of all the ML algorithms.

Hybrid Approach: For the task of identifying IFD-positive sentences, we experimented with combining the outputs of the ML classifier with the automatic keyword extraction technique, using a Conservative rule: if *either* of the methods assigned a positive label to the target sentence, it was labeled as IFD-positive.

4.2.2 Report-Level Classifiers

For report-level IFD classification, heuristic rules and machine learning approaches were used to perform binary classification (positive/speculative vs negative).

Heuristic Rules Approach: This approach leveraged the sentence-level classifiers described in Section 4.2.1 by applying simple rules over the sentence-level classifiers in order to minimise false negatives and achieve high Recall. Two candidate heuristic rules were defined as follows:

- **Conservative:** label a report as IFD-positive if **any** sentence in it is labeled IFD-positive;

- **Balanced:** label a report as IFD-positive when it contains more sentences labelled as IFD-positive than IFD-negative.

Machine Learning Approach: ML was applied *directly* to report classification, using the methods described in Section 4.2.1. For this task, the two classes of features presented previously—i.e., "Bag" and "Structural"—were used; note that one of the "Structural" feature types was the output of sentence-level classification.

In order to maximise Recall, we also combined the outputs of the best ML approaches voting in a conservative way, i.e., assigning a label indicating IFD-positive whenever a sentence-level classifier did so. Both "Bag" and "Structural" feature-based methods were tested. Also evaluated was performance using the top-k systems using "Bag" features, for various k.

4.2.3 Patient-Level Classification

A simple heuristic was used for patient-level classification: a positive label was assigned to a patient if **any** of their reports was classified as positive. This was done so as to minimise false negatives at this level, i.e., missed patients with IFD.

4.3 Evaluation Framework

We used the standard accepted metrics of *Precision*, *Recall*, and *F-score* to evaluate the performance of the various binary classifiers constructed. High recall is crucial at report and patient levels; it is also likely to be an important factor when identifying sentences that are positive for IFD. High precision is also desirable, to avoid the cost of false positives.

For our evaluation of sentence classification, 10-fold cross-validation over the Development Dataset was applied. We evaluated classifier performance at sentence, report, and patient levels. We then trained our

classifiers over the Development Data (classified at sentence-level), and tested over the *Held-Out-Verified* (annotated at report level), measuring performance at report and patient levels. Finally, systems were trained over the *Development Dataset* and evaluated at patient level over the *Held-Out-Unverified*, which could only be used to evaluate at patient level.[3]

Timeliness of detection was also analysed, i.e., determining the first report deemed to be IFD-positive by the classifiers (if there was one), for all IFD-positive patients. This provided an indication of the potential efficacy of using our approach for early detection of IFD incidence.

5   Results I: Classification over the Development Corpus

Presented here are results for the classification tasks over sentences, scan-reports, and patients, using the gold-standard Development Dataset of 120 patients, using 10-fold cross-validation.

5.1   Sentence-level Classification

As discussed in Section 3, binary classification was performed at sentence level for the labels *"positive and specific to IFD"* and *"important negative for IFD"*.

Baseline. Table 8 shows performance results for baseline systems that use a keyword-matching approach, as described in Section 4.2.1. Rules using the manually-defined list of IFD-indicative keywords resulted in high precision (0.850) but low recall (0.434). Rules using the automatic log-likelihood technique to construct lists of IFD-indicative keywords achieved maximal F-score (0.639) when using a log-likelihood threshold of 1.6 for term-extraction.

ML Classifiers. Having constructed these baselines, we explored the use of different Machine Learning (ML) classifiers and feature sets over the Development Dataset.

The first columns of Table 9 show results for all the systems, together with the baseline. Feature Selection was required when using Bayesian Networks and Random Forest due to their computational costs. The scores illustrate that Naive Bayes provided high recall (0.858), but at the cost of very low precision (0.438 to 0.361 at this Recall). The next highest recall scores (0.690) were obtained using SVMs, with considerably better precision (up to 0.741) than for Naive Bayes; SVM produced the highest overall F-scores (0.705). Feature Selection did not improve performance when combined with SVMs. Given these results, we chose SVM as the positive sentence-level classifier when performing classification at report and patient level.

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[3]Recall that patients were pre-known to have been diagnosed with IFD or not.

Classifying for Negative Indicators. We evaluated the performance of binary sentence classification for the label *"important negative for IFD"*, using only the ML approach.

The center columns of Table 9 show the performance results for the different configurations. For this task, lower Recall may result in more *false positives* at the report level, which is regarded not as harmful as *false negatives* for our task setting. We therefore prefer Precision over Recall for this class. SVM classification using BOP as features was the best performing in terms of both Precision (0.773) and overall F-score (0.772). Feature Selection was again detrimental for SVMs. This further supports the choice of SVMs for sentence-classification for use in the report- and patient-classification tasks.

5.2 Report-level Classification

Report-level classification, i.e., classifying scan reports as IFD-positive or IFD-negative, is a critical task for surveillance, with Recall as the most important metric: a false negative at the report level may translate into a missed opportunity to raise an early alarm of the presence of an IFD.

Direct Document Classification. The first experiment evaluated a traditional document classification approach: report-level features were extracted and used to build models and generate predictions. As a reference for the expected precision from the simplest of methods, we used a naive baseline system that annotated all reports as IFD-positive.

Results for various classifiers are shown in the rightmost columns of Table 9. The highest Recall obtained was 0.847, using SVM and BOP features: i.e., almost 15% of positive reports would be missed. Precision and Recall were balanced for the various systems, whereas the aim was to maximise Recall. The naive baseline approach—which labelled every report as positive—itself produced an F-score of 0.741, which was similar in performance to the weakest ML configurations.

Using Sentence-Classifier Output. We sought to improve report-level performance by leveraging the output of the sentence-level classifiers and applying the heuristic rules (Conservative and Balanced) defined in Section 4.2.2.

For sentence classification, the best-performing ML approaches for positive- and negative-sentence classification were used: these were SVMs with different feature sets. Table 10 presents the results of using SVMs with BOP as features.[4] When using the *Conservative* heuristic we obtained 0.893 recall and 0.810 precision.

Alternative **hybrid** approaches were also applied: these combined learned rules with the use of ML

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[4]Performance results were similar using feature sets BOC and BOW.

systems. As per Section 5.1, using different log-likelihood thresholds for extracting relevant terms resulted in different term-matching rules. Table 10 shows results obtained when using log-likelihood thresholds in the range 1.4-1.8, which achieved the best performance for sentence classification. Recall of 0.930 and Precision 0.790 were obtained when using 1.8 as log-likelihood threshold.

Overall, use of rules over sentence-classification output outperformed the direct document-classification approach, and the results suggest that the *Conservative* heuristic is preferable to the *Balanced* one, particularly for maximising Recall.

The use of *Structural* features was also explored—i.e., use of *scan-type* as a feature combined with the output of sentence classifiers *used as features* rather than as the basis of the heuristic rules. SVMs (using BOP features) were used to classify sentences. Different classifiers were then applied at the report level, using sentence-classification results as features, along with the other structural features described in Section 4.1. The results are shown in Table 11. Bayesian Networks performed best, with F-score of 0.844, but with lower recall (0.842) than our previous approaches.

Ensemble Classifiers. Finally, ensemble classifiers were evaluated by combining the outputs of the best ML approaches voting in a Conservative way, i.e., by assigning a positive label to a report whenever *any* classifier at the sentence-level assigned a positive label. Both *Bag* and *Structural* feature types were tested. Performance when using only the top-*k* systems (for various *k*) for *Bag* features was also tested. The results are shown in Table 12. The use of top-3 systems reached 0.930 Recall and 0.779 Precision. Recall improved to 0.995 when systems using *Structural* features were added, although with a drop in precision (0.700).

Table 13 summarises the best approaches for report-level classification over the Development Dataset. The results indicate very high recall using various methods (0.995 when using all features), with clear improvement over the baseline in Precision in all cases. The highest F-score (0.855) was achieved using the Conservative heuristic for report-classification over SVM sentence predictions, with 1.8 as the log-likelihood threshold for term-extraction for creating keyword-matching rules.

5.3 Patient-level Classification

The final set of evaluations over the Development Dataset was performed for patient level classification, to test the ability of the classifiers to discriminate IFD-positive patients from control patients. Achieving high Recall was the overriding aim of this task. Thus, a conservative approach over our different report-level classifiers was used: if any scan report for a given patient was classified IFD-positive, then the corresponding patient was also labeled IFD-positive. Table 13 shows patient-level results using the main

methods evaluated for report classification.

Two of the systems achieved close to perfect recall (0.985): each of these systems produced only a single false negative. The false-negative patient was different in each case, but each patient had few (one and three) scan reports, each of which was short and came from the same hospital (Royal Melbourne Hospital). The precision at patient level was well above the baseline (0.550) in all cases, particularly for Bayesian Networks with Structural features (0.734).

6   Results II: Evaluation Over the Held-Out Datasets

Presented here are results from testing over the two Held-Out datasets described in Section 3, i.e., *Held-Out-Verified* (containing 40 patients annotated at report-level) and *Held-Out-Unverified* (containing 393 patients, unannotated): these datasets were not used during training. System configurations were evaluated at report and patient levels using the Held-Out-Verified, and at patient level only for Held-Out-Unverified.

Report-Level Classification. Table 14 shows a summary of report-level classification performance over the Held-Out-Verified test set. As with the Development data (refer to Table 13), the use of Conservative heuristics with a threshold of 1.8 was again best performing, with improved Recall of 0.997, at a cost to precision (best of 0.731). The overall F-scores were slightly lower (highest of 0.812), but the improvement over the baseline was greater, due to the better balanced distribution of IFD-positive and control reports in this dataset. Overall, we demonstrated high recall (0.950) at acceptable precision (0.70). Furthermore, all classifiers reached precision well above the baseline.

Patient-Level Classification. Table 14 shows performance results at patient level over the Held-Out-Verified test dataset. In this case, most system configurations obtained perfect recall (1.0), which translates into no IFD-positive patient being missed. Precision was slightly lower compared to evaluation over the Development set (best of 0.654 vs 0.734) (refer to Table 13), but was still well above the baseline. Finally, the systems were evaluated over the Held-Out-Unverified test dataset, for which only patient-level classifications are known: i.e., this dataset contains reports that were not manually classified by our medical expert annotators, and all that is known is the original classification of the patients as either known IFD-positive or control. Table 15 shows the results of performing patient-level classification over this dataset.

As explained in Section 3, some of these patients may have been determined to be IFD-positive for reasons other than from using scan-report results (e.g., using pathology results). Hence, our approach — which

uses only scan-reports to classify patients — may be at a disadvantage. The systems however once again displayed very high Recall, with Precision considerably above the baseline. Best performance trade-off between Recall and Precision was achieved by the ML system classifying reports directly using BOP features, without relying on sentence classifiers (F-score: 0.799); next-best were systems using Conservative heuristics over sentence-classification (F-score: 0.756).

Overall, the configuration using Conservative heuristics over sentence classifiers was the most robust over the most reliable datasets (Development and Held-Out-Verified). Performance of this system over Held-Out-Unverified patient-level data was examined in more detail. This configuration, combined with a log-likelihood threshold of 1.8, achieved a Recall of 0.979, equivalent to five false negatives. Manual review of the reports for these missed cases found that none of them contained any positive indications for IFD in the text—i.e., these were patients that were likely assigned a diagnosis of IFD using clinical evidence alternative to the CT scans.

7   Discussion

We have explored various architectures for classifying sentences, scan reports, and patients into useful categories for IFI surveillance tasks that leverage information in CT scan reports. Over different datasets, our models reached precision scores well above the majority-class baselines, and produced very high recall at both report and patient levels. We saw that the intermediate step of classifying sentences into categories is beneficial for report classification. In a practical Decision-Support System, sentence classification could also be useful for highlighting pertinent evidence for the benefit of the clinical decision-making user. Regarding the best performing methods, at report level the strongest performance was achieved using Conservative rules over sentence-classification output. The use of log-likelihood calculations for automatically deriving keywords performed robustly over the Development and Held-Out-Verified datasets, resulting in recall of 93% and 95%, and precision of 79% and 71%, respectively.

Results for patient-classification confirmed the superior performance of the 2-layer approach (Conservative rules applied to ML sentence predictions), where recall scores of 98% and 100% were achieved over Development and Held-Out-Verified datasets respectively (corresponding precisions were 69% and 63%). Interestingly, the use of log-likelihood thresholding benefits the performance at scan level, but not at patient level, where the recall is already high. The final results over the patient-level annotated data (Held-Out-Unverified) were similar, but our manual analysis of false positives showed that this data is not completely reliable: some patients seem to have been diagnosed with IFD using clinical evidence other

than the CT scan reports.

These overall results, and error analysis of false negatives, indicate that we have largely achieved our goal of avoiding missed cases of IFD. Over the Development set, only a single positive patient was missed by the best-performing 2-layered system; it is important to note that this patient had only a single scan, and agreement between human annotators was not perfect at scan level (see Section 3). For the Held-Out-Verified set, no IFD-positive patient was missed by the classifier.

Precision, which quantifies the number of "false alarms", was acceptable but significantly lower than Recall. While high Recall is the more important characteristic to the surveillance task, minimising false positives is nevertheless desirable. The drop in Precision is particularly evident in experiments over the Held-Out datasets. Analysis of the false positives suggests that this may be due to subtleties in the annotation, which may have been biased towards Recall, with more highly speculative sentences in these examples being annotated as negative by the physicians. One approach to addressing the problem would be to develop a more sophisticated treatment of speculative language [54].

Regarding the impact of Precision at report level, we note that not all false positives have the same impact in our setting. If a patient has already had a scan flagged as positive by the system, in a practical setting an action to monitor the patient should follow. Subsequent scans marked as positive for the same patient should imply less overhead in a monitoring system than the alerts for patients without prior positive scans. Another interesting situation arises when a false positive refers to a patient that will eventually have a positive scan (even if the current scan is negative). In this case the classifier may have found an early indicator of risk, and the effort of monitoring this patient was well worthwhile.

We examined the distribution of the positive scans from our most robust classifier in order to better understand the impact of the different types of positive scans. Our evaluation showed that our 2-layer system performs at 79% precision at scan level over the Development set; i.e., 53 of the 253 (21%) predicted positive scans are false positives. In 26 cases (49% of all false positives), the system indicated a prior scan for that patient as positive. In 13 cases (25% of all false positives), the false positive was an early alert for a patient. We manually examined the early indicators and found a large number of sentences that our annotators had considered *"Positive but not specific to IFD"* (see Section 3): e.g., "A focus of fungal infection cannot be excluded". Thus, for only 14 cases (26% of the false positives) is there an alert for a patient that ends up being negative for IFD.

Over the Held-Out-Verified set (precision 71%), we received 17 false positives from the 58 scans that were predicted as positive (29%). The number of cases where the system predicted a previous positive scan for

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the given patient was 9 (53% of all false positives), and the number of early indicators in this case is 0; therefore only for 8 cases (47% of the false positives) was there an alert raised for a patient that does not end up being IFD-positive.

8 Conclusions

This paper has explored the task of analysing the text in radiology reports, specifically of CT-scans, for evidence suggestive of an Invasive Fungal Disease (IFD). The text classification systems—developed from reports derived from three major Melbourne hospitals—achieved high Recall (i.e., minimal missed incidence) at both report and patient levels. High Recall is an important attribute of a pervasive surveillance system intended to screen patients in order to identify those with potential fungal infection. Invasive fungal diseases are challenging to definitively diagnose, due to poorly sensitive tests compounded by patients often being too unwell to undergo invasive diagnostic procedures. Automatically mining the narrative of CT reports offers the possibility of eventually making real-time surveillance of these infections feasible for hospitals

The task of surveillance using CT reports requires accurate discrimination of patients with IFD from those without IFD, and in particular, minimal missed cases. The Recall achieved with the best-performing classifiers at report-level and especially at patient-level was very high, with all patients in our test data with an abnormal scan (as determined by the clinical experts) being successfully identified at some point during their clinical encounter.

The report classification task underpins the patient-level surveillance but is also a useful task in its own right. Real-time prospective continuous surveillance via report processing could be used to: link to clinical decision support through the triggering of treatment protocols; alert hospitals to potential outbreak; strengthen antifungal stewardship in hospitals; assist clinicians in evaluating the effectiveness of preventative strategies such as antifungal drug prophylaxis or infection prevention practices; inform clinical trial design with contemporary incidence rates; and provide an opportunity for tracking disease trends in response to rapid advances in medical and transplant practices.

Future work will concentrate on prospective evaluation of the classifier in clinical environments with broader engagement from end-users.

Competing interests

The authors declare that they have no competing interests.

Ethics approval

Ethics approval was obtained via Alfred Health, under a Memorandum of Understanding with the other hospitals (reference: project 429/09).

Authors' contributions

DM led the development of the classifiers and their evaluation. MAR, MS, KT proposed the original study conception and design. MAR and KT collected the data. MAR, DM, MAR, HS developed the annotation scheme. MAR, KT, MS annotated the data. All authors performed data analysis and interpretation. DM, LC, MAR, HS, KT drafted and refined the manuscript. All authors provided critical revision of the manuscript.

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References

1. Kontoyiannis DP, Marr KA, et al: **Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database.** *Clinical Infectious Diseases* 2010, **50**(8):1091–100.

2. Pagano L, Caira M, et al: **Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study.** *Haematologica* 2010, **95**(4):644–50.

3. Ananda-Rajah MR, Cheng A, et al: **Attributable hospital cost and antifungal treatment of invasive fungal diseases in high-risk hematology patients: an economic modeling approach.** *Antimicrobiol Agents Chemotherapy* 2011, **55**(5):1953–60.

4. Menzin J, Meyers JL, et al: **The economic costs to United States hospitals of invasive fungal infections in transplant patients.** *Am. J. Infection Control* 2011, **39**(4):e15–20.

5. Neofytos D, Lu K, et al: **Epidemiology, outcomes, and risk factors of invasive fungal infections in adult patients with acute myelogenous leukemia after induction chemotherapy.** *Diagnostic Microbiololgy and Infectious Diseases* 2013, **75**(2):144–9.

6. Nivoix Y, Velten M, et al: **Factors associated with overall and attributable mortality in invasive aspergillosis.** *Clinical Infectious Diseases* 2008, **47**(9):1176–84.

7. Steinbach WJ, Marr KA, et al: **Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry.** *J. Infection* 2012, **65**(5):453–64.

8. Haematology BCoSi: **Writing Group of the British Committee on Standards in Haematology. Guidelines on the management of invasive fungal infection during therapy for haematological malignancy** 2008.

9. Tomblyn M, Chiller T, et al: **Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective.** *Biology of Blood and Marrow Transplant* 2009, **15**(10):1143–238.

10. Yokoe D, Casper C, et al: **Infection prevention and control in health-care facilities in which hematopoietic cell transplant recipients are treated.** *Bone Marrow Transplantation* 2009, 44(8):495–507.

11. Panackal AA, Li H, et al: **Geoclimatic influences on invasive aspergillosis after hematopoietic stem cell transplantation.** *Clinical Infectious Diseases* 2010, **50**(12):1588–97.

12. Kainer MA, Reagan DR, et al: **Fungal infections associated with contaminated methylprednisolone in Tennessee.** *New England Journal of Medicine* 2012, **367**(23):2194–203.

13. Denning DW, Marinus A, et al: **An EORTC multicentre prospective survey of invasive aspergillosis in haematological patients: diagnosis and therapeutic outcome. EORTC Invasive Fungal Infections Cooperative Group.** *J. Infection* 1998, **37**(2):173–80.

14. De Pauw B, Walsh TJ, et al: **Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group.** *Clinical Infectious Diseases* 2008, **46**(12):1813–21.

15. Nicolle MC, Benet T, et al: **Invasive aspergillosis in patients with hematologic malignancies: incidence and description of 127 cases enrolled in a single institution prospective survey from 2004 to 2009.** *Haematologica* 2011, **96**(11):1685–91.

16. Chang DC, Burwell LA, et al: **Comparison of the use of administrative data and an active system for surveillance of invasive aspergillosis.** *Infect Control Hosp Epidemiol* 2008, **29**:25–30.

17. Marom EM, Kontoyiannis DP: **Imaging studies for diagnosing invasive fungal pneumonia in immunocompromised patients.** *Current Opinion in Infectious Diseases* 2011, **24**(4):309–14.

18. Travers D, Wu S, Scholer M, Westlake M, Waller A, McCalla A: **W W Chapman and J N Dowling and M M Wagner.** *Journal of Biomedical Informatics* 2004, **37**(2):120–127.

19. Travers D, Wu S, Scholer M, Westlake M, Waller A, McCalla A: **Evaluation of a chief complaint pre-processor for biosurveillance.** *AMIA Annual Symposium Proceedings* 2007, :736–740.

20. Elkin P, Froehling D, Wahner-Roedler D, Trusko B, Welsh G, Ma H, Asatryan A, Tokars J, Rosenbloom S, Brown S: **NLP-based identification of pneumonia cases from free-text radiological reports.** *AMIA Annual Symposium Proceedings* 2008, :172–176.

21. South B, Chapman W, Delisle S, Shen S, Kalp E, Perl T, Samore M, Gundlapalli A: **Optimizing a syndromic surveillance text classifier for influenza-like illness: Does document source matter?** *AMIA Annual Symposium Proceedings* 2008, :692–696.

22. Murff H, Fitzhenry F, Matheny M, Gentry N, Kotter K, Crimin K, Dittus R, Rosen A, Elkin P, Brown S, Speroff T: **Automated identification of postoperative complications within an electronic medical record using natural language processing.** *The Journal of the American Medical Association* 2011, **306**(8):848–855.

23. Jones M, DuVall S, Spuhl J, Samore M, Nielson C, Rubin M: **Identification of methicillin-resistant Staphylococcus aureus within the nation's Veterans Affairs medical centers using natural language processing.** *BMC Medical Informatics and Decision Making* 2012, **12**:34.

24. Matheny M, Fitzhenry F, Speroff T, Green J, Griffith M, Vasilevskis E, Fielstein E, Elkin P, Brown S: **Detection of infectious symptoms from VA emergency department and primary care clinical documentation.** *International Journal of Medical Informatics* 2012, **81**(3):143–156.

25. Demner-Fushman D, Chapman W, McDonald C: **What can Natural Language Processing do for Clinical Decision Support?** *J. Biomedical Informatics* 2009, **42**(5):760–772.

26. Haug P, Koehler S, Lau LM, Wang P, Rocha R, Huff S: **A Natural Language Understanding System Combining Syntactic and Semantic Techniques.** In *Proc. AMIA Symposium* 1994:247–251.

27. Friedman C, Alderson PO, Austin JH, Cimino JJ, Johnson SB: **A general natural-language text processor for clinical radiology.** *J. American Medical Informatics Assoc.* 1994, **1**(2):161–174.

28. Xu Y, Tsujii J, Chang EIC: **Named entity recognition of follow-up and time information in 20,000 radiology reports.** *J. American Medical Informatics Assoc.* 2012, **19**:792–799.

29. Elkins JS, Friedman C, Boden-Albala B, Sacco RL, Hripcsak G: **Coding Neuroradiology Reports for the Northern Manhattan Stroke Study: A Comparison of Natural Language Processing and Manual Review**. *Computers and Biomedical Research* 2000, **33**:1–10.

30. Friedlin J, McDonald CJ: **A Natural Language Processing System to Extract and Code Concepts Relating to Congestive Heart Failure from Chest Radiology Reports**. In *Proc. AMIA Symposium* 2006:269–273.

31. Solti I, Cooke CR, Xia F, Wurfel MM: **Automated Classification of Radiology Reports for Acute Lung Injury: Comparison of Keyword and Machine Learning Based Natural Language Processing Approaches**. *IEEE Int'l Conference on Bioinformatics and Biomedicine* 2009, :314–319.

32. Womack A, Scotch M, Gibert C, Chapman W, Yin M, Justice AC, Brandt C: **A Comparison of Two Approaches to Text Processing: Facilitating Chart Reviews of Radiology Reports in Electronic Medical Records**. In *Perspectives in Health Information Management* 2010.

33. Chapman WW, Bridewell W, Hanbury P, Cooper G, Buchanan B: **A simple algorithm for identifying negated findings and diseases in discharge summaries**. *J. Biomed Informatics* 2001, **34**(5):301–310.

34. Tinoco A, Evans S, Staes CJ, Lloyd JF, Rothschild JM, Haug PJ: **Comparison of computerized surveillance and manual chart review for adverse events**. *J. American Medical Informatics Assoc.* 2011, **18**:491–497.

35. Mendonça EA, Haas J, Shagina L, Larson E, Friedman C: **Extracting information on pneumonia in infants using natural language processing of radiology reports**. *Journal of Biomedical Informatics* 2005, **38**:314–321.

36. Travers D, Wu S, Scholer M, Westlake M, Waller A, McCalla A: **Evaluation of a chief complaint pre-processor for biosurveillance**. *AMIA Annual Symposium Proceedings* 2007, :736–740.

37. Jones1 M, DuVall1 SL, Spuhl1 J, Samore MH, Nielson C, Rubin M: **Identification of methicillin-resistant Staphylococcus aureus within the Nation's Veterans Affairs Medical Centers using natural language processing**. *BMC Medical Informatics and Decision Making* 2012, **12**(34). [Http://www.biomedcentral.com/1472-6947/12/34].

38. Elkin PL, Froehling D, Wahner-Roedler D, Trusko B, Welsh G, Ma H, Asatryan AX, Tokars JI, Rosenbloom ST, Brown SH: **NLP-based identification of pneumonia cases from free-text radiological reports**. *AMIA ... Annual Symposium proceedings / AMIA Symposium. AMIA Symposium* 2008, :172–6, [http://www.pubmedcentral.nih.gov/articlerender.fcgi\?artid=2656026\&tool=pmcentrez\&rendertype=abstract].

39. Bejan CA, Xia F, Vanderwende L, Wurfel MM, Yetisgen-Yildiz M: **Pneumonia identification using statistical feature selection**. *J. American Medical Informatics Assoc.* 2012, **19**:817–823.

40. Ehrentraut C, Tanushi H, Dalianis H, Tiedmann J: **Detection of Hospital Acquired Infections in sparse and noisy Swedish patient records.: A machine learning approach using Naive Bayes, Support Vector Machines and C4. 5**. *Sixth Workshop on Analytics for Noisy Unstructured Text Data, AND, held in conjunction with Coling 2012* 2012.

41. Cooley L, Spelman D, et al: **Infection with Scedosporium apiospermum and S. prolificans, Australia**. *Emergency Infectious Diseases* 2007, **13**(8):1170–7.

42. Ananda-Rajah M, AP G, K T, A B, M S: **Prophylactic Effectiveness and Safety Of Intermittent Liposomal Amphotericin In High Risk Haematological Patients**. In *51st Interscience Conference on Antimicrobial Agents and Chemotherapy ASM*, Chicago 2011:abstract no M–280.

43. Ananda-Rajah MR, Grigg A, et al: **Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period**. *Haematologica* 2012, **97**(3):459–63.

44. Morrissey CO, Chen SC, et al: **Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: a randomised controlled trial**. *Lancet Infectious Diseases* 2013, **13**(6):519–28.

45. Walsh TJ, Anaissie EJ, et al: **Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America**. *Clinical Infectious Diseases* 2008, **46**(3):327–60.

46. Carletta J: **Assessing agreement on classification tasks: The kappa statistic.** *Computational Linguistics* 1996, **22**(2):249–254.

47. Landis JR, Koch GG: **The measurement of observer agreement in categorical data.** *Biometrics* 1977, **33**:159–174.

48. Tomanek K, Wermter J, Hahn U: **A reappraisal of sentence and token splitting for life science documents.** In *MEDINFO 2007 - Proceedings of the 12th World Congress on Medical Informatics* 2007.

49. Aronson AR: **Effective mapping of biomedical text to the UMLS Metathesaurus: the MetaMap program.** In *AMIA Annual Symposium Proceedings*, Washington DC 2001:17–21.

50. Tsuruoka Y, Tateishi Y, Kim JD, Ohta T, McNaught J, Ananiadou S, Tsujii J: **Developing a Robust Part-of-Speech Tagger for Biomedical Text.** In *Advances in Informatics - 10th Panhellenic Conference on Informatics*, Volas, Greece 2005:382–392.

51. Greene RE, Schlamm HT, Oestmann JW, Stark P, Durand C, Lortholary O, Wingard JR, Herbrecht R, Ribaud P, Patterson TF, Troke PF, Denning DW, Bennett JE, de Pauw BE, Rubin RH: **Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign.** *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2007, **44**(3):373–9, [http://www.ncbi.nlm.nih.gov/pubmed/17205443].

52. Hall M: **Correlation-based Feature Subset Selection for Machine Learning.** *PhD thesis*, Department of Computer Science, University of Waikato, New Zealand 1999.

53. Witten IH, Frank E: *Data Mining: Practical machine learning tools and techniques.* San Francisco, USA: Morgan Kaufmann 2005.

54. Velupillai S: **Shades of Certainty: Annotation and Classification of Swedish Medical Records.** *PhD thesis*, Computer and Systems Science, Stockholm University 2012. [DSV Report Series No. 12-002].

Appendix: Supplementary Tables

Table 5 – Distribution of patients and scans-reports over hospitals for the Development Dataset

Hospital		*Development*		*Held-Out Verified*		*Held-Out Unverified*	
		Patients	Reports	Patients	Reports	Patients	Reports
Alfred Hospital	Control	31	76	8	18	67	155
	IFD-+ve	24	118	5	21	88	469
Royal Melbourne	Control	20	28	10	23	119	222
	IFD-+ve	22	75	7	18	32	139
Peter MacCallum	Control	10	23	5	10	19	54
	IFD-+ve	13	45	5	14	68	208
Total	Control	61	127	23	51	205	431
	IFD-+ve	59	238	17	53	188	816

Table 5: Distribution of patients and scan-reports over hospitals for the *Development Dataset*

Table 6 – Manually curated keywords that are indicative of IFD, compiled from the literature.

Concept id	Associated terms
C0026946	*Fungal Infection, Mycosis, Fungal Disease, Fungal, Disease caused by fungus...*
C0339961	*Fungal pneumonia, Pneumonia in mycoses ...*
C2021209	*x-ray of chest, alveolar air bronchogram...*
C0034079	*Lung nodule, pulmonary nodule, small mass of the lung ...*
C0028259	*nodule*
C0205297	*nodular*
C0233205	*halo, halo sign*

Table 6: Manually curated keywords that are indicative of IFD, compiled from the literature.

Table 7 – Automatically extracted features that are indicative of IFD

Positive terms
Collocation("nodular","seen")
Collocation("glass","nodular")
Collocation("nodular","opacity")
Collocation("ground","nodular")
Collocation("nodule","right-upper-lobe")
...

Table 7: Automatically extracted features that are indicative of IFD.

Table 8 - Summary of performance on positive sentence classification

Method	Threshold	Precision	Recall	F-score
Manual		**0.850**	0.434	0.574
Automatic	0	0.276	**0.924**	0.425
	0.4	0.328	0.908	0.481
	0.8	0.344	0.886	0.496
	1.2	0.448	0.766	0.565
	1.6	0.610	0.671	**0.639**
	2.0	0.828	0.399	0.539
	2.4	0.831	0.084	0.153

Table 8: Summary of performance on positive sentence classification using manual and automatic keyword-based methods over Development data. The best results per column are given in bold.

Table 9 - ML classifiers over the Development dataset: positive/negative sentence, and report classification.

Classifier	Feature set	Positive Sentence			Negative Sentence			Report		
		Rec.	Prec.	F-sc	Rec.	Prec.	F-sc	Rec.	Prec.	F-sc
Baseline: All positive	-	1.000	0.090	0.166	1.000	0.146	0.255	1.000	0.589	0.741
BayesNet	BOW	-	-	-	-	-	-	0.767	0.797	0.782
BayesNet-FS	BOC	0.632	0.608	0.620	0.744	0.440	0.553	0.753	**0.835**	0.792
BayesNet-FS	BOP	0.552	0.698	0.617	0.539	0.659	0.593	0.753	0.818	0.785
BayesNet-FS	BOW	0.557	0.643	0.597	0.441	0.673	0.533	0.749	0.782	0.765
NaiveBayes	BOC	**0.858**	0.338	0.485	**0.915**	0.381	0.538	0.805	0.797	0.801
NaiveBayes	BOP	0.849	0.345	0.490	0.861	0.433	0.577	0.795	0.803	0.799
NaiveBayes	BOW	0.842	0.361	0.505	0.849	0.442	0.582	0.805	0.808	0.807
NaiveBayes-FS	BOC	0.690	0.548	0.611	0.795	0.431	0.559	0.805	0.820	0.812
NaiveBayes-FS	BOP	0.711	0.569	0.632	0.598	0.511	0.551	0.805	0.805	0.805
NaiveBayes-FS	BOW	0.725	0.562	0.634	0.562	0.494	0.526	0.767	0.789	0.778
RandomForest	BOC	-	-	-	-	-	-	0.767	0.764	0.766
RandomForest	BOP	-	-	-	-	-	-	0.740	0.791	0.764
RandomForest	BOW	-	-	-	-	-	-	0.726	0.746	0.736
RandomForest-FS	BOC	0.585	0.770	0.665	0.569	0.754	0.649	0.781	0.824	0.802
RandomForest-FS	BOP	0.569	0.795	0.664	0.549	0.737	0.629	0.795	0.792	0.794
RandomForest-FS	BOW	0.566	0.787	0.659	0.511	0.713	0.596	0.763	0.785	0.774
SVM	BOC	0.690	0.715	0.702	0.769	0.749	0.759	0.837	0.826	0.831
SVM	BOP	0.679	0.721	0.699	0.772	**0.773**	**0.772**	**0.847**	0.824	**0.835**
SVM	BOW	0.672	0.741	**0.705**	0.781	0.758	0.769	0.814	0.795	0.805
SVM-FS	BOC	0.571	0.796	0.665	0.540	0.741	0.625	0.814	0.810	0.812
SVM-FS	BOP	0.566	0.794	0.661	0.519	0.745	0.612	0.823	0.816	0.819
SVM-FS	BOW	0.524	**0.816**	0.638	0.454	0.683	0.545	0.740	0.795	0.766

Table 9: ML classifiers over the Development dataset: positive/negative sentence, and report classification.

Table 10 - Rules for report classification over the Development dataset

Sentence-Classifier	Report-Rule	Recall	Precision	F-score
SVM	Conservative	0.893	0.810	0.850
SVM and rules (1.4 thr.)		**0.977**	0.707	0.820
SVM and rules (1.6 thr.)		0.967	0.730	0.832
SVM and rules (1.8 thr.)		0.930	0.791	**0.855**
SVM	Balanced	0.567	**0.938**	0.707
SVM and rules (1.4 thr.)		0.772	0.838	0.804
SVM and rules (1.6 thr.)		0.744	0.860	0.798
SVM and rules (1.8 thr.)		0.670	0.923	0.776

Table 10: Rules for report classification over the Development dataset. The best results per column are given in bold.

Table 11 - ML for scan-report classification over the Development dataset using structural features

Report-Classifier	Recall	Precision	F-score
Bayesian Nets	**0.842**	**0.846**	**0.844**
Naive Bayes	0.833	0.743	0.785
Random Forest	0.791	0.821	0.806
SVM	0.781	0.836	0.808

Table 11: ML for scan-report classification over the Development dataset using structural features. The best results per column are given in bold.

Table 12 - Combinations of classifier outputs via Conservative voting over the Development dataset

Combined Systems		Recall	Precision	F-score
Bag of items	Structural			
All	All	**1.000**	0.634	0.776
None	All	0.940	0.727	0.819
All	None	0.977	0.652	0.782
Top-3 Prec.	None	0.916	**0.779**	**0.842**
Top-3 Rec.	None	0.930	0.769	**0.842**
Top-5 Prec.	None	0.949	0.750	0.838
Top-5 Rec.	None	0.944	0.749	0.835
Top-3 Prec.	All	0.995	0.700	0.822
Top-3 Rec.	All	0.986	0.694	0.815
Top-5 Prec.	All	0.995	0.687	0.813
Top-5 Rec.	All	0.995	0.689	0.814

Table 12: Combinations of classifier outputs via Conservative voting over the Development dataset. The best results per column are given in bold.

Table 13 - Summary of Report- and Patient-level classification over the Development dataset

System Type	Characteristics	Report-level			Patient-level		
		Recall	Precision	F-score	Recall	Precision	F-score
Baseline	All positive	**1.000**	0.589	0.741	**1.000**	0.550	0.710
ML - "Bag of Items"	SVM - BOP	0.847	0.824	0.835	0.924	0.726	**0.813**
ML - "Structural"	BayesNet	0.842	**0.846**	0.844	0.879	**0.734**	0.800
ML - Combine "Bag of Items"	Top-3 Precision	0.916	0.779	0.842	0.970	0.681	0.800
ML - Combine "Structural"	All	0.940	0.727	0.819	0.939	0.653	0.770
ML - Combine All	Top-3 Prec and All Struct	0.995	0.700	0.822	0.985	0.637	0.774
Report Rules - Conservative	Sentence SVM	0.893	0.810	0.850	0.939	0.689	0.795
Report Rules - Conservative	Sentence SVM, thr = 1.8	0.930	0.791	**0.855**	0.985	0.677	0.802

Table 13: Summary of Report- and Patient-level classification over the Development dataset. The best results per column are given in bold.

Table 14 - Summary of Report and Patient-level results over report-level Held-Out-Verified dataset

System Type	Characteristics	Report-level			Patient-level		
		Recall	Precision	F-score	Recall	Precision	F-score
Baseline	All positive	**1.000**	0.423	0.595	**1.000**	0.425	0.59
ML - "Bag of Items"	SVM - BOP	0.907	0.629	0.743	0.941	0.593	0.727
ML - "Structural"	BayesNet	0.884	0.704	0.784	**1.000**	0.630	0.773
ML - Combine "Bag of Items"	Top-3 Precision	0.884	0.644	0.745	0.941	0.552	0.696
ML - Combine "Structural"	All	0.884	0.704	0.784	**1.000**	0.630	0.773
ML - Combine All	Top-3 Precision and All Struct	0.977	0.606	0.748	**1.000**	0.531	0.694
Report Rules - Conservative	Sentence SVM	0.884	**0.731**	0.800	**1.000**	**0.654**	**0.791**
Report Rules - Conservative	Sentence SVM, thr = 1.8	0.953	0.707	**0.812**	**1.000**	0.630	0.773

Table 14: Summary of Report- and Patient-level results over report-level Held-Out-Verified dataset. The best results per column are given in bold (ignoring the 100% recall of the baseline).

Table 15 - Patient-level results over patient-level Held-Out-Unverified dataset

System Type	Characteristics	Recall	Precision	F-score
Baseline	All positive	**1.000**	0.478	0.647
ML - "Bag of Items"	SVM - BOP	0.941	**0.694**	**0.799**
ML - "Structural"	BayesNet	0.952	0.615	0.747
ML - Combined "Bag of Items"	All	**1.000**	0.553	0.712
ML - Combined "Structural"	All	0.952	0.615	0.747
Report Rules - Conservative	Sentence SVM	0.947	0.622	0.751
Report Rules - Conservative	Sentence SVM, thr = 1.8	0.979	0.615	0.756

Table 15: Patient-level results over patient-level Held-Out-Unverified dataset. The best results per column are given in bold.

Appendix 8

ORIGINAL

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The role of general quality improvement measures in decreasing the burden of endemic MRSA in a medical–surgical intensive care unit

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Abstract *Purpose:* To determine whether any of several quality improvement interventions with none specifically targeting methicillin-resistant *Staphylococcus aureus* (MRSA) were associated with a decline in endemic MRSA prevalence in an intensive care unit (ICU) where active screening and contact isolation precautions for known MRSA colonised patients are not practised. *Setting:* Medical–surgical ICU with 2,000 admissions/year. *Design:* 8.5-year retrospective time-series analysis. *Interventions:* ICU re-location, antibiotic stewardship utilising computerised decision-support and infectious-diseases physician rounds, dedicated ICU infection control practitioners, alcohol-based hand rub solution (ABHRS). *Method:* Regression modelling was used to evaluate trends in *S. aureus* prevalence density (monthly clinical isolates per 1,000 patient-days), antibiotic consumption, infection control consumables, ABHRS and their temporal relationship with MRSA prevalence. *Results:* Methicillin-resistant *S. aureus* prevalence density decreased by 83% [95% confidence interval (CI) −68% to −91%, $p < 0.001$]. Rates of MRSA bacter-aemia decreased 89% (95% CI −79% to −94%, $p = 0.001$) with no statistically significant change in methicillin-sensitive *S. aureus* bacteraemia. Hospital MRSA prevalence density decreased 17% (95% CI −5% to −27%, $p = 0.005$), suggesting that ICU was not shifting MRSA elsewhere. In ICU, broad-spectrum antibiotic use decreased by 26% (95% CI −12% to −38%, $p = 0.008$), coinciding with a decrease in MRSA, but time-series analysis did not show a significant association. On multi-variate analysis, only ABHRS was significantly associated with a decrease in MRSA, but it was formally introduced late in the study period when MRSA was already in decline. *Conclusion:* General quality improvement measures were associated with a decrease in endemic MRSA in a high-risk setting without use of resource-intensive active surveillance and isolation practices.

Keywords Methicillin-resistant *Staphylococcus aureus* · Infection control · Intensive care unit · Nosocomial infections

Introduction

The optimal strategy for control of methicillin-resistant *Staphylococcus aureus* (MRSA) in endemic settings is unresolved. The "search and destroy" approach involving screening, contact isolation precautions and decolonisation used successfully in low-prevalence settings may not be practical in settings of high endemicity. Active

surveillance cultures (ASC) aim to identify the asymptomatic reservoir of colonised patients, in order to interrupt person-to-person transmission, thereby preventing new acquisition which is associated with subsequent disease [1]. The intensive care unit (ICU) may serve as a "hub" for MRSA acquisition and dissemination [2], yet studies with ICU-based MRSA control efforts have had mixed results, including lack of benefit from isolation in single rooms or cohorts [3], disappointing results with ICU compared with hospital admission screening [4], success with screening using conventional cultures [5] but limited benefit using rapid molecular tests unless also combined with pre-emptive isolation [6]. Recently, controlled studies in non-ICU areas have not conclusively demonstrated a benefit of ASC in reducing nosocomial MRSA infection or acquisition rates [7, 8]. Accordingly, some professional societies have moderated their stance on the role of ASC for MRSA, suggesting a potential benefit only if basic infection control (IC) measures are failing [9].

Methicillin resistance rates in healthcare-associated S. aureus infection reached 64% in US ICUs in 2003 [10], 40% in European ICUs [11] and over 40% in the major hospitals of Eastern Australia [12]. Use of percentage MRSA as a surveillance metric may, however, mask important declining trends in MRSA incidence if the incidence of methicillin-sensitive S. aureus (MSSA) is decreasing as well [13]. Recently, several US states have reported declines in ICU MRSA central line-associated bloodstream infections (CLABSI) pre-dating mandatory reporting of healthcare-associated infections and ASC for MRSA, but the factors responsible remain unclear [13]. In our institution, ASC, routine contact isolation of MRSA colonised and infected patients and decolonisation therapies have never been adopted. Since 2000, several IC initiatives, with none specifically targeting MRSA, were introduced to our hospital. Pathogen data collected to monitor our antibiotic stewardship program showed a sustained decline in ICU MRSA

prevalence over a prolonged period, prompting an investigation into the contributory factors. Using change-point analysis and autoregressive models we evaluated the impact of multiple IC interventions and aggregate antibiotic use on MRSA prevalence within ICU and the wider hospital.

Methods

Study design and setting

We undertook a retrospective time-series analysis assessing the impact of multiple quality improvement interventions, consumption of antibiotics and IC consumables on ICU MRSA prevalence from 1 January 2000 to 30 June 2008. Data prior to 2000 were unavailable.

The Royal Melbourne Hospital (RMH) is a 690-bed adult university-affiliated tertiary hospital with a 24-bed medical–surgical ICU comprising 6 single rooms and 18 open bays. ICU patient characteristics are presented in Table 1. The ICU has approximately 2,000 admissions per year, with a mean (median) length of stay of 4.1 (3.0) days in 2007 and 4.4 (3.0) days in 2000. Surgical patients including trauma, cardiothoracic, neurosurgery and general specialities comprise 70% of ICU admissions. In 2005, RMH became one of two statewide major trauma centres, with an annual increase in trauma admissions from a mean of 9.6% (2000–2004) to 17% in 2005. Throughout the study period, nurse-to-patient ratios were 1:1 and 1:2 for step-down care. A clinical microbiologist, two infectious diseases (ID) physicians and two infection control practitioners (ICPs) oversee ICU infection control. MRSA is endemic, but outbreaks did not occur. MRSA clonality is unknown, as genotyping is not routine. A point-prevalence survey in December 2005 showed that 6.9% of 288 patients (95% CI 4.3–10.5%) were MRSA colonised on ICU discharge.

Table 1 ICU patient characteristics

Year	Admissions, n	Male (%)	Age, mean (years)	LOS, mean (days)	Trauma (%)	Surgical (%)	Transfers (%), from ward, ED, inter-hospital	APACHE II score, mean	Mortality (%)
2000	1,376	63	59	4.4	9	67	*	*	10.1
2001	2,069	64	61	4.3	9	69	*	*	7.7
2002	1,893	63	62	4.3	8	64	*	15.1	8.1
2003	1,978	67	60	4.2	10	64	*	15.0	7.0
2004	2,067	64	60	4.0	12	69	*	14.2	8.4
2005	2,001	65	59	4.1	17	78	64, 29, 5.7	13.9	8.4
2006	1,909	67	59	4	17	77	66, 29, 4.8	14.0	6.4
2007	1,996	66	58	4.1	16	72	63, 32, 4.0	14.6	8.8
Mean	1,911	65	60	4.2	12.3	70	64, 30, 4.8	10.9	8.1

LOS length of stay, ED emergency department, APACHE Acute Physiology and Chronic Health Evaluation
* Data not available

Infection control procedures

For all patient contact in ICU, staff wear a single-use disposable plastic apron. Screening cultures for MRSA are not routine. MRSA colonised and infected patients, identified through clinical isolates, are cared for among the general ICU population without use of gowns, gloves or single-room isolation or cohorting. Decolonisation is not attempted. Use of alcohol-based hand rub solution (ABHRS) is RMH policy for hand disinfection.

From May 2007, ICU patients underwent screening for MRSA on admission, discharge and twice weekly as part of a separate research study. Results were available on the pathology system but were not directly communicated to ICU health-care workers (HCWs) and were not specifically acted upon.

Microbiology data

Monthly clinical isolates of *S. aureus* (excluding screening swabs and duplicates within 7 days from sterile and 30 days from non-sterile sites) from ICU and elsewhere in the hospital were electronically extracted from the microbiology database and expressed per 1,000 patient-days (prevalence density). Isolates obtained within the first 48 h of hospital admission were not excluded. *S. aureus* bloodstream isolates from ICU were separately analysed, as they unequivocally represented infection. Laboratory identification methods did not change over the study period.

Antibiotic consumption

Monthly quantities of antibiotics prescribed in ICU were obtained from pharmacy records and expressed as the number of defined daily doses (DDD) per 1,000 patient-days. These included third/fourth-generation cephalosporins, fluoroquinolones, carbapenems, anti-pseudomonal penicillins (ticarcillin–clavulanate, piperacillin–tazobactam), aminoglycosides, glycopeptides and macrolides. Broad-spectrum antibiotics comprised all antibiotic classes excluding glycopeptides (which specifically target MRSA) and macrolides, because erythromycin, the most frequently prescribed macrolide in our ICU, is used principally as an intestinal pro-kinetic agent.

Infection control consumables

Monthly quantities of IC consumables used in ICU were obtained from the purchasing department. These included medicated soap, gloves, plastic aprons, disposable gowns and alcohol-impregnated wipes expressed as numbers per 1,000 patient-days. Data on plastic aprons were missing from 1 July 2006 to 30 June 2007. Medicated soap and ABHRS usage was expressed as litres per 1,000 patient-days.

Interventions

An antibiotic stewardship program incorporating a computerised decision-support system (CDSS) to guide antibiotic prescribing, introduced to ICU (January 2001), was associated with significant decreases in total and broad-spectrum antibiotic usage in ICU [14]. A CDSS, implemented in non-ICU areas (January 2005), led to hospital-wide reductions in antibiotic consumption [15]. Mandatory statewide surveillance of ICU infections [CLABSI, ventilator-associated pneumonia (VAP)] began in 2002 [16]. Minocycline-impregnated vascular catheters were used throughout the study period. In April 2004, the ID service commenced twice-weekly ICU ward rounds.

An outbreak of non-multiresistant *Acinetobacter* (March 2004–November 2005) prompted the appointment in ICU of two full-time ICPs (November 2004), enabling 7-day cover. These senior ICU nurses led a series of interventions (reported elsewhere), achieving outbreak control [17]. Contact precautions (long-sleeved gowns and gloves) were instituted for non-primary HCWs of *Acinetobacter* colonised patients for 3 months from October 2005.

A 70% ethanol ABHRS, used in ICU from January 2000 to March 2004, was replaced by another product (61.5% ethanol) introduced in July 2003. ABHRS was widely promoted following a hospital-wide campaign in April 2005. ICPs assessed hand hygiene compliance for 16 months thereafter using daily observations over three 4-week intervals [17].

Statistical analysis

Time of onset and magnitude of change in ICU MRSA prevalence density was determined using change-point analysis (the change-point being the time of change in slope of the prevalence density of MRSA over time). Because multiple interventions occurred during the study, we chose a statistical model that allowed only one change-point but made no assumptions about its timing, which was estimated by best fit to the data using nonlinear regression. The model for the change-point analysis was:

$$Y = a + bX \text{ if } X \leq k$$

$$Y = a + bk + (b + c)(X - k) \text{ if } X > k,$$

where Y is the prevalence density, X is time, a is the intercept, b is the slope prior to the change-point, k, and c is the change in slope. Hence an estimated $c < 0$ represents a reduction of, while $c > 0$ represents an increase in,

prevalence density. All p values used in the change-point analysis refer to the null hypothesis that $c = 0$. Data prior to October 2000 were graphically displayed but excluded from analysis as they were from the older, crowded ICU. The percentage decrease in ICU MRSA prevalence density was calculated using modelled values at the change-point and end of the study period. Change-point analysis, using the methodology described above, was used to determine when a change in broad-spectrum antibiotic use occurred. The change in trend of MRSA prevalence density and broad-spectrum antibiotic use was the difference in gradients before and after the change-point.

Linear regression was used to examine trends in consumption of IC consumables, ABHRS, individual antibiotic classes, ICU *S. aureus* bacteraemias, ICU MSSA prevalence density and hospital MRSA prevalence density over the study period. For only these proportionate change data, the outcome (dependent) variable was log transformed. Percentage change in explanatory variables over the study period was calculated using the following formula:

$$\text{Percent change} = (1 - \exp(-\beta X)) \times 100\%,$$

where X is the time period over which the change is measured and β is the slope of the log-transformed regression line after the change-point.

Because consecutive rates of MRSA are not independent variables, an autoregressive model (Prais–Winsten) accounting for autocorrelation, was chosen for multivariate analysis to assess temporal relationships between explanatory variables and ICU MRSA prevalence density. We selected a first-order autoregressive model using ICU MRSA prevalence density in the previous month as a predictor variable in the model to account for colonisation pressure such that

$$Y_t = \alpha Y_{t-1} + \beta \mathbf{X}_t + \varepsilon_t,$$

where α is the coefficient associated with the previous time period measure, β is a vector of coefficients that refer to all of the covariates we tested, $\mathbf{X}$ is a matrix with columns being the time periods and rows being the features of each that correspond to the covariates (e.g. numbers of gloves used per 1,000 patient-days) and ε is the error term. All analyses used Stata 10 (Stata Corp., College Station, TX, USA). A p value of ≤ 0.05 was considered statistically significant.

Results

Trends in the prevalence of MRSA and MSSA

The change in ICU MRSA prevalence density occurred in January 2004 (95% CI for date of change: August 2002–May 2005, $p < 0.001$), decreasing by 83% (95% CI 68–91% reduction, $p < 0.001$) at the end of the study period compared with the change-point value (Fig. 1). The gradient was 0.019/month (95% CI −0.14 to 0.17/month) before January 2004 and −0.23/month (95% CI −0.31 to −0.20/month) thereafter, denoting a change of −0.25/month (95% CI −0.33 to −0.17/month, $p < 0.001$), meaning that MRSA clinical isolates in ICU decreased by 0.25 isolates per 1,000 patient-days per month after the change-point. By log-linear regression, ICU MSSA prevalence density increased 38% (95% CI 1.3–84% increase, $p = 0.04$) over the study period.

Table 2 shows trends in consumption of infection control consumables, antibiotics, and *S. aureus* prevalence density. The ICU MRSA bacteraemia rate decreased by 89% from 2001 (95% CI 79–94% decrease, $p = 0.001$), while the MSSA bacteraemia rate did not significantly change, although confidence intervals are wide (Fig. 2). Whole-hospital MRSA prevalence density also reduced, but much less dramatically (Table 2).

Trends in consumption of infection control consumables, alcohol-based hand rub solution and antibiotics in ICU

By log-linear regression, the use of all IC consumables, with the exception of medicated soap and alcohol-impregnated wipes, increased significantly. ABHRS use increased from January 2000–March 2005 compared with April 2005–June 2008, from a median of 7.7 to 132 l/1,000 patient-days, respectively, following the hand hygiene campaign. Hand hygiene compliance at baseline, 4 and 16 months was 33% (95% CI 30–36%), 49% (95% CI 46–52%) and 39% (95% CI 36–42%), respectively. Consumption of individual classes of antibiotics in ICU decreased significantly over the study period, with the exception of carbapenems (trend not statistically significant) and anti-pseudomonal penicillins, which increased, the latter likely reflecting the preference of intensivists and a change to the febrile neutropenia protocol in January 2005, recommending piperacillin–tazobactam for empiric therapy (Fig. 3). Using change-point analysis, broad-spectrum antibiotic use decreased by 26% (95% CI 12–38% reduction, $p = 0.008$) from August 2003 (gradient before 2.25/month, 95% CI −0.13 to 4.58/month; gradient after −2.15/month, 95% CI −3.43 to −0.87/month; change −4.40/month, 95% CI for the change in gradient −7.24 to −1.69/month, $p = 0.001$; 95% CI for date of change February 2003–February 2004, $p < 0.001$).

Impact of infection control consumables and antibiotic consumption on MRSA

Results of an autoregressive model evaluating the impact of all explanatory variables on ICU MRSA prevalence

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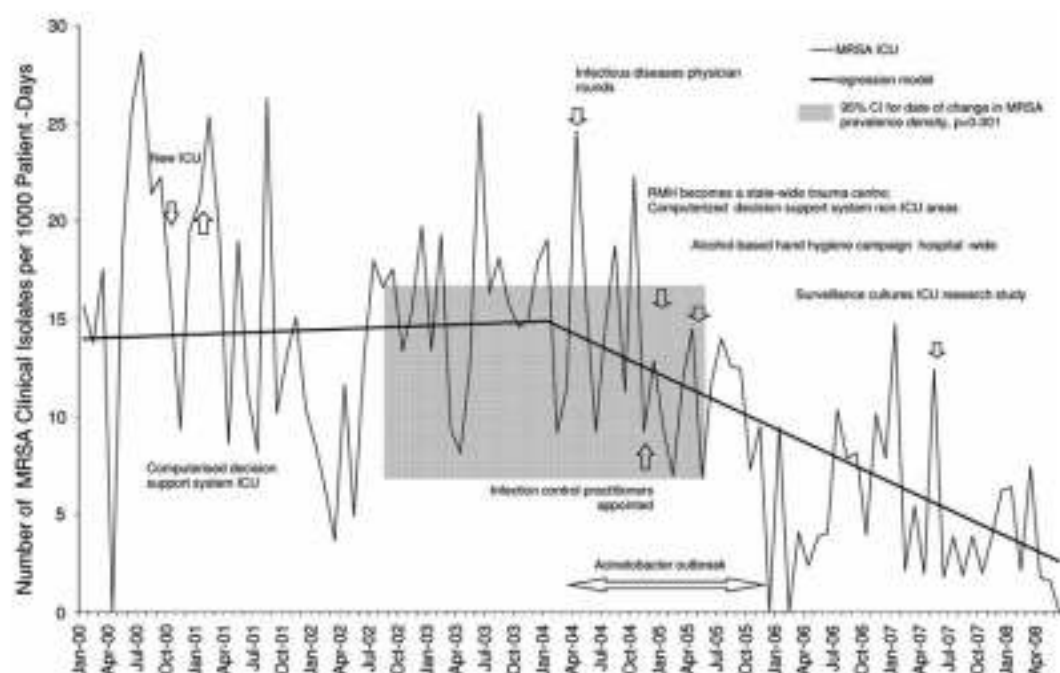
Fig. 1 ICU MRSA prevalence density and quality improvement interventions throughout ICU and hospital, 1 January 2000–30 June 2008. MRSA prevalence density decreased 83% (95% CI 68–91% reduction, p < 0.001) with a gradient change of −0.25/month (95% CI −0.33 to −0.17/month, p < 0.001) at January 2004 (95% CI for date of change, August 2002–May 2005)

Table 2 Relative change in usage of infection control consumables (numbers per 1,000 patient-days) and antibiotics (DDD per 1,000 patient-days) in ICU and burden of *S. aureus*, 1 November 2000–30 June 2008

Variable	Relative % change (95% CI)	p Value
Medicated soap	−26 (−51 to 13)	0.04
Disposable gowns	120 (11 to 329)	<0.001
Plastic aprons	270 (56 to 780)	0.003
Alcohol-impregnated wipes	6.8 (−3.4 to 18)	0.2
Gloves	84 (61 to 101)	<0.001
Fluoroquinolones	−35 (−1.4 to −58)	0.03
Cephalosporins (third and fourth generation)	−55 (−35 to −64)	<0.001
Carbapenems	13 (−13 to 39)	0.33
Aminoglycosides	−69 (−45 to −82)	<0.001
Anti-pseudomonal penicillins	820 (480 to 1360)	<0.001
Glycopeptides	−20 (−3.8 to −33)	0.03
Macrolides	−94 (−84 to −98)	0.001
MSSA ICU prevalence density[a]	38 (1.3 to 84)	0.04
MRSA whole-hospital prevalence density[a]	−17 (−5 to −27)	0.008
MRSA bacteraemias ICU[b]	−89 (−79 to −94)	0.001
MSSA bacteraemias ICU[b]	18 (−18 to 66)	0.55

DDD Defined daily dose

[a] Expressed as clinical isolates excluding duplicates or screening isolates per 1,000 patient-days

[b] From 1 January 2001 to 31 December 2008

density are shown in Table 3. Univariate analysis demonstrated significant temporal relationships for ABHRS, aminoglycosides, anti-pseudomonal penicillins and broad-spectrum antibiotics; however, multivariate analysis included only ABHRS and broad-spectrum antibiotic use. Individual classes of antibiotics were not analysed because: (a) the ecologic impact of aggregate broad-spectrum antibiotic use was our primary interest, and its analysis precluded the inclusion of component antibiotics; and (b) changes in antibiotic consumption reflected natural variations in prescribing practices without interventions targeting specific antibiotic classes. On multivariate analysis, only ABHRS use was associated with a significant decrease in MRSA prevalence density, i.e. use of one litre of ABHRS/1,000 patient-days reduced MRSA prevalence by 0.04 clinical isolates/1,000 patient-days/month (95% CI −0.024 to −0.064 clinical isolates/1,000 patient-days/month, p < 0.001).

Discussion

Using ecological data we report a sustained decline in endemic MRSA in an ICU following general IC and
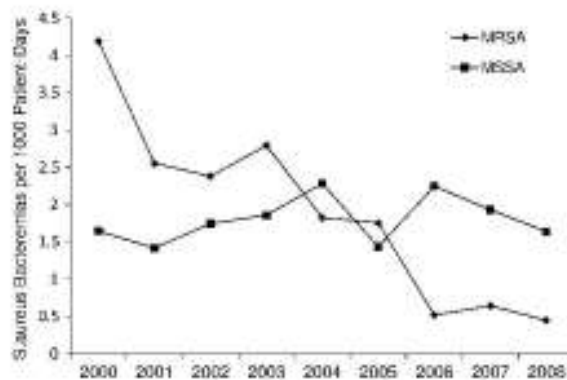
Fig. 2 Annual rates of *S. aureus* bacteraemias; ICU MRSA bacteraemia rates decreased significantly from 2001. Data from 2000 are shown but excluded from analysis as they occurred in the old ICU

antibiotic stewardship interventions without the adoption of ASC or contact isolation of MRSA colonised patients. MRSA prevalence density decreased by 83% (95% CI 68–91% decrease, $p < 0.001$), coinciding with a period of intensified quality improvement activities from early 2004. On multivariate analysis, only ABHRS was significantly associated with a decrease in MRSA prevalence, but in reality MRSA fell in the context of multiple other interventions whose relative contributions could not be determined. A parallel reduction in the MRSA bacteraemia rate of 89% (95% CI 79–94% reduction, $p = 0.001$) compares favourably with the 75% reduction over 16 months achieved by Huang et al. [18] in an ICU using active MRSA surveillance cultures and contact isolation precautions. Like others [4, 18, 19], we observed no reduction in MSSA bacteraemia (in fact, ICU

MSSA prevalence density increased significantly during the study period), suggesting that our interventions, aimed at preventing the emergence and transmission of antibiotic-resistant pathogens, were interrupting the transmission of MRSA. These interventions would not be expected to reduce infections due to endogenous flora such as MSSA, which is less influenced by measures designed to minimise cross-transmission of pathogens such as single rooms [20]. Had we adopted care bundles for the prevention of CLABSI or VAP, MSSA infections may have decreased, as MSSA is the predominant cause of these common ICU infections [21]. Of interest, increasing trauma admissions, a known risk factor for MRSA acquisition in ICU [22], did not lead to an expected increase in MRSA prevalence when RMH became a statewide trauma centre.

It is probable that ABHRS potentiated the decline in MRSA, but it alone is unlikely to explain the whole effect, as it was promoted as part of a hospital-wide campaign late in the study period. Although alcohol-based hand disinfection decreases nosocomial MRSA infection [23], compliance is consistently lowest in ICU areas [24]. Our rates are comparable to other US ICUs [25] and close to a postulated threshold of >40% proposed by modelling studies as necessary to prevent outbreaks of staphylococcal infection [26, 27]. It is conceivable that the hand hygiene audit tool used during the study period underestimated compliance due to its more stringent criteria [17] compared with later versions employed for this purpose [28].

Antibiotic stewardship and IC interventions may be complementary activities in controlling MRSA, but few studies have examined their influence concurrently. Recent time-series analyses have shown a consistent correlation between reduced hospital-wide use of

Fig. 3 ICU antibiotic consumption with change-point analysis of broad-spectrum antibiotic use. Broad-spectrum antibiotics include the sum total of displayed antibiotics. Broad-spectrum antibiotic use decreased 26% (95% CI 12–38% reduction, $p = 0.008$) from August 2003 (95% CI for date of change, February 2003–February 2004) with a gradient change of −4.40/month (95% CI −7.24 to −1.69/month, $p = 0.001$)

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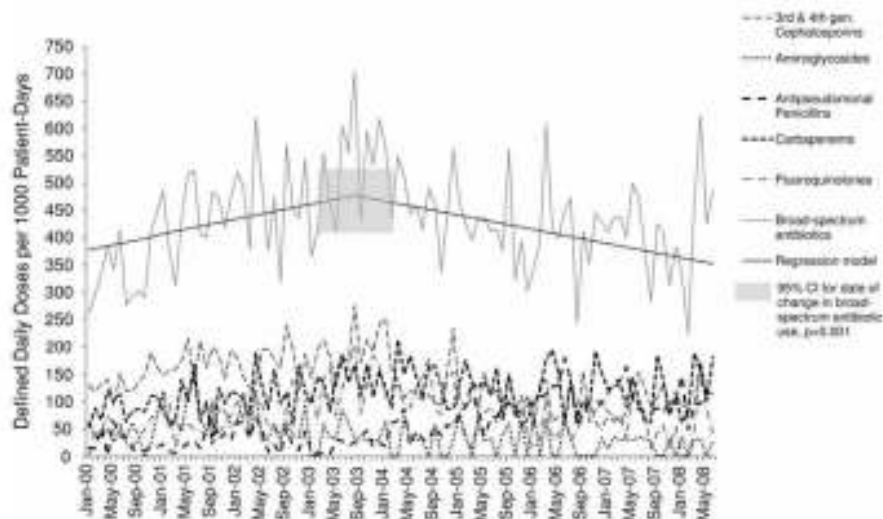
Table 3 Temporal relationship of ABHRS (litres per 1,000 patient-days), infection control consumables (numbers per 1,000 patient-days) and antibiotic use (DDD per 1,000 patient-days) on monthly ICU MRSA prevalence density by univariate and multivariate analysis, 1 November 2000–30 June 2008

Variable	Coefficient[a] (95% CI)	p Value
Univariate analysis		
ABHRS	−0.05 (−0.07 to −0.30)	<0.001
Medicated soap	0.02 (−0.01 to 0.04)	0.28
Disposable gowns	0.001 (−0.0001 to 0.002)	0.07
Plastic aprons	−0.00006 (−0.0002 to 0.00005)	0.26
Alcohol-impregnated wipes	0.0002 (−0.0003 to 0.0007)	0.38
Gloves	−0.00004 (−0.00009 to 7×10^{-6})	0.10
Fluoroquinolones	0.01 (−0.02 to 0.04)	0.37
Cephalosporins (third and fourth generation)	0.02 (−0.005 to 0.05)	0.11
Carbapenems	0.02 (−0.003 to 0.05)	0.08
Aminoglycosides	0.05 (0.02 to 0.08)	0.004
Anti-pseudomonal penicillins	−0.08 (−0.06 to −0.1)	<0.001
Broad-spectrum antibiotics[b]	0.01 (0.0008 to 0.03)	0.04
Multivariate analysis[c]		
ABHRS	−0.04 (−0.024 to −0.064)	<0.001
Broad-spectrum antibiotics	0.009 (−0.004 to 0.023)	0.165

MRSA prevalence density is expressed as clinical isolates excluding duplicates or screening isolates per 1,000 patient-days

DDD defined daily dose, ABHRS alcohol-based hand rub solution

[a] Size and direction of the effect of the explanatory variable on MRSA prevalence density

[b] Sum total of above-stated antibiotics

[c] Multivariate analysis included ABHRS (which was significant on univariate analysis) and broad-spectrum antibiotics (sum total of above stated antibiotics, component antibiotic classes excluded)

fluoroquinolones, cephalosporins and macrolides and decreased MRSA infection or colonisation [29, 30]. It is encouraging then that significant reductions in fluoroquinolones, cephalosporins, aminoglycosides, glycopeptides and macrolides were observed. Although the autoregressive model did not demonstrate an effect of antibiotic selection pressure on MRSA burden, MRSA fell in the context of significant reductions in broad-spectrum antibiotics (26%, 95% CI 12–38% reduction, $p = 0.008$), suggesting a possible association. Perhaps the 1-month time lag in the model was too short to show the impact of antibiotics on MRSA when other investigations have reported delays of 3 months or more [29, 30], or the analysis of antibiotics in aggregate may have masked their individual effect on MRSA.

Few studies describe the long-term efficacy of multifaceted MRSA control programs in ICU without the use of ASC. A single centre noted a 73% reduction ($p < 0.001$) in ICU device-associated MRSA infection over 4 years without adoption of admission screening, but unlike our setting, contact precautions for colonised

patients were routine [31]. Likewise, another Australian ICU with high levels of endemic MRSA achieved significant reductions in MRSA colonisation and infection ($p < 0.047$) over 5.5 years without screening or isolation [24].

Population-based IC measures may have a greater proportional benefit on all nosocomial infections compared with single-organism measures such as ASC for MRSA [32]. Daily chlorhexidine-based washing of ICU patients decreased acquisition of MRSA by 32% ($p = 0.046$) and vancomycin-resistant enterococcus (VRE) by 50% ($p = 0.008$) along with VRE bacteraemias ($p = 0.008$) [33], while a 66% reduction in CLABSI was achieved in US ICUs using evidence-based care bundles and organisational culture change [34].

Active surveillance cultures and contact isolation precautions for MRSA colonised patients are cost beneficial provided MRSA infections are prevented [5], but resource constraints, attendant opportunity costs and limited isolation rooms in our setting have tempered our support for this approach. Perhaps of most concern to our intensivists is the finding that single-room isolation is associated with a halving of HCW contact [35].

One of the limitations of this study is that we were unable to determine the significance of isolates because of lack of clinical information. This was partially mitigated by excluding screening swabs and duplicates and by analysing bacteraemias separately. Though not ideal, the use of all clinical isolates as a surveillance measure has been shown to correlate with MRSA incidence from sterile sites, with the advantages of being more sensitive to changes in MRSA incidence and less susceptible to the stochastic variation inherent in bacteraemia measures [36]. Distinguishing community from nosocomial acquisition was not possible from the dataset used, however MRSA in our setting is overwhelmingly healthcare associated [37]. Chance events accounting for the decline in MRSA are possible, but the long study period argues against this. Changing strain properties are unlikely, as more transmissible or persistent strains are likely to be selected over time, thereby increasing MRSA rather than causing the reduction we observed [38]. Our discharge MRSA prevalence of 6.9% is lower than the admission prevalence in other local tertiary ICUs [23, 39], but the survey was performed at a time when MRSA was already in decline.

Decreased detection effort is not a likely confounder, as we used isolates collected for clinical reasons only and laboratory identification methods did not change. Response to the *Acinetobacter* outbreak reinforced general quality improvement measures and perhaps, for this reason, may also have had an effect on MRSA. No comparator pathogen with similar transmission dynamics to MRSA was available. *Acinetobacter* was unsuitable due to the outbreak, and clinical isolates of VRE were too few for statistical analysis. With respect to other

nosocomial pathogens, carbapenem-susceptible *Pseudomonas aeruginosa* has increased since the introduction of our CDSS [40]. ASC as part of a research project are unlikely to have been influential, as they commenced late in the study period and were not acted upon. Finally, a decreasing length of stay in ICU over time may lead to a spurious reduction in MRSA prevalence, but the 17% reduction ($p = 0.005$) in hospital MRSA argues against exportation of a MRSA problem from ICU into the wards.

Turning the tide of endemic MRSA may be achievable without ASC and contact isolation precautions. Multimodal measures including adequate staffing, dedicated ICPs, ABHRS and antibiotic stewardship can be effective over the long term, even when the risk of nosocomial infection is high and the presence of endemic MRSA considerable. The relative efficacies of these measures could not be determined in our study, but in combination they confirm that successful interventions are often multifactorial [23, 34]. If the realistic aim in an endemic setting is to reduce rather than eliminate MRSA then our experience provides a compelling example of how this can be achieved without "search and destroy" IC measures.

Conflict of interest None.

References

1. Davis KA, Stewart JJ, Crouch HK, Florez CE, Hospenthal DR (2004) Methicillin-resistant *Staphylococcus aureus* (MRSA) nares colonization at hospital admission and its effect on subsequent MRSA infection. Clin Infect Dis 39:776–782

2. Jeyaratnam D, Edgeworth JD, French GL (2006) Enhanced surveillance of methicillin-resistant *Staphylococcus aureus* bacteraemia in a London teaching hospital. J Hosp Infect 63:365–373

3. Cepeda JA, Whitehouse T, Cooper B, Hails J, Jones K, Kwaku F, Taylor L, Hayman S, Cookson B, Shaw S, Kibbler C, Singer M, Bellingan G, Wilson AP (2005) Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units: prospective two-centre study. Lancet 365:295–304

4. Robicsek A, Beaumont JL, Paule SM, Hacek DM, Thomson RB Jr, Kaul KL, King P, Peterson LR (2008) Universal surveillance for methicillin-resistant *Staphylococcus aureus* in 3 affiliated hospitals. Ann Intern Med 148:409–418

5. Clancy M, Graepler A, Wilson M, Douglas I, Johnson J, Price CS (2006) Active screening in high-risk units is an effective and cost-avoidant method to reduce the rate of methicillin-resistant *Staphylococcus aureus* infection in the hospital. Infect Control Hosp Epidemiol 27:1009–1017

6. Harbarth S, Masuet-Aumatell C, Schrenzel J, Francois P, Akakpo C, Renzi G, Pugin J, Ricou B, Pittet D (2006) Evaluation of rapid screening and pre-emptive contact isolation for detecting and controlling methicillin-resistant *Staphylococcus aureus* in critical care: an interventional cohort study. Crit Care 10:R25

7. Harbarth S, Fankhauser C, Schrenzel J, Christenson J, Gervaz P, Bandiera-Clerc C, Renzi G, Vernaz N, Sax H, Pittet D (2008) Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and nosocomial infection in surgical patients. JAMA 299:1149–1157

8. Jeyaratnam D, Whitty CJ, Phillips K, Liu D, Orezzi C, Ajoku U, French GL (2008) Impact of rapid screening tests on acquisition of meticillin resistant *Staphylococcus aureus*: cluster randomised crossover trial. BMJ 336:927–930

9. Calfee DP, Salgado CD, Classen D, Arias KM, Podgorny K, Anderson DJ, Burstin H, Coffin SE, Dubberke ER, Fraser V, Gerding DN, Griffin FA, Gross P, Kaye KS, Klompas M, Lo E, Marschall J, Mermel LA, Nicolle L, Pegues DA, Perl TM, Saint S, Weinstein RA, Wise R, Yokoe DS (2008) Strategies to prevent transmission of methicillin-resistant *Staphylococcus aureus* in acute care hospitals. Infect Control Hosp Epidemiol 29(Suppl 1):S62–S80

10. Klevens RM, Edwards JR, Tenover FC, McDonald LC, Horan T, Gaynes R (2006) Changes in the epidemiology of methicillin-resistant *Staphylococcus aureus* in intensive care units in US hospitals, 1992–2003. Clin Infect Dis 42:389–391

11. Fluit AC, Wielders CL, Verhoef J, Schmitz FJ (2001) Epidemiology and susceptibility of 3,051 *Staphylococcus aureus* isolates from 25 university hospitals participating in the European SENTRY study. J Clin Microbiol 39:3727–3732

12. Nimmo GR, Pearson JC, Collignon PJ, Christiansen KJ, Coombs GW, Bell JM, McLaws ML (2007) Prevalence of MRSA among *Staphylococcus aureus* isolated from hospital inpatients, 2005: report from the Australian Group for Antimicrobial Resistance. Commun Dis Intell 31:288–296

13. Burton DC, Edwards JR, Horan TC, Jernigan JA, Fridkin SK (2009) Methicillin-resistant *Staphylococcus aureus* central line-associated bloodstream infections in US intensive care units, 1997–2007. JAMA 301:727–736

14. Thursky KA, Buising KL, Bak N, Macgregor L, Street AC, Macintyre CR, Presneill JJ, Cade JF, Brown GV (2006) Reduction of broad-spectrum antibiotic use with computerized decision support in an intensive care unit. Int J Qual Health Care 18:224–231

15. Buising KL, Thursky KA, Robertson MB, Black JF, Street AC, Richards MJ, Brown GV (2008) Electronic antibiotic stewardship—reduced consumption of broad-spectrum antibiotics using a computerized antimicrobial approval system in a hospital setting. J Antimicrob Chemother 62:608–616

16. VICNISS Hospital Acquired Infection Surveillance Coordinating Centre. VICNISS surveillance activities in our hospitals. http://www.vicniss. org.au/SurveillanceActivities.aspx. Accessed 12 Dec 2009

17. Rose L, Rogel K, Redl L, Cade JF (2009) Implementation of a multimodal infection control program during an *Acinetobacter* outbreak. Intensive Crit Care Nurs 25:57–63

18. Huang SS, Yokoe DS, Hinrichsen VL, Spurchise LS, Datta R, Miroshnik I, Platt R (2006) Impact of routine intensive care unit surveillance cultures and resultant barrier precautions on hospital-wide methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis 43:971–978

19. National Audit Office Report (HC 560 2008–2009): trends in rates of healthcare associated infection in England 2004 to 2008. http://web.nao.org.uk/search/search.aspx?Schema=&terms=health+care+associated+infections. Accessed 12 Dec 2009

20. Bracco D, Dubois MJ, Bouali R, Eggimann P (2007) Single rooms may help to prevent nosocomial bloodstream infection and cross-transmission of methicillin-resistant *Staphylococcus aureus* in intensive care units. Intensive Care Med 33:836–840

21. Zhanel GG, DeCorby M, Laing N, Weshnoweski B, Vashisht R, Tailor F, Nichol KA, Wierzbowski A, Baudry PJ, Karlowsky JA, Lagace-Wiens P, Walkty A, McCracken M, Mulvey MR, Johnson J, Hoban DJ (2008) Antimicrobial-resistant pathogens in intensive care units in Canada: results of the Canadian National Intensive Care Unit (CAN-ICU) study, 2005–2006. Antimicrob Agents Chemother 52:1430–1437

22. Marshall C, Wolfe R, Kossmann T, Wesselingh S, Harrington G, Spelman D (2004) Risk factors for acquisition of methicillin-resistant *Staphylococcus aureus* (MRSA) by trauma patients in the intensive care unit. J Hosp Infect 57:245–252

23. Johnson PD, Martin R, Burrell LJ, Grabsch EA, Kirsa SW, O'Keeffe J, Mayall BC, Edmonds D, Barr W, Bolger C, Naidoo H, Grayson ML (2005) Efficacy of an alcohol/chlorhexidine hand hygiene program in a hospital with high rates of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Med J Aust 183:509–514

24. Harrington G, Watson K, Bailey M, Land G, Borrell S, Houston L, Kehoe R, Bass P, Cockroft E, Marshall C, Mijch A, Spelman D (2007) Reduction in hospitalwide incidence of infection or colonization with methicillin-resistant *Staphylococcus aureus* with use of antimicrobial hand-hygiene gel and statistical process control charts. Infect Control Hosp Epidemiol 28:837–844

25. McGuckin M, Waterman R, Govednik J (2009) Hand hygiene compliance rates in the United States—a one-year multicenter collaboration using product/volume usage measurement and feedback. Am J Med Qual 24:205–213

26. Cooper BS, Medley GF, Scott GM (1999) Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects. J Hosp Infect 43:131–147

27. McBryde ES, Pettitt AN, McElwain DL (2007) A stochastic mathematical model of methicillin resistant *Staphylococcus aureus* transmission in an intensive care unit: predicting the impact of interventions. J Theor Biol 245:470–481

28. Hand Hygiene Australia. Resources for healthcare workers. http://www.hha.org.au/ForHealthcareWorkers.aspx. Accessed 12 Dec 2009

29. Vernaz N, Sax H, Pittet D, Bonnabry P, Schrenzel J, Harbarth S (2008) Temporal effects of antibiotic use and hand rub consumption on the incidence of MRSA and *Clostridium difficile*. J Antimicrob Chemother 62:601–607

30. Kaier K, Hagist C, Frank U, Conrad A, Meyer E (2009) Two time-series analyses of the impact of antibiotic consumption and alcohol-based hand disinfection on the incidences of nosocomial methicillin-resistant *Staphylococcus aureus* infection and *Clostridium difficile* infection. Infect Control Hosp Epidemiol 30:346–353

31. Edmond MB, Ober JF, Bearman G (2008) Active surveillance cultures are not required to control MRSA infections in the critical care setting. Am J Infect Control 36:461–463

32. Wenzel RP, Bearman G, Edmond MB (2008) Screening for MRSA: a flawed hospital infection control intervention. Infect Control Hosp Epidemiol 29:1012–1018

33. Climo MW, Sepkowitz KA, Zuccotti G, Fraser VJ, Warren DK, Perl TM, Speck K, Jernigan JA, Robles JR, Wong ES (2009) The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and healthcare-associated bloodstream infections: results of a quasi-experimental multicenter trial. Crit Care Med 37:1858–1865

34. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, Sexton B, Hyzy R, Welsh R, Roth G, Bander J, Kepros J, Goeschel C (2006) An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 355:2725–2732

35. Evans HL, Shaffer MM, Hughes MG, Smith RL, Chong TW, Raymond DP, Pelletier SJ, Pruett TL, Sawyer RG (2003) Contact isolation in surgical patients: a barrier to care? Surgery 134:180–188

36. Walker S, Peto TE, O'Connor L, Crook DW, Wyllie D (2008) Are there better methods of monitoring MRSA control than bacteraemia surveillance? An observational database study. PLoS ONE 3:e2378

37. Nimmo GR, Coombs GW (2008) Community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) in Australia. Int J Antimicrob Agents 31:401–410

38. Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, Duckworth GJ, Lai R, Ebrahim S (2003) Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling. Health Technol Assess 7:1–194

39. Marshall C, Harrington G, Wolfe R, Fairley CK, Wesselingh S, Spelman D (2003) Acquisition of methicillin-resistant *Staphylococcus aureus* in a large intensive care unit. Infect Control Hosp Epidemiol 24:322–326

40. Yong MK, Buising KL, Cheng AC, Thursky KA (2010) Improved susceptibility of Gram-negative bacteria in an intensive care unit following implementation of a computerized antibiotic decision support system. J Antimicrob Chemother 65:1062–1069

Appendix 9

CMV infection (*see **Appendix** A for definition*)

☐   No

☐   Yes → ☐   PCR , site_____

                 ☐   pp65 Antigenemia

                 ☐   Other (→ *specify*)_____

Proven CMV disease & site (*see **Appendix** A for definition*)

☐   No

☐   Yes → Date of onset   _____/_____/_____

Describe organ involvement & complete table below:

Conditioning Regimen

☐   Myeloablative

☐   Non-myeloablative (ie *mini allo*)

Regimen:

☐   Cyclophosphamide / TBI / ATG

☐   Cyclophosphamide / TBI

☐   Cyclophosphamide / TBI/ Other

☐   Busulphan / TBI

☐   Busulphan / Cyclophosphamide

☐   Busulphan / Melphalan

☐   Busulphan / TBI

☐   Fludarabine / Cyclophosphamide

☐   Fludarabine / Cyclophosphamide / Alemtuzumab (Campath)

☐   Fludarabine / Cyclophosphamide / Other

☐   Fludarabine / Melphalan

☐   Busulphan

☐   Melphalan

☐   TBI / Cyclophosphamide

☐   TBI / Other

☐   Carmustine / Etoposide / Cytarabine / Melphalan (BEAM)

☐   Etoposide / Cyclophosphamide / Carmustine

☐   Cyclophosphamide / Irradiation other than TBI /+/- Other

☐   Lomustine / Etoposide / Cytarabine / Cyclophosphamide

☐   Fludarabine / Idarubicin

☐   Other (*specify→*)_____

Neutrophil Engraftment:

☐   No, never engrafted

☐   Yes   → ANC nadir_____ &   Date_____ / _____ / _____

☐   Yes , ANC 0.1×10^5 or more Date[1]_____ / _____ / _____

☐   Yes , ANC 0.5×10^5 or more Date[2]_____ / _____ / _____

Notes: [1] *date= 1st day ANC $\geq 0.1 \times 10^5$ for 3 consecutive days.*

[2] *date= 1st day ANC $\geq 0.5 \times 10^9$ for 3 consecutive days.*

Monocyte recovery
Monocytes more than >120 cells/ml for 3 consecutive days

☐   No, monocyte count never recovered

☐   Yes→ Date (1st day)_____ / _____ / _____

GVHD

GVHD prophylaxis

☐   No

☐   Yes →*Please fill in the table for prophylaxis below*

Name of Drugs	Date Started	Date Finished
	____ / ____	____ / ____
	____ / ____	____ / ____
	____ / ____	____ / ____
	____ / ____	____ / ____
	____ / ____	____ / ____
	____ / ____	____ / ____
	____ / ____	____ / ____
	____ / ____	____ / ____
	____ / ____	____ / ____
	____ / ____	____ / ____
	____ / ____	____ / ____
	____ / ____	____ / ____

Acute GVHD (0-100 day post HSCT) (*see Appendix B for definitions & sites*)

☐ No→ *go to next page*
☐ Yes→ *please fill the table below*

Site (eg. skin, liver, gut, other..)	Grade/Stage (0-4, only highest grade per site)	Date of onset

Treatment of acute GVHD

☐ No → *go to next page*
☐ Yes

☐ Dicluzimab (anti-IL2R)   ☐ Rituximab (anti-CD20)
☐ Infliximab (anti-TNF)   ☐ Visilizumab (anti CD3)
☐ Basiliximab (anti-IL2)   ☐ ABX-CBF (antiCD147)
☐ Alemtuzumab (campath-antiCD52)
☐ ATG (antithymocyte globulin)
☐ Other acute GVTx antibody (*specify*→)_____

Other Treatment of acute GVHD

Treatment	Daily Dose (mg)	Date started	Date finished
☐ Methylprednisolone		/ /	/ /
☐ Prednisolone		/ /	/ /
☐ Mycophenolate mofetil (MMF)		/ /	/ /
☐ Tacrolimus		/ /	/ /
☐ Cyclosporin A		/ /	/ /
☐ Other (*specify* →) _____		/ /	/ /

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Chronic GVHD (>100days post HSCT)   ☐ No

☐ Yes→ *please fill in the table below*

Site *(specify: eg. Skin, liver, gut, other..)*	Extent *(please circle one)*	Date of onset
	Limited / Extensive / Unknown	
	Limited / Extensive / Unknown	
	Limited / Extensive / Unknown	
	Limited / Extensive / Unknown	
	Limited / Extensive / Unknown	

Treatment of Chronic GVHD

Treatment *(please tick the all drugs prescribed)*	Date started	Date finished
☐ Methylprednisolone	/ /	/ /
☐ Prednisolone	/ /	/ /
☐ Prednisolone + Cyclosporin	/ /	/ /
☐ Prednisolone + Tacrolimus	/ /	/ /
☐ Prednisolone + Sirolimus (Rapamycin)	/ /	/ /
☐ MMF/ Tacrolimus	/ /	/ /
☐ Cyclosporin A	/ /	/ /
☐ PUVA	/ /	/ /
☐ Extracorporeal photochemotherapy (ECP)	/ /	/ /
☐ Rituximab	/ /	/ /
☐ Pentostatin	/ /	/ /
☐ Lymphoid Irradiation	/ /	/ /
☐ Penicillamine	/ /	/ /
☐ Plaquenil	/ /	/ /
☐ Etretinate	/ /	/ /
☐ Other chronic therapy (*specify* →) _____	/ /	/ /

Outcome of Acute and/or Chronic GVHD Treatment/s

☐ Controlled
☐ Uncontrolled
☐ Unknown/Not Reported

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Antifungal Prophylaxis[1] *(see outpt and inpt notes)* ☐ No→*go to next page* ☐ Yes →*complete the table below*

Antifungal Drug Name *USE GENERIC NAMES*	Indication[2] (number)	Daily dose (mg)	Route	Start Date	Finish Date	Reason for discontinuation[3]

Notes[1]: *Prophylaxis is usually fluconazole, itraconzole, voriconazole or another antifungal drug started on admission or at the start of chemotherapy. It is <u>not the same</u> as treatment of neutropenic fever.*

Indication[2] **for antifungal prophylaxis**

1. Post chemotherapy for acute leukaemia (routine indication)
2. Post allogeneic HSCT (routine indication)
3. Acute GVHD
4. Chronic GVHD
5. Secondary prophylaxis due to previous IFI
6. Other (*specify* →)_____

Notes[3]: **Reason for discontinuation:**

Choose reason for discontinuation and fill in that field with the appropriate code:

A = Toxicity (*please see AppendixC*)
B = Lack of efficacy
C = Non-compliance
D = Treatment completed
E = Step down therapy
F = Other (*please specify*)

Consultations by Health Care Professionals *(assign code in table below)*

Allied Health	*Medical/surgical units*
A. Audiology	P. Medical unit, specify
B. Dietetics	Q. Surgical unit, specify
C. Music therapy	
D. Occupational therapy	
E. Orthoptics	
F. Orthotics	
G. Pastoral care	
H. Pharmacy	
I. Physiotherapy	
J. Podiatry	
K. Prosthetics	
L. Psychology	
M. Social work	
N. Speech pathology	
O. Other, specify	

Health Care Professional Consultations	Date (s)

INVASIVE FUNGAL INFECTION

Data Collection Form: <u>Part B</u>

UR Number_____

EORTC classification of IFI (External Reviewer to determine, see Appendix D)

IFI diagnosis: ☐ possible
☐ probable
☐ proven

Date of IFI diagnosis: _____/_____/_____ (External Reviewer to determine)

Date of IFI diagnosis: _____/_____/_____ (Based on clinical suspicion from notes)

Pathogen

❑ Invasive aspergillus

☐ fumigatus
☐ flavus
☐ niger
☐ terreus
☐ nidulans
☐ versicolor
☐ aspergillus galactomannan antigen index
☐ aspergillus (*not otherwise specify*→)

❑ Candida species

☐ C albicans
☐ C glabrate
☐ C krusei
☐ C parapsilosis
☐ C tropicalis
☐ C lusitaniae
☐ C dubliniensis
☐ Candida (*not otherwise specify*→)

❑   Other fungi

      ☐   scedosporium prolificans
      ☐   scedosporium apiospermum (aka pseudallescheria boydii)
      ☐   fusarium species
      ☐   trichosporon species
      ☐   other (*specify→*)_____

❑   Unspecified mold *(eg hyphae only seen on history but no culture)*
❑   Unspecified yeast *(organism seen on histology but no culture)*
❑   PCR *(specimen and species identified)*_____
❑   Galactomannan antigen test & date_____

Research nurses to supply the following:

Include **key investigations** (*attach key reports including microscopy, culture, serology, antigen detection eg galactomannan antigen test, PCR, blood culture results, histopathology or radiology: CXR, CT, MRI)*

Risk factors in 30days prior to diagnosis of IFI

      ☐   neutropenia (PMN<500/mm^3) for >10 days before date of IFI
      ☐   prolonged prednisolone use for 2 wks or more in 2 months prior to IFI diagnosis.

          ❑   <2mg/kg/day
          ❑   ≥ 2mg/kg/day

If not prednisolone please specify c-steroid and daily dose (mg/kg)

_____

      ☐   Ganciclovir administration
      ☐   CMV disease
      ☐   Mononuclear cell count <120 cells/mm^3 at time of IFI diagnosis
      ☐   Other immunosuppressive drugs→

          ◇   Cyclophosphamide
          ◇   Cyclosporine
          ◇   TNF alpha inhibitors
          ◇   Alemtuzamab
          ◇   Nucleoside analogues
          ◇   Mycophenolate
          ◇   Other→*specify*_____

Patient comorbid conditions

- ☐ Diabetes*
- ☐ Diabetes with organ damage*
- ☐ solid organ transplant recipient
- ☐ heart failure*
- ☐ mycocardial infarction*
- ☐ peripheral vascular disease*
- ☐ chronic renal insufficiency
- ☐ moderate-severe renal disease*
- ☐ mild liver disease*
- ☐ moderate-severe liver disease*
- ☐ any tumour (within the last 5 yrs)*
- ☐ metastatic solid tumour*
- ☐ chronic respiratory disease
- ☐ chronic obstructive airways disease*
- ☐ peptic ulcer disease*
- ☐ cerebrovascular disease*
- ☐ hemiplegia*
- ☐ dementia*
- ☐ HIV/AIDS*
- ☐ smoking status→ ☐ current   ☐ never   ☐ ex-   ☐ unk
- ☐ connective tissue disorder* (*eg. SLE, RA specify→*)_____
- ☐ primary (non-HIV) immunodeficiency state (*ie. SCID, chronic granulomatous disease...*)_____
- ☐ Other diagnosis, specify_____

required for calculation of the Charlson Comorbidity Index (see below)

Charlson comorbidity index (Note:an aggregate measure of comorbidity to be calculated by data entry personnel using an electronic calculator)

Age unadjusted CCI score_____

Age adjusted CCI score_____

Severity of Illness Assessment

McCabe Jackson Score [1]

Date_____

    ☐ rapidly fatal illnesses expected to die within 2 wks , score = 1

    ☐ ultimately fatal diseases expected to live for <5 yrs, score = 2

    ☐ non-fatal illness, score = 3

[1]**Note:** An illness severity score which should be ideally performed 48h prior to recognition of IFI for case patients or if case patients admitted with IFI then should be calculated within 24h of admission; for control patients should be calculated within 24h of admission.

Extent of IFI

    ☐   localised

    ☐   disseminated (2 or more non-contiguous sites affected or positive blood culture)

Site:

- ☐ lung
- ☐ sinus
- ☐ CNS
- ☐ eye
- ☐ endocarditis
- ☐ skin
- ☐ soft tissue
- ☐ liver
- ☐ spleen
- ☐ hepatosplenic
- ☐ bone / joint
- ☐ intraabdominal / peritoneal
- ☐ fungaemia
- ☐ urinary tract → O upper: kidney, ureter
  -           O lower: bladder, urethra
- ☐ other

Antifungal Treatment (*see outpt and inpt notes*)

Antifungal Drug Names	Indication[1]	Daily Dose (mg)	Route	Start Date	Finish Date	Reason for discontinuation[2]

<u>*Notes*</u>:

[1]A= Treatment of IFI;   B=Treatment of neutropenic fever

[2]**Reason for discontinuation:**
Choose reason for discontinuation and fill in that field with the appropriate code:

A = Toxicity (*specify in box below*)   **D** = Treatment completed
B = Lack of efficacy   **E** = Step down therapy
C = Non-compliance   **F** = Other (*specify*)

Antifungal toxicity (*see Appendix C*)   ☐   no   ☐   yes → Date _____/_____/_____

Describe:

Other measures:

Granulocyte Infusion

    ☐   No

    ☐   Yes → Start date: _____/_____/_____

                               _____ _____ _____

                               _____ _____ _____

Intensive care unit admission

    ☐   No

    ☐   Yes) → *(fill table below)*

Admission Date	Discharge Date	Mechanical Ventilation	Apache II Score on Admission[1]
/ /	/ /	☐ no ☐ yes	
/ /	/ /	☐ no ☐ yes	
/ /	/ /	☐ no ☐ yes	
/ /	/ /	☐ no ☐ yes	

Notes: [1] To be obtained from ICU database

Surgery or Therapeutic/Diagnostic Procedure(s)

    ☐   No

    ☐   Yes →

Date(s) &Description:

Outcome post IFI diagnosis

☐   **Death** → Date _____ / _____ / _____

              Reason: ☐ related to IFI
                                ☐ unrelated to IFI
                                ☐ with IFI but due to another cause

Narrative description of death (attach hospital discharge summary, photocopy of relevant case notes)

              Autopsy performed: ☐ no
                                      ☐ yes, *attach report if available*
                                      ☐ unknown / no report

Results of autopsy (if no report available)

☐   **Alive** → *Complete the section of outcome below*

Duration post IFI diagnosis	Outcome*
1 month	
3 months	
6 months	
12 months	
>12 months→*date of last review* / /	

*Notes: *fill **code number** in the table above*
1 = complete response (>90% resolution of symptoms and signs)
2 = partial response (50-90% resolution of symptoms and signs)
3 = stable (<50% resolution of symptoms and signs)
4 = progression (deterioration of symptoms and signs)
5 = unknown

Discharge Destination

- ☐ Home
- ☐ Expired
- ☐ Nursing home
- ☐ Hostel
- ☐ Rehabilitation facility
- ☐ Palliative Care Facility
- ☐ Other hospital
- ☐ Other→ *specify*_____
- ☐ Unknown/Not recorded

Other comments

END OF FORM

Discharge Destination

☐ Home

☐ Expired

☐ Nursing home

☐ Hostel

☐ Rehabilitation facility

☐ Palliative Care Facility

☐ Other hospital

☐ Other→ *specify*_____

☐ Unknown/Not recorded

Other comments

END OF FORM

Acute Leukemia Invasive Fungal Infection

Data Collection Form

Study Number: ☐ ☐ ☐ ☐ ☐ ☐ (for Thao use only)

Sex: ☐ Male ☐ Female

Weight (kgs):

Current smoker: ☐ Yes
☐ No → ☐ Ex ☐ Never ☐ Unk/Not stated
☐ Unk/ Not stated

Primary haematological malignancy:

☐ AML
☐ ALL
☐ Transformed MDS / Lymphoproliferactive

Leukemia :

Diagnose Dated: _____ / _____ / _____

☐ AML *If ticked, please circle one* → ● M1 ● M2 ● M3

● M4 ● M5 ● M6

● M7

☐ ALL *If ticked, please circle one* → ● Pre B ● T

● Other

Leukemia Treatment Protocol

Episode	Admission Date	ANC Count (on admission date)	Days of Low ANC*	Treatment Protocol	Type of Treatment	Date Started
1	___/___/___	_____	_____	☐ High dose ARAC + Idarubicin ☐ MIDAC ☐ FLAG ☐ German protocol ☐ Other (specify →)_____	☐ Induction ☐ Consolidation ☐ Re-induction for relapse ☐ Consolidation for relapse	___/___/___
2	___/___/___	_____	_____	☐ High dose ARAC + Idarubicin ☐ MIDAC ☐ FLAG ☐ German protocol ☐ Other (specify →)_____	☐ Induction ☐ Consolidation ☐ Re-induction for relapse ☐ Consolidation for relapse	___/___/___
3	___/___/___	_____	_____	☐ High dose ARAC + Idarubicin ☐ MIDAC ☐ FLAG ☐ German protocol ☐ Other (specify →)_____	☐ Induction ☐ Consolidation ☐ Re-induction for relapse ☐ Consolidation for relapse	___/___/___
4	___/___/___	_____	_____	☐ High dose ARAC + Idarubicin ☐ MIDAC ☐ FLAG ☐ German protocol ☐ Other (specify →)_____	☐ Induction ☐ Consolidation ☐ Re-induction for relapse ☐ Consolidation for relapse	___/___/___

* *ANC < 0.5 x 10^2/L : Low*　　　　　　　* *Day 1 : the 1st day of chemo*

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Chest CT Scan :   ☐ No   → *go to next page*
                    ☐ Yes

Number of CT scan: _____

Chest CT Scan				
Date	**Type**	**Report**	**Radiologist's grading**	**ANC** *(on day CT done)**
____ / ____ / ___	☐ HRCT ☐ Regular ☐ Low dose helical & HRCT	☐ Nodule ☐ Wedge shaped infarct ☐ Air crescent ☐ Halo sign ☐ Other *(specify →)*_____ _____	☐ Likely ☐ Intermediate ☐ Other pathology	_____
____ / ____ / ___	☐ HRCT ☐ Regular ☐ Low dose helical & HRCT	☐ Nodule ☐ Wedge shaped infarct ☐ Air crescent ☐ Halo sign ☐ Other *(specify →)*_____ _____	☐ Likely ☐ Intermediate ☐ Other pathology	_____
____ / ____ / ___	☐ HRCT ☐ Regular ☐ Low dose helical & HRCT	☐ Nodule ☐ Wedge shaped infarct ☐ Air crescent ☐ Halo sign ☐ Other *(specify →)*_____ _____	☐ Likely ☐ Intermediate ☐ Other pathology	_____

Reviewer Notes: *If the ANC was not measured on the day of CT scan, the ANC taken 1-2 days before or 1-2 days after can be recorded*

Lung Sampling

1. Bronchoscopy

Performed	Test	Date	Result *(please circle)*	Organism
☐ Yes → ☐ No		____/____/____ ____/____/____ ____/____/____	Pos / Neg / Unk Pos / Neg / Unk Pos / Neg / Unk	

2. Biopsy

☐ No (→ *Go to* **3. Resection** section)

☐ Yes →   ○ Core
        ○ FNA

↘ *If YES, please indicate if the tests listed in the table below were performed, if so, complete the relevant information.*

Test	Performed	Date	Result/Type	
Histology	☐ Yes → ☐ No ☐ Unk	____/____/____	☐ Fungal hyphae → ☐ Negative ☐ Other *(specify→)*____ _____	☐ C/w aspergillus ☐ C/w mucor ☐ Unable to specify ☐ No comment
Culture	☐ Yes → ☐ No ☐ Unk	____/____/____	☐ Positive → ☐ Negative ☐ No report / Unk	*Name organism*
PCR	☐ Yes → ☐ No ☐ Unk	____/____/____	☐ Positive → ☐ Negative ☐ No report / Unk	*Name organism*

3. __Resection:__

☐ No   (→ *Go to next page*)
☐ Yes →   Site :_____
↘
If YES, please indicate if the tests listed in the table below were performed, if so, complete the relevant information

Test	Performed	Date	Result/Type	
Histology	☐ Yes → ☐ No ☐ Unk	_____/_____/_____	☐ Fungal hyphae → ☐ Negative ☐ Other *(specify→)*____ _____	☐ C/w aspergillus ☐ C/w mucor ☐ Unable to specify ☐ No comment
Culture	☐ Yes → ☐ No ☐ Unk	_____/_____/_____	☐ Positive → ☐ Negative ☐ No report / Unk	*Name organism*
PCR	☐ Yes → ☐ No ☐ Unk	_____/_____/_____	☐ Positive → ☐ Negative ☐ No report / Unk	*Name organism*

Additional notes:

Test Results of <u>All Other Sites</u>

*(Reviewer note : Only record <u>**POSITIVE RESULTS**</u> for FUNGAL INFECTION . Please indicate if any of the specimen listed below were collected and if so, complete the relevant information .)*

Specimen	Date	Test *(onlyMC&S, PCR, biopsy, CT, histology)*	Organism/Result
Blood ☐ Yes → ☐ No *(Please note: Plasma PCR/antigen not included)*	____/____/____ ____/____/____		
Sputum ☐ Yes → ☐ No	____/____/____ ____/____/____		
Wound ☐ Yes → ☐ No	____/____/____ ____/____/____		
Nasal Swab ☐ Yes → ☐ No	____/____/____ ____/____/____		
Sinus Aspirate ☐ Yes → ☐ No	____/____/____ ____/____/____		
CSF ☐ Yes → ☐ No *(Cerebrospinal fluid)*	____/____/____ ____/____/____		
Joint Fluid ☐ Yes → ☐ No	____/____/____ ____/____/____		

Test Results of <u>All Other Sites</u>

*(Reviewer note : Only record <u>**POSITIVE RESULTS**</u> for FUNGAL INFECTION . Please indicate if any of the specimen listed below were collected and if so, complete the relevant information .)*

Specimen	Date	Test *(onlyMC&S, PCR, biopsy, CT, histology)*	Organism/Result
Ocular Fluid ☐ Yes → ☐ No	_____/_____/_____ _____/_____/_____		
Other ☐ Yes → ☐ No *specify_____*	_____/_____/_____ _____/_____/_____ _____/_____/_____ _____/_____/_____		

Additional notes:

Anti-Fungal Prophylaxis

(Reviewer note: Please list all anti-fungal drugs prescribed & specify whether Intravenous (IV) or Oral (O) – USE GENERIC NAMES)

Episode	Treatment stage	Name of Anti-fungal Drug	Date Started	Date Ceased	Reason *

Note: Please put suitable code number for Treatment stage

1. = Induction
2. = Consolidation
3. = Re-induction for relapse
4. = Consolidation for relapse

* *Please choose only ONE reason for each and fill in that field with the appropriate code :*

A =	diarrhoea/ GIT intolerance	C =	non-compliance	E =	other
B =	abnormal LFT	D =	treatment completed	F =	failure

Anti-Fungal Drug Level				
Episode	Drug Names	Blood Level (mg/ml)	Daily Dose	Date Ckecked

Anti-Fungal Treatment

Treatment given : ☐ No → *Go to next page*
☐ Yes → *Complete the section and the outcome below*

Episode	**Name of Anti-fungal Drug** *(Please list all anti-fungal drugs prescribed & specify whether Intravenous (IV) or Oral (O))* *USE GENERIC NAMES*	**Date Started**	**Date Ceased**	**Reason***

* *Please choose only **ONE** reason for each and fill in that field with the appropriate code :*

A = diarrhoea/ GIT intolerance
B = abnormal LFT
C = non-compliance
D = treatment completed
E = other
F = renal impaired
G = infusion toxicity

Outcome of invasive fungal infection :
(If unsure, please see Appendix 1 - Outcome of IFI)

     ☐   Cure
     ☐   Partial response
     ☐   Progressive infection

Classification of invasive fungal disease:
(If unsure, please see Appendix 2 - the check list for IFI classification)

     ☐   Definite
     ☐   Probable
     ☐   Possible
     ☐   None

Outcome of Patient :

Died :   ☐   No
          ☐   Yes → Date of death: /   /

Cause of death:

     ☐   Due to invasive fungal infection
     ☐   With invasive fungal infection but from other cause
     ☐   Due to other cause, invasive fungal infection cured
     ☐   Never had invasive fungal infection

Post-mortem:

☐   No
☐   Yes   *(Please attach results and complete the relevant information)*

Site:_____ _

Test	Performed	Date	Result/Type	
Histology	☐ Yes → ☐ No ☐ Unk	_____/_____/_____	☐ Fungal hyphae → ☐ Negative ☐ Other *(specify →)*____ _____	☐ C/w aspergillus ☐ C/w mucor ☐ Unable to specify ☐ No comment
Culture	☐ Yes → ☐ No ☐ Unk	_____/_____/_____	☐ Positive → ☐ Negative ☐ No report / Unk	*Name organism*
PCR	☐ Yes → ☐ No ☐ Unk	_____/_____/_____	☐ Positive → ☐ Negative ☐ No report / Unk	*Name organism*

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Appendix 11

Liposomal-AmB for Invasive Fungal Infections

Patient Demographics:

UR Number _____   Study Number *(Thao's use only)* _____

Sex: ☐   Male   ☐   Female

Date of birth: _____/_____/_____

Weight: _____(kgs)

Date of admission: _____/_____/_____

Date of discharge: _____/_____/_____

Indication for L-AmB prophylaxis: (*please circle*)

1   Patient with ALL, mixed lineage acute leukaemia, Burkitt's lymphoma, mantle cell lymphoma or other aggressive lymphoid malignancy requiring vincristine based therapy

2   AML patient in whom azoles contraindicated at the outset due to some issue eg abnormal liver function

3   AML commenced on azole but intolerant due to azole specific side effect (*specify* in tick box below)

4   AML commenced on azole but intolerant of any oral medication due to subsequent GIT issues eg diarrhoea, mucositis, nausea & vomiting

5   Non-BMT patient with prolonged neutropenia

6   BMT patient post-engraftment with gut GVHD

7   BMT patient post-engraftment, intolerant of azoles due to non-GIT issues eg due to abnormal liver function

8   Early peri-BMT in patient who received anti-thymocyte globulin

9   Early peri-BMT in patient in whom prolonged neutropenia is expected eg. cord blood transplant

10   BMT patient pre-engraftment who is intolerant of azoles due to GIT issues eg mucositis or diarrhoea

11   Other eg prolonged neutropenia due to delayed engraftment, aplastic anaemia, unexplained

        *specify*_____

Azole specific side effect

☐   Rash
☐   Liver toxicity
☐   Other, *specify*_____

Underlying Malignancy / Condition for all patients

☐ Pre-B ALL
☐ T ALL
☐ Mixed lineage leukaemia
☐ Burkitt lymphoma
☐ AML
☐ Aplastic Anaemia
☐ Other, *specify*_____

Status of Malignancy / Condition for all patients

☐ New diagnosis, untreated
☐ Relapse/failed induction
☐ Other

Neutrophil Engraftment/ Recovery for all patients:

First date of ANC nadir *ie lowest ANC count either before or after chemotherapy* _____/_____/_____

☐ No, never engrafted/ recovered
☐ Yes→ Date ANC $\geq$0.5 x10^9/L[1]   _____/_____/_____

Notes: [1] *date= 1st day ANC $\geq$0.5x10^9/L for 3 consecutive days*

Duration of neutropenia[4] _____ (days)   [4] *Notes:*   ANC <0.5 x10^9/L[4]

Patient's Treatment type:

☐ AML
☐ ALL/ Aggressive Lymphoma
☐ Haematological Stem Cell Transplant → *go to next page*

Haematological Stem Cell Transplant

Date of transplant: _____ / _____ / _____

Match of Allogeneic HSCT (*donor type, see below*)

□ HLA identical sibling

□ HLA unrelated

□ HLA related, mismatched

Conditioning Regimen for HSCT

Type of HSCT conditioning:

□   Myeloablative *(1-4 listed below)*

□   Non-myeloablative *(5,6 listed below)*

□   Reduced intensity *(7 listed below)*

Antifungal Prophylaxis[1] (From 2 weeks prior to L-AmB prophylaxis, for all patients): ☐ No ☐ Yes→ *complete the relevant information*

Antifungal Drug Name	Dose (mg)	Frequency[2] (enter code)	Route	Start Date	Finish Date	Reason for cessation[3] (Enter code below)

Notes: [1]: *Prophylaxis is usually fluconazole, itraconzole, voriconazole, posaconazole or L-AmB started on admission or at the start of chemotherapy. It is not the same as treatment of neutropenic fever.*

[2]: **Frequency codes for L-AmB**: *(Note: exclude patient if given daily or 2ⁿᵈ daily)* ; **and for other drugs:**

　　　　　　1 = Three times per week | **3** = twice a day 　　**5** = daily
　　　　　　　　　　　　　　　　　　　　　| **4** = three times a day

[3]: **Reason for cessation:**

　　　　　　A = Toxicity/intolerance (*see Appendix A for appropriate code*) **D** = Treatment completed
　　　　　　B = Lack of efficacy 　　　　　　　　　　　　　　　　　**E** = Step down therapy
　　　　　　C = Non-compliance 　　　　　　　　　　　　　　　　　**F** = Other (*specify*)

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Nephrotoxicity (all patients)

Renal function at defined time intervals *(Day1 denotes first day of L-AmB ie baseline; use closet date available)*

Variable	Day1	Day4	Day7	Day14	Day 21	Day28	Last L-AmB dose
Date	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___
Serum Creat (Umol/L)							
Creatinine clearance[1] (ml/min)							

[1] : Use ***Cockcroft-Gault equation***, *external reviewer to determine*

Did a clinically significant decrease in renal function occur? *(see Appendix B for definitions, to be completed by Michelle)*

☐   No   ☐   Yes

Did a sustained decrease in renal function occur? *(see Appendix B for definitions, to be completed **by Michelle**)*

☐   No
☐   Yes→ *Michelle to complete the following*
                    ☐   25% sustained decrease
                    ☐   50% sustained decrease

Did this patient require haemodialysis?

☐   No   ☐   Yes

Was this patient taking concomitant nephrotoxic medications? *(see Appendix B for list of medications)*

☐   No   ☐   Yes

Cumulative dose of L-AmB _____(g)

Cumulative dose of L-AmB adjusted for patient weight _____(g/kg)

Baseline hepatic function as determined by serum bilirubin : _____ (Umol/L)
(Notes:Severe organ ie. renal or hepatic dysfunction may be independent predictors of death)

Baseline renal function as determined by baseline creatinine clearance: _____(mmol/s)

FUNGAL INFECTION DATA (all patients)

Q.1- **Did this patient develop oropharyngeal candidiasis <u>while on</u> L-AmB prophylaxis?**

☐ No → *go to Q. 2*
☐ Yes → Date of diagnosis _____ / _____ / _____

    ☐ Clinical suspicion only *ie no mycological evidence* → *go to Q.2*
    ☐ Biopsy or culture confirmed *ie mycological evidence present (pos MC&S)* → *complete below*
         ○ C albicans
         ○ C glabrata
         ○ C krusei
         ○ C parapsilosis
         ○ C tropicalis
         ○ C lusitaniae
         ○ C dubliniensis
         ○ Candida species (*not otherwise specified*)

Q.2- **Did this patient develop an invasive fungal infection?**

☐ No → *go to page 11*
☐ Yes →

    1. <u>Classification of IFI</u>

    IFI diagnosis: ☐ possible *(no mycological evidence)*
                  ☐ Probable *(positive microscopy or culture from non-tissue specimens, or positive galactomannan)*
                  ☐ Proven *(positive microscopy or culture from tissue or culture sample from a normally sterile site*

    Date1 of IFI diagnosis: _____ / _____ / _____ *(based on clinical suspicion from notes)*

    Date2 of IFI diagnosis: _____ / _____ / _____ *(based on external reviewers interpretation of key diagnostics)*

Please supply the following:

Key investigations *(attach key reports including microscopy, culture, biomarkers eg galactomannan antigen test, PCR, blood culture results, histopathology or radiology: CXR, CT, MRI)*

2. **Pathogen**   ☐   No   ☐   Yes→ *complete the relevant information*

☐   Invasive aspergillus

        ☐   fumigatus
        ☐   flavus
        ☐   niger
        ☐   terreus
        ☐   nidulans
        ☐   versicolor
        ☐   aspergillus galactomannan antigen index
        ☐   aspergillus (*not otherwise specified*)

☐   Candida species

        ☐   C albicans
        ☐   C glabrata
        ☐   C krusei
        ☐   C parapsilosis
        ☐   C tropicalis
        ☐   C lusitaniae
        ☐   C dubliniensis
        ☐   Candida (*not otherwise specified*)

☐   Other fungi

        ☐   scedosporium prolificans
        ☐   scedosporium apiospermum (aka pseudallescheria boydii)
        ☐   fusarium species
        ☐   trichosporon species
        ☐   other (*specify→*)_____

☐   Unspecified mold *(eg hyphae only seen on microscopy but culture negative)*
☐   Unspecified yeast *(organism seen on microscopy but culture negative)*
☐   PCR *(specimen and species identified)*_____
☐   Galactomannan antigen test _____

SITE/s of IFI

Extent of IFI: ☐   localised

☐   disseminated (2 or more non-contiguous sites or positive blood culture)

Site(s) of IFI: ☐   lung

☐   sinus

☐   CNS

☐   eye

☐   endocarditis

☐   skin

☐   soft tissue

☐   liver

☐   spleen

☐   hepatosplenic

☐   bone / joint

☐   intraabdominal / peritoneal

☐   urinary tract →○ upper: kidney, ureter

○ lower: bladder, urethra

☐   fungaemia

☐   other

Outcome Data

☐ Alive
☐ Death → date _____ / _____ / _____

Narrative description of death

<u>Autopsy performed</u>: ☐ no
                                     ☐ yes, *attach report if available*
                                     ☐ unknown / no report

Results of autopsy (if no report available)

Additional comments

END OF FORM

APPENDIX A: ANTIFUNGAL TOXICITY (record adverse event as A1, A2, A3 etc)

A. Infusion Related Reactions (occurring during infusion of antifungal drug)

1. Fever (increase >1 degree C during infusion)
2. Chills
3. Rigors
4. Flushing
5. Dyspnoea
6. Tachypnoea (>22 breaths/min)
7. Hypoxia (Oxygen saturation <90%)
8. Tachycardia (>120 beats/min)
9. Hypotension (systolic BP <90 mmHg)

B. General Adverse Events

1. Allergic reaction
2. Cardiac arrhythmia
3. Pain-cardiovascular
4. Pain- pulmonary/upper respiratory
5. Pain- GIT
6. Pain-musculoskeletal
7. Pain-neurological
8. Injection site reaction
9. Photosensitivity
10. Pruritis/itching
11. Urticaria
12. Rash
13. Diarrhoea
14. Nausea
15. Vomiting
16. Heartburn
17. Fever
18. Rigors/chills
19. Hypotension
20. Dizziness
21. Neuropathy-sensory
22. Neuropathy-cranial
23. Seizure
24. Syncope (fainting)
25. Tremor
26. Hallucinations
27. Delusions
28. Elevated alkaline phosphatase
29. Elevated ALT
30. Elevated AST
31. Elevated Bilirubin
32. Elevated GGT
33. Elevated Creatinine
34. Hypomagnesaemia
35. Hypokalaemia
36. Blurred vision

38. Hypoxia
39. Bronchospasm
40. Phelbitis
41. Hypotension
42. Other, specify

37. Dyspnoea

APPENDIX B: NEPHOTOXICITY

- A **clinically significant** decrease in renal function is defined as:
1. A decrease in creatinine clearance to < 50 mls/min if the baseline was ≥ 50mls/min
2. A decrease in creatinine clearance ≥ 10ml/min if the baseline was < 50ml/min

- A **sustained reduction** in renal function is defined as:
1. A 25% or greater decrease in creatinine clearance from baseline over at least 2 sequential measurements
2. A 50% or greater decrease in creatinine clearance from baseline over at least 2 sequential measurements

- Nephrotoxic medications include:

  - Aminoglycosides
  - Diuretics
  - ACE inhibitors
  - Cyclosporine
  - tacrolimus
  - Cyclophosphamide
  - Cisplatin
  - NSAIDS

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