Antimicrobial stewardship programs in a hospital setting

Development of quality indicators and implementation of interventions

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THE FUTURE DEPENDS ON WHAT YOU DO TODAY

Mahatma Gandhi

Aan Ruth en onze kinderen Matteo, Noor en Arthur

Aan mijn ouders

Dissertation submitted to fulfill the requirements for the degree of PhD in Medical Sciences
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Frequently used abbreviations

AMR = antimicrobial resistance
AMT = antibiotic management team
ASP = antimicrobial stewardship program
ATC = Anatomical Therapeutic Chemical classification
BAPCOC = Belgian Antibiotic Policy Coordination Committee
CDC = Centers for Disease Control and Prevention of the United States
DDD = defined daily doses
ECDC = European Centre for Disease Prevention and Control
EARS = European Antimicrobial Resistance Surveillance Network
ED = emergency department
EPOC = Cochrane Effective Practice and Organisation of Care
ESAC = European Surveillance of Antimicrobial Consumption
MIT = multidisciplinary infectious diseases team
PK/PD= pharmacokinetic/pharmacodynamic
TATFAR = Transatlantic Task Force on Antimicrobial Resistance
TFAD = time to first antibiotic dose
WHO = World Health Organization

CHAPTER 1: INTRODUCTION

1. General introduction

The discovery of penicillin by Alexander Fleming in 1929 triggered the development of different antimicrobials during the following decennia (1). Antimicrobials have contributed to the control of infectious diseases that seven decades ago represented the leading cause of human morbidity and mortality. Effective antimicrobial therapy rendered many fields of modern medicine feasible, such as major surgery, the care of premature infants, cancer chemotherapy, care of the critically ill, and transplantation medicine (2).

At present however health care is challenged by the emergence of antimicrobial resistance and the low number of truly new antimicrobials against multi-resistant bacteria (3,4) (Figure 1). From the 1940s up to the 1970s the pharmaceutical industry developed several antimicrobials with new mechanisms to treat problems caused by bacterial resistance. Since then, only three systemically-administered antibiotics (quinupristindalfopristin, linezolid and daptomycin), including two from new classes (oxazolidinones and lipopeptides,) have been marketed in the EU to treat infections caused by multidrug-resistant Gram-positive bacteria. The other systemic antimicrobials that have reached the EU market during this period belong to existing classes of antimicrobials and had no superior activity against the majority of organisms already resistant to other agents in the same class (4). There may be some new treatments, such as ceftazidim/avibactam against a range of resistant Gram negatives. With this paucity of options, the field has been pushed into the reintroduction of old, often poorly documented antimicrobials, such as colistin.

Figure 1. Discovery of new classes of antibiotics
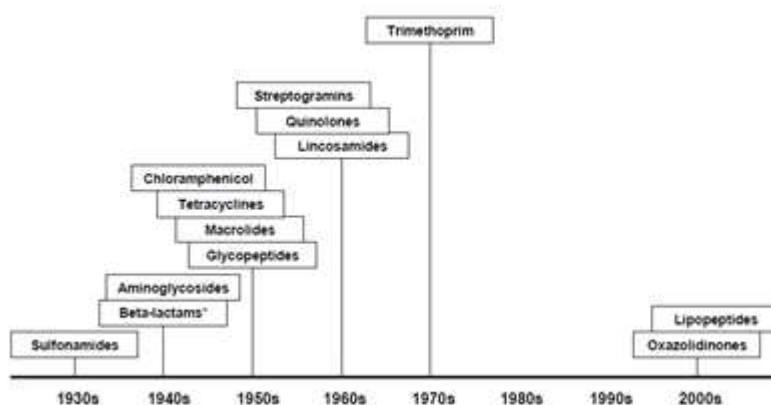
Recently a new cell wall inhibitor, teixobactin, was discovered in a screen of uncultured bacteria. Hopefully the methodology used can lead in the future to the discovery of other uncultured bacteria that are likely to harbour new antimicrobials (5).

The World Health Organization (WHO) has recognized antimicrobial resistance (AMR) as a growing global health threat, and has called upon Member States and the international community to take measures to curtail the emergence and spread of antimicrobial resistance (6). The most important cause of AMR has been a massive overuse of antimicrobials worldwide across all ecosystems over the past decades, including humans, animals, aquaculture, and agriculture (7).

The Centers for Disease Control and Prevention of the United States (CDC) prioritized bacteria into one of three categories: urgent, serious, and concerning (7) (Table 1). Bacteria within the category "urgent" are immediate public health threats that require urgent and aggressive action. Bacteria defined as "serious threat" require prompt and sustained action to ensure the problem does not grow. Careful monitoring and prevention action are needed for bacteria within the "concerning" category.

Table 1. CDC's prioritized list (categories: urgent, serious, and concerning) with bacteria regarding level of concern

Urgent Threats	Serious Threats	Concerning Threats
Clostridium difficile	Multidrug-resistant Acinetobacter	Vancomycin-resistant Staphylococcus aureus (VRSA)
Carbapenem-resistant Enterobacteriaceae (CRE)	Drug-resistant Campylobacter	
	Fluconazole-resistant Candida (a fungus)	Erythromycin-resistant Group A Streptococcus
Drug-resistant Neisseria gonorrhoeae	Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)	
	Vancomycin-resistant Enterococcus (VRE)	Clindamycin-resistant Group B Streptococcus
	Multidrug-resistant Pseudomonas aeruginosa	
	Drug-resistant Non-typhoidal Salmonella	
	Drug-resistant Salmonella Typhi	
	Drug-resistant Shigella	
	Methicillin-resistant Staphylococcus aureus (MRSA)	
	Drug-resistant Streptococcus pneumoniae	
	Drug-resistant tuberculosis	

CDC defines four core actions that will help fight deadly infections (7):

- preventing infections and preventing the spread of resistance (immunization, safe food preparation, handwashing, and using antimicrobials according guidelines and only when necessary)

- tracking resistant bacteria

- improving the use of current antimicrobials

- promoting the development of new antimicrobials and developing new diagnostic tests for resistant bacteria

On a European level, the European Parliament adopted a non-legislative resolution on antimicrobial resistance in which it stresses that AMR has become a huge issue (8). EU surveillance systems have been developed to monitor AMR (European Antimicrobial Resistance Surveillance Network-EARS) and the consumption of antimicrobials (European Surveillance of Antimicrobial Consumption, ESAC). These systems provide key information and data in support of prevention and control of AMR. Although the levels of resistance in Gram-positive pathogens (*Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecium* and *Enterococcus faecalis*) tend to stabilize, or even decrease -in some countries-, there is a general increase across Europe of antimicrobial resistance in the Gram-negative pathogens (*Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) (9).

2. Resistance impacts on clinical outcome

Antimicrobial resistance is associated with increased patient mortality, longer hospital stays, and increased healthcare costs (10). Increasing resistance compromises effective treatment. This may result in failure of initial therapy if an ineffective agent is chosen, and effective therapy may be delayed by several days until the culture and sensitivity results for a resistant organism are available (11). If the organism is resistant to multiple antimicrobial drugs, the cure may be severely limited and in a few cases there may be no effective therapy. Due to increased emergence of bacterial resistance and declining development of new antimicrobials, 'older' compounds, previously banned because of efficacy/toxicity considerations (colistin, fosfomycin, fusidic acid) are being reintroduced into the clinic for multidrug resistant bacteria (12). As these antimicrobials have never been subjected to the contemporary drug development process, their redevelopment using contemporary analytical and pharmacokinetic/pharmacodynamic methods are critical in order to optimize therapy. Colistin is an example of successful redevelopment in which the use of new state-of-the-art bioanalytical, microbiological and pharmacokinetic/pharmacodynamic approaches has generated an improved understanding of its clinical pharmacology, and has enabled rational optimization of patient therapy (12).

In a recent systematic review the health impact of infections caused by third generation cephalosporin resistant (including ESBL) *E. Coli*, fluoroquinolone resistant *E. Coli*, third generation cephalosporine resistant *K. pneumonia* , carbapenem resistant *K. pneumonia and MRSA* was assessed . For all type of infections there was a significant increase of all cause mortality. Bacterium-attributable mortality was significant increased except for infections with fluoroquinolone resistant *E. Coli* and carbapenem resistant *K. pneumonia.* Hospital LOS was significant increased for *MRSA* infections. Admission to an ICU was significant increased for fluoroquinolone resistant *E. Coli* and third generation cephalosporin resistant *K. pneumonia* (13).

Roberts et al. reported that twice as many patients with antimicrobial-resistant infections died than patients infected with nonresistant organisms. When multiresistant pathogens are prevalent, clinicians are forced to use broader spectrum and usually more expensive agents to treat seriously ill patients. All of these effects contribute to increasing healthcare and societal costs (14).

An estimation of the yearly human burden of infections due to selected antimicrobial-resistant bacteria in EU Member States, Iceland and Norway in 2007 showed 386.100 cases of infection, 25.100 extra deaths and 2.536.000 extra hospital days (9). This resulted in an overall cost of 1.534.100.000 euro (927.800.00 EUR extra in hospital costs, 10.000.000 EUR extra outpatient costs, 150.400.000 EUR productivity losses due to absence from work and 445.900.000 EUR productivity losses due to patients who died from their infection.

Smith et al published recently a report on the economic burden of antimicrobial resistance. They concluded that the current estimates of antimicrobial resistance show a low economic impact (15). They add that all of the published studies do not consider a world which there are no effective antimicrobial available and concluded that we may not ever be able to make an accurate forecast of costs. They suggest that rather than see expenditure on antimicrobial policies as costs, we should think of it as an insurance policy against a catastrophe (15).

3. The Antimicrobial Stewardship balance

The yearly report on "Surveillance of antimicrobial consumption in Europe 2012"of the European Centre for Disease Prevention and Control (ECDC) demonstrated that the consumption in the community varied by a factor of 2.8 between the highest consumption (31.9 defined daily doses (DDD) per 1 000 inhabitants and per day in Greece) and the lowest (11.3 DDD per 1 000 inhabitants and per day in the Netherlands) (16) (Figure 2). With a consumption of 29.8 DDD per 1 000 inhabitants, Belgium has a high consumption of antibiotics in the community comparable with Greece, Romania, Cyprus and France. The ECDC report concludes that a significant increasing trend in the consumption during 2008–2012 was observed in Belgian community. However a recent study by

Coenen et al showed that the number of package is a more appropriate measure than the number of DDDs when assessing outpatient antibiotic use (17). Doing so consumption figures demonstrate no increase of antibiotic consumption expressed in number of packages during 2008–2012 in Belgium. Increasing numbers of DDDs per package (more items per package and higher doses per unit for amoxicillin and co-amoxiclav) explain these discrepancies. The authors observed less frequent treatments of fewer individuals with higher amounts of active substance (more DDDs) and higher proportions of recommended antibiotics (more amoxicillin) since the start of the national public antibiotic awareness campaigns in Belgium.

Figure 2. Consumption of antibacterials for systemic use (ATC group J01) in the community sector in EU/EEA countries, 2012, expressed as DDD per 1 000 inhabitants and per day
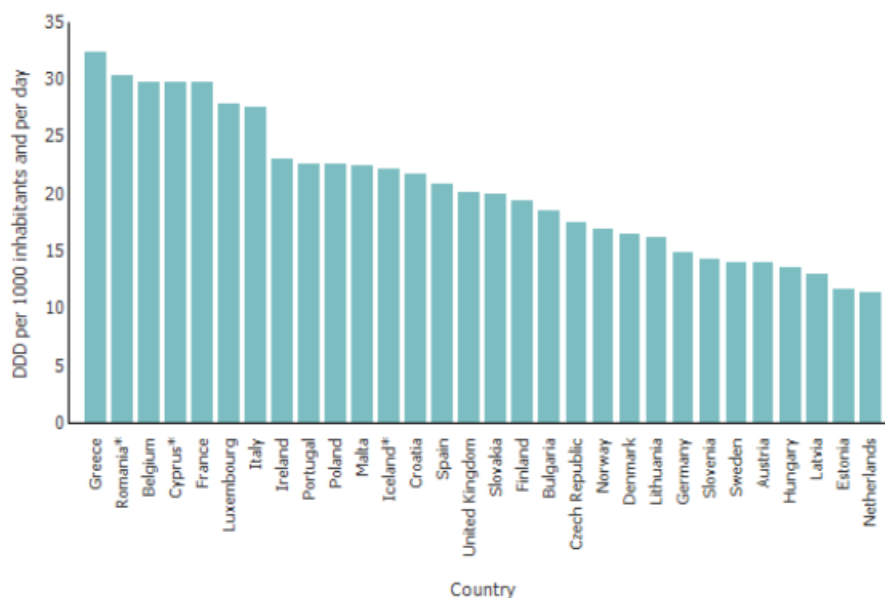
In 2012, the consumption of antibacterials for systemic use (Anatomical Therapeutic Chemical (ATC) classification system group J01) in the hospital sector varied from 1.00 (the Netherlands) to 2.8 DDD per 1 000 inhabitants and per day (Finland) with a median of 2.0 DDD per 1 000 inhabitants and per day (16) (Figure 3). With 1.71 DDD per 1000 inhabitants and per day, Belgian hospitals have a moderate consumption of antibacterials for systemic use (ATC group J01) compared with other European countries (16). In Belgium 10% of the total consumption (DDD) of antibacterials for systemic use is used in hospitals.

Figure 3. Consumption of antibacterials for systemic use (ATC group J01) in the hospital sector in EU/EEA countries, 2012, expressed as DDD per 1 000 inhabitants and per day
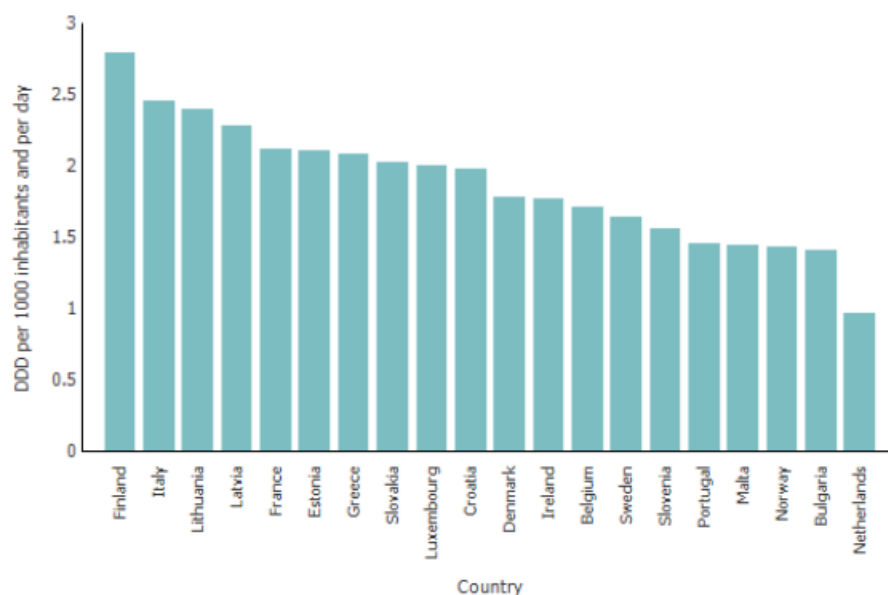
For several antimicrobial–pathogen combinations, e.g. fluoroquinolone-resistance *in E. coli, K. pneumoniae*, *P. aeruginosa* and for *MRSA*, a north-to-south gradient is evident in Europe. In general, lower resistance percentages are reported in the north and higher percentages in the south of Europe. These geographical differences may reflect differences in infection control practices and antimicrobial use in the reporting countries (9). A recent systematic review of the effects of antibiotic consumption on antibiotic resistance in Europe confirmed that studies conducted in southern Europe were more likely to find a strong positive relationship between antibiotic consumption and resistance whereas studies that examined B-lactam consumption or MRSA tended to find a weaker relationship between consumption and resistance (18).

Recent data from the Belgian Scientific Institute of Public Health show an antibiotic consumption of 548.2 DDD (median) per 1000 beddays (p25 = 541.6; p 75= 603.2) in 2013 (Table 2).

Table 2. Evolution antibiotic use (J01) in Belgian hospitals for non-paediatric departments (DDD/1000 patient days). (Source:Anne INGENBLEEK. Scientific Institute of Public Health, Brussels,Belgium)

Antibiotics (J01)	Non- Paediatric Departements (including Intensive Care & Haemato-oncology)						
	2007	**2008**	**2009**	**2010**	**2011**	**2012**	**2013***
Frequency	54	95	98	96	96	92	70
Mean	534.1	528.6	537.5	541.9	557.9	567.6	541.6
P25	453.8	459.7	465.9	477.9	474.8	484.9	472.4
Median	518.9	523.3	530.6	535.4	553.5	555.0	548.2
P75	620.7	580.2	601.8	605.3	620.8	631.9	603.2

2013*: Provisional (but representative) data

Antimicrobials account up for an important part of the hospital pharmacy budgets while literature shows that up to 50% of antimicrobial use is inappropriate, adding considerable cost to patient care (19).

The European Surveillance of Antimicrobial Consumption (ESAC) has established a method for point prevalence of antimicrobial prescribing interventions to improve antimicrobial prescribing practices for hospital inpatients. Results of the "2009 survey" show that the indication for treatment was not compliant with local or national guidelines in 38% of patients (20).

Appropriate use of antimicrobials is necessary to extend their useful lifetime. This means that a prospective, formalized, strategy is needed to ensure that antimicrobials are used appropriately. Programs developed from this strategy are called antimicrobial stewardship programs (ASPs) (21).

The ultimate objective is to achieve a balance between an effective antimicrobial treatment and the risk for collateral damage through the selection of resistant pathogens (Figure 4).

Figure 4. The Antimicrobial Stewardship balance

An effective antimicrobial treatment for patients

Unnecessary use of broad-spectrum antimicrobials resulting in the selection of resistant pathogens
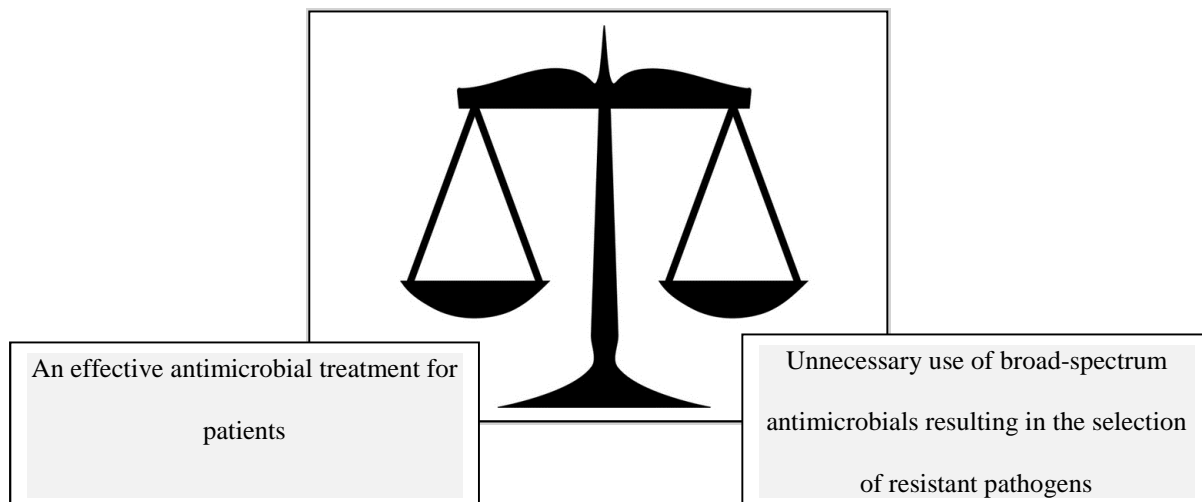
In 2007, the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) jointly published guidelines for the development of programs to enhance antimicrobial stewardship in the institutional setting (19). The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance. A secondary goal of antimicrobial stewardship is to reduce health care costs without adversely impacting quality of care (19,22,23,24).

## 4. Belgian Antibiotic Policy Coordination Committee

In 1999, the Belgian Ministry of Health established by Royal Decree the Belgian Antibiotic Policy Coordination Committee (BAPCOC) (25,26,27). The objectives of BAPCOC are to promote judicious use of antimicrobials in humans and animals and enhance infection control and hospital hygiene, with the overall aim of reducing antimicrobial resistance. To address these specific tasks BAPCOC founded five multidisciplinary working groups: ambulatory care, hospital care, awareness campaigns, infection control and veterinary medicine. The BAPCOC working Group Hospital Care was able to secure federal funding, provide technical guidance and offer advanced specialist training for the formal establishment and follow-up of antibiotic management teams (AMTs) for all Belgian hospitals. The minimum composition, mandate and tasks of hospital AMTs have been consolidated in legislation through publication of the Royal Decree of 12 February 2008 on the norms for AMTs as dedicated subgroups of the hospital Drugs and Therapeutic Committee (25,26). AMTs are responsible for the development of an antibiotic formulary and clinical practice guidelines on antimicrobial therapy and prophylaxis, active initiatives to limit the inappropriate use of antimicrobials, education of healthcare workers, audit with feedback to prescribers and surveillance of local antibiotic consumption and microbial resistance. The AMTs must provide yearly activity reports and consumption figures (25,26,27). Each AMT receives a yearly compiled report from the BAPCOC working Group Hospital Care. The Belgian Scientific Institute of Public Health provides an online tool where each hospital can compare their own consumption figures with national figures.

Antimicrobial stewardship by itself is not the only solution for the problem of antimicrobial resistance. It is a necessary part of a global approach including regulatory policies, interventions to control antibiotic use in livestock, educational measures and triggering incentives to the research and development of new classes of safe and effective antimicrobials (28).

5. Complexity of anti-infective management

An infectious disease is explored by determining the site of infection, defining the host (immunocompromised, diabetic, of advanced age), and establishing, when possible, the microbiological cause (29) (Figure 5). A successful anti-infective management depends on the immunity of the host, the management of the infection site and on the choice of an appropriate antimicrobial agent (30). The initiation of the therapy should be guided by the urgency of the situation. In critically ill patients, such as those in septic shock, and patients with bacterial meningitis, empiric therapy should be initiated immediately after or concurrently with collection of diagnostic specimens (31). The optimal dose of an antimicrobial agent depends on the pharmacokinetic/pharmacodynamic properties of the agent and the pathophysiology (distribution, clearance, ..) of the patient.

Figure 5. Complexity of anti-infective management (Blot S, 2008 - all rights reserved (with permission)
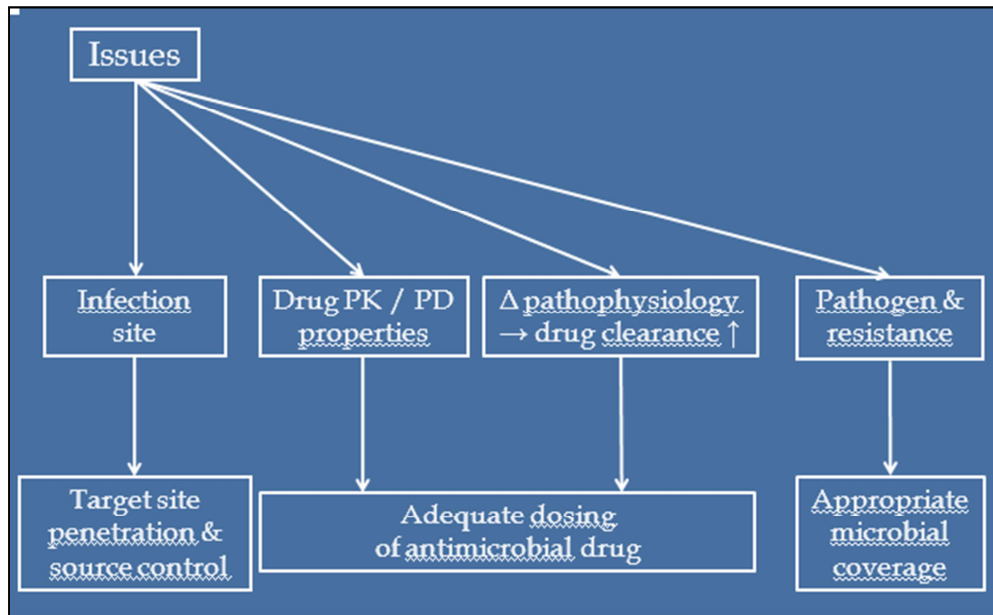
6. A closer look at the antimicrobial stewardship program in current literature

The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America describe two proactive strategies as foundation of an antimicrobial stewardship program (19).

An effective program should include a prospective audit with direct intervention and feedback to the provider and/or preauthorization requirements for antimicrobial use (19) (Figure 6). Other elements with good evidence in literature are education, multidisciplinary development of evidence-based practice guidelines, streamlining or de-escalation of therapy, optimization of antimicrobial dosing (based on individual patient characteristics, causative organism and pharmacokinetic/ pharmacodynamic characteristics of the drug) and a systematic plan for parenteral to oral conversion of antimicrobials with excellent bioavailability. Moderate evidence exists for antimicrobial order forms and poor evidence for antimicrobial cycling and combination therapy.

Core members of an optimal multidisciplinary antimicrobial stewardship team include an infectious diseases physician, a clinical microbiologist, a clinical pharmacist with infectious diseases training, an information system specialist and infection control professional.

Effective audit with intervention and feedback can be facilitated through computer assisted surveillance of antimicrobial use, allowing the screening of specific services or units where problems exist, as well as identification of patients receiving particular agents or combinations of agents that might benefit from intervention (19).

Figure 6. Type of antimicrobial stewardship interventions according to the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America
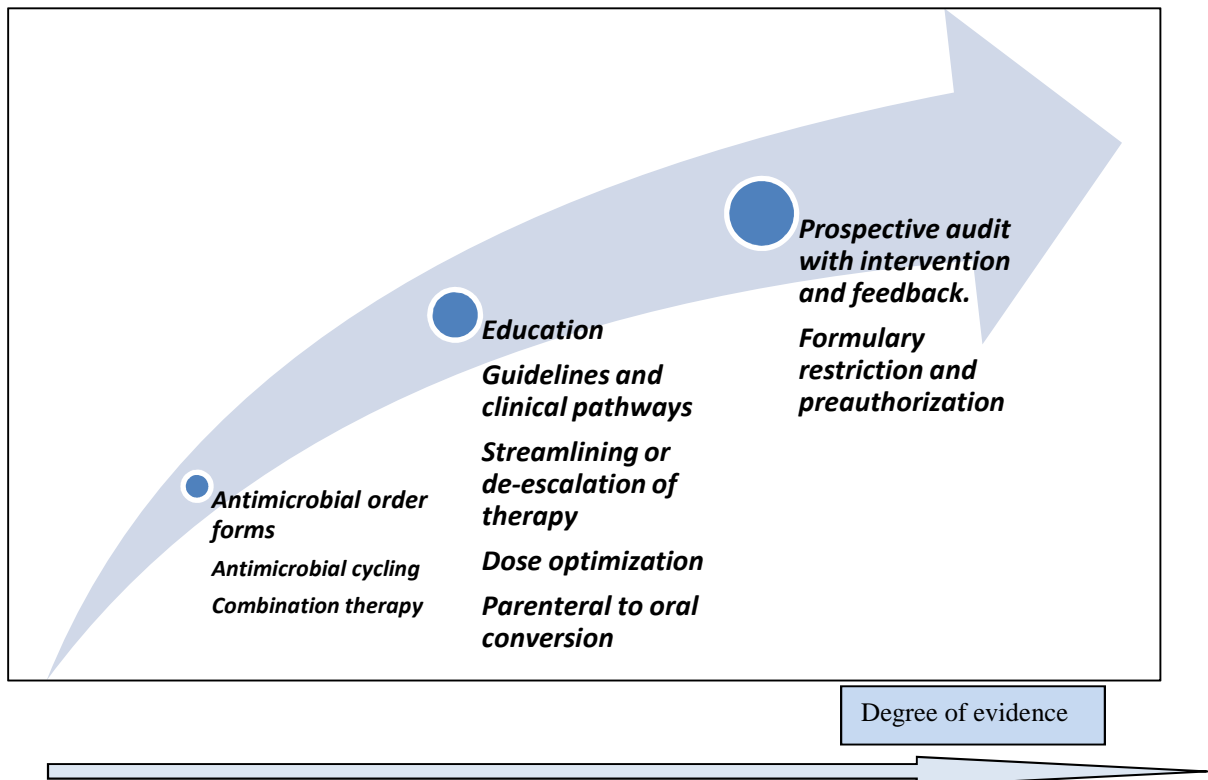
Structure, process and outcome indicators can be used to evaluate the grade of implementation and the results of antimicrobial stewardship programs (32, 33, 34).

The Cochrane Collaboration recently updated a systematic review "Interventions to improve antibiotic prescribing practices for hospital inpatients" (35). This review showed that of all literature published, only one fifth or 89 studies could be included. In other words, literature is still dominated by inadequate interrupted time series (ITS) or uncontrolled before-after (CBA) studies that do not provide interpretable or conclusive data.

In the Cochrane Collaboration review outcome measures were antibiotic prescribing process measures (decision to treat, choice of drug, dose, route or duration of treatment), clinical outcome measures (mortality, length of hospital stay) and microbial outcome measure (colonization or infection with *Clostridium difficile* or antibiotic-resistant bacteria). Interventions were categorized based on the Cochrane Effective Practice and Organisation of Care (EPOC) criteria. We can distinguish restrictive, persuasive and structural interventions (figure 7).

Figure 7 Interventions to improve antibiotic prescribing practices for hospital inpatients according The Cochrane Collaboration
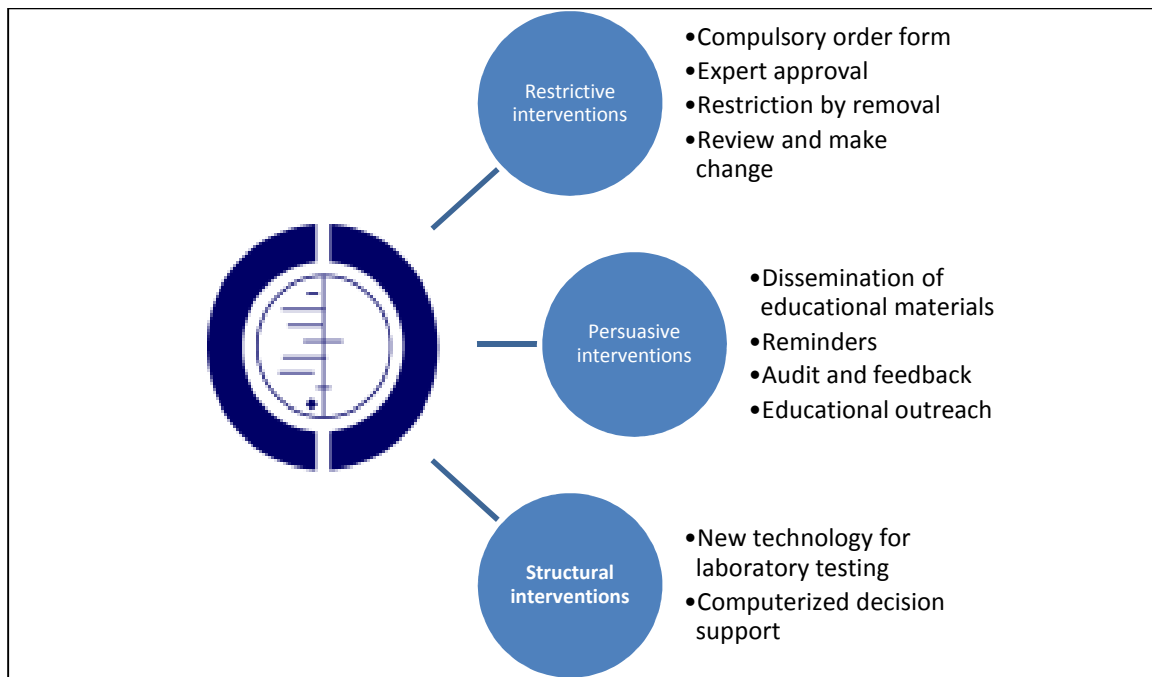
Restrictive interventions were implemented through restriction of the freedom of prescribers to select some antibiotics using compulsory order forms, preliminary expert approval, restriction by removal (for example by removing restricted antibiotics from wards) and review and make change (here the reviewer changes the prescription rather than giving health professionals either a verbal or written recommendation). Persuasive interventions used one or more of the following methods for changing professional behavior: dissemination of educational resources, reminders, audit and feedback, or educational outreach. Structural interventions described the rapid reporting of laboratory results and on the introduction of tests of inflammatory markers (35).

In the Cochrane Collaboration review several clinical outcomes were analysed (35,36) (Table 3). Interventions intended to increase effective prescribing did not significantly affect mortality (RR=0.92 [95% CI 0.69, 1.22]; n=3). Interventions intended to increase effective prescribing by increasing guideline compliance in patients with pneumonia reduced mortality (RR=0.89 [95% CI 0.82, 0.97]; n=4). Based on meta-analysis of 10 RCTs and 1 CCT, interventions intended to decrease excessive prescribing did not affect mortality (RR=0.92 [95% CI 0.81, 1.06]). Six of the studies reported length of stay and found no significant difference (mean difference -0.04 [95% CI -0.34, 0.25] days). Five studies reported readmission. The combined result was a significant increase in overall readmissions (RR=1.26 [95% CI 1.02, 1.57]).

Table 3. Clinical outcome by Intervention Aim (from Davey et al 2013)

Intervention aim	Outcome	Risk Ratio [95% Confidence Interval]	I^2	Study designs, number of participants (n)
Increase effective prescribing	Mortality	0.92 [0.69, 1.22]	72%	2 RCTs, 1 CCT, n=1,484
Increase guideline compliance (CAP)	Mortality	0.89 [0.82, 0.97]	0%	1 RCT, 3 CBAs; n=22,526
Decrease excessive prescribing	Mortality	0.92 [0.81, 1.06]	0%	7 RCTs, 3 cluster RCTs, 1 cluster CCT; n=9,817
Decrease excessive prescribing	Length of stay	Mean difference (days) -0.04 [-0.34, 0.25]	63%	4 RCTs, 2 cluster RCTs; n=8,071
Decrease excessive prescribing	Readmission (all cause or infection related)	1.26 [1.02, 1.57]	9%	4 RCTs, 1 cluster RCT; n=5,856

I^2 = test for heterogeneity; RCT = randomized controlled trial; CBA = controlled before and after trial; CCT = controlled clinical trial

The impact on prescribing outcome for persuasive, restrictive and structural interventions is mentioned in Table 4 (36). For the persuasive interventions, the median (interquartile range) change in antibiotic prescribing was 42.3% for the interrupted interrupted time series studies (ITSs), 31.6% for the controlled interrupted time series studies (CITSs), 17.7% for the controlled before-after studies (CBAs), 3.5% for the cluster-randomized controlled trials (CRCTs) and 24.7% for the randomized controlled trials (RCTs). The restrictive interventions had a median effect size of 34.7% for the interrupted time series designs, 17.1% for the controlled before-after designs and 40.5% for the randomized controlled trials. The structural interventions had a median effect of 13.3% for the RCTs and 23.6% for the cluster-RCTs.

The Cochrane update provides evidence that increase in effective treatment can be associated with reduced mortality and that decrease in excessive antibiotic use can be associated with improvement in microbial outcome without compromising clinical outcomes. It provides also stronger evidence about clinical outcomes and lists 11 interventions that aimed to decrease exposure to antibiotics by reducing the percentage of patients that received treatment or by shortening duration of a treatment or prophylaxis.

Table 4 Median Change* in Antimicrobial Prescribing by Intervention Type and Study Design (from Davey et al., 2013)

Intervention type	RCT	CRCT	CBA	ITS	CITS
Persuasive	24.7%	3.5%	17.7%	42.3%	31.6%
Dissemination of educational materials		-3.1% (n=1)	16.1% (n=2)	10.6% (n=2)	42.5% (n=1)
Reminders	27.4% (n=3)			20.0% (n=5)	
Audit and feedback		3.5% (n=1)	7.5% (n=2)	32.7% (n=4)	24.3% (n=2)
Educational outreach	25.0% (n=10)		20% (n=1)	46.3% (n=10)	
Restrictive	40.5%		17.1%	34.7%	
Compulsory order forms				7.3% (n=5)	
Expert approval			- 2.8% (n=1)	24.1% (n=7)	
Removal by restriction			37.0% (n=1)	60.7% (n=7)	
Review and make change	40.5% (n=2)			94.3% (n=2)	
Structural	13.3% (n=6)	23.6% (n=2)			

RCT = randomized controlled trial; CRCT = cluster randomized controlled trial; CCT = controlled clinical trial; CBA = controlled before and after study; ITS = interrupted time series; CITS = controlled interrupted time series; n = number of studies

*Positive change is a change in the direction of the intended change

Interventions intended to decrease excessive prescribing were associated with reduction in *Clostridium difficile* infections and colonization or infection with aminoglycoside- or cephalosporin-resistant gram-negative bacteria, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*. Meta-analysis of clinical outcomes showed that four interventions intended to increase effective prescribing for pneumonia were associated with significant reduction in mortality (risk ratio 0.89, 95% CI 0.82 to 0.97), whereas nine interventions intended to decrease excessive prescribing were not associated with significant increase in mortality (risk ratio 0.92, 95% CI 0.81 to 1.06).

Interventions to reduce excessive antibiotic prescribing to hospital inpatients can reduce antimicrobial resistance or hospital-acquired infections, and interventions to increase effective prescribing can improve clinical outcome. The meta-analysis supports the use of restrictive interventions when the need is urgent (such as in an outbreak situation), but suggests that persuasive and restrictive interventions are equally effective after six months.

The objective evaluation of outcomes poses a particularly difficult problem for studies of antimicrobial stewardship interventions. Multiple factors - not just appropriate antimicrobial prescription - determine antimicrobial resistance rates and clinical outcomes. Controlling of the confounding factors is difficult as the great majority of published antimicrobial stewardship studies

have been of quasi-experimental design, typically before- and after-implementation studies, where "treatment" allocation and other potential confounding factors are not controlled (28).

The result of the Cochrane review demonstrates that changing hospital antibiotic use is a challenge of paramount complexity. Many determinants as cultural, contextual, and behavioral aspects, can affect antibiotic use in hospitals (33,34). To improve physicians' antimicrobial practice, it is important to identify barriers to and facilitators of guideline adherence (39). Cortoos et al demonstrated that staff members are influenced by previous routine and habits, while residents are guided by external influences such as how much control they experience. For both groups of physicians different approaches to improving antimicrobial use may be necessary.

It seems obvious that education on antimicrobial stewardship is likely to be more successful when started at the time knowledge; attitude and behavior of professionals are being shaped (40). That is the reason why education on prudent antibiotic prescribing should also be an important part of undergraduate medical/professional curriculum (40).

Successful antimicrobial stewardship programs include all the elements of successful quality improvement programs and measuring the effectiveness of program activities is a key component. In an ASP, this usually includes measuring antimicrobial use, auditing the quality of prescribing, and monitoring process and outcome indicators. This information can then be used to provide feedback to prescribers, and inform the AMT and drug and therapeutics committee of the effect of stewardship initiatives on antimicrobial use and resistance patterns (41).

Controlling for confounding can be a special problem for studies of antimicrobial stewardship because while antimicrobial use is a major factor that determines antimicrobial resistance, it is not the only factor. Other factors can be changes in patient demographic profile, changes in patient case mix or changes in infection control measures or their intensity (33).

In general, hospitals need to make choices and to focus on a limited bundle of measures that are feasible and likely to be implemented rather than to elaborate an expanded set of measures.

References

1. Bentley R. The Development of Penicillin: Genesis of a Famous Antibiotic. Perspectives in Biology and Medicine 2005 48;3: 444-452

2. Gould I, Bal A. New antibiotic agents in the pipeline and how they can help overcome microbial resistance. Virulence 2013;4:185–191

3. ECDC/EMEA joint technical report. The bacterial challenge: time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents September 2009 ISBN 978-92-9193-193-4

4. World Health Organization. The evolving threat of antimicrobial resistance Options for action ISBN 978 92 4 (www.who.org accessed July 9th 2013)

5. Ling L, Schneider T, Peoples A, Spoering A, Engels I, Conlon B, Mueller A, Scha¨berle T, Hughes D, Epstein S, Jones M, Lazarides L, Steadman V, Cohen D, Felix C, Fetterman K, Millett W, Nitti A, Zullo A, Chen R, Lewis K. A new antibiotic kills pathogens without detectable resistance. Nature 2015;517;455

6. Carlet J, Jarlier V, Harbarth S, Voss A, Goossens H and Pittet D, for the Participants of the 3rd World Healthcare-Associated Infections Forum. Ready for a world without antibiotics? The Pensières Antibiotic Resistance Call to Action. Antimicrobial Resistance and Infection Control 2012, 1:11

7. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013 http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf (accessed Januari 21th 2014)

8. Communication from the commission to the European Parliament and the council. Action plan against the rising threats from Antimicrobial Resistance Brussels, 15.11.2011 (accessed June 28th http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf

9. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2011. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net).Stockholm: ECDC; 2012. ISSN 1831-9491

10. Goff D. Antimicrobial stewardship: bridging the gap between quality care and cost. Curr Opin Infect Dis 2011:24:11–20

11. French G. Clinical impact and relevance of antibiotic resistance Advanced Drug Delivery Reviews 2005;57:1514–1527

12. Bergen P, Landersdorfera C, Leea H, Lia J, Nationa R. Old' antibiotics for emerging multidrug-resistant. Curr Opin Infect Dis 2012;25:626–633

13. Antimicrobial resistance. Global report on surveillance WHO 2014. ISBN 978 92 4 156474 8. Last accessed May 9th 2015. www.who.int

14. Roberts R, Hota B, Ahmad I, Scott R, Foster S, Abbasi F, Schabowski S, Kampe L, Ciavarella G, Suppino M, Naples J, Cordell R, Levy S, Weinstein R. Hospital and societal costs of

antimicrobial-resistant infections in a Chicago teaching hospital: implications for antimicrobial stewardship. Clin Infect Dis 2009;49:1175-1184

15. Smith R, Coast J. The true cost of antimicrobial resistance. BMJ 2013;:346;f1493

16. The European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe, 2012. Stockholm: ECDC; 2014 ISBN 978-92-9193-589-5

17. Coenen S, Gielen B, Blommaert A, Beutels P, Hens N, Goossens H. Appropriate international measures for outpatient antibiotic prescribing and consumption: recommendations from a national data comparison of different measures . J Antimicrob Chemother 2014; 69: 529–534

18. Bell B, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance BMC Infectious Diseases 2014, 14:13

19. 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

20. Zarb P, Amadeo B, Muller A, Drapier N, Vankerckhoven V, Davey P and Goossens H on behalf of the ESAC-3 hospital care subproject Group. Identification of targets for quality improvement in antimicrobial prescribing: the web-based ESAC Point Prevalence Survey 2009 J Antimicrob Chem 2011; 66:443–449

21. Owens R. Antimicrobial stewardship: concepts and strategies in the 21st century. Diagnostic Microbiology and Infectious Disease.2008;61:110–128

22. Infectious Diseases Society of America (IDSA). Combating Antimicrobial Resistance:Policy Recommendations to Save Lives. Clin Infect Dis 2011;52:397–428

23. MacDougall C, Polk R. Antimicrobial Stewardship Programs in Health Care Systems Clinical Microbiology Reviews 2005;18:638–656

24. Society for Healthcare Epidemiology of America; Infectious Diseases Society of America;Pediatric Infectious Diseases Society. Policy Statement on Antimicrobial Stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS) Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; Pediatric Infectious Diseases Society. Infect Control Hosp Epidemiol 2012;33(4):322-327

25. Sourdeau L, Struelens MJ, Peetermans WE et al. Implementation of antibiotic management teams in Belgian hospitals. Acta Clin Belg 2006; 6: 58–63

26. Van Gastel E, Costers M, Peetermans W, Struelens M , and on behalf of the Hospital Medicine Working Group of the Belgian Antibiotic Policy Coordination Committee Nationwide implementation of antibiotic management teams in Belgian hospitals: a self-reporting survey J. Antimicrob. Chemother. 2010;65: 576-580.

27. Goossens H, Coenen S, Costers M, De Corte S, De Sutter, A, Gordts B, Laurier L, Struelens MJ. Achievements of the Belgian Antibiotic Policy Coordination Committee (BAPCOC). Euro Surveill. 2008;13(46):pii=19036. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19036 (accessed on January 14 th 2014)

28. Chung G, Wu J,Yeo C, Chan D and Hsu L. A review of prospective audit and feedback systems and an objective evaluation of outcomes. Virulence 2013;4:151–157

29. Leekha S, Terrell C, Edson R. General principles of antimicrobial therapy. Mayo Clin Proc. 2011; 86:156-67

30. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH., The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest. 2000;118:146-55

31. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589-96

32. Donabedian A (1988) The quality of care: How can it be assessed? JAMA 260:1743-1748

33. McGowan J Antimicrobial Stewardship—the State of the Art in 2011:Focus on Outcome and Methods Infect Control Hosp Epidemiol 2012;33(4):331-337

34. Thern J, de With K, Strauss R. Steib-Bauert M, Weber N, Kern W. Selection of hospital antimicrobial prescribing quality indicators: a consensus among German antibiotic stewardship (ABS) networkers. Infection 2014 DOI 10.1007/s15010-013-0559-z

35. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, Wilcox M. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD003543.

36. Filice G, Drekonja D, Greer N, Butler M, Wagner B, MacDonald R, Carlyle M, Rutks I, Wilt TJ. Antimicrobial Stewardship Programs in Inpatient Settings: A Systematic Review. Washington (DC): Department of Veterans Affairs (US); 2013. VA Evidence-based Synthesis Program Reports.

37. Hulscher M, Grol R, van der Meer J. Antibiotic prescribing in hospitals: a social and behavioural scientifi c approach. Lancet Infect Dis 2010; 10: 167–75

38. Charani E, Edwards R, Sevdalis N, Alexandrou B, Sibley E, Mullett D, Franklin B, Holmes A. Behavior Change Strategies to Influence Antimicrobial Prescribing in Acute Care: A Systematic Review. Clin Infect Dis 2011;53:651–662

39. Cortoos PJ, Schreurs B, Peetermans W, De Witte K, Laekeman G. Divergent Intentions to Use Antibiotic Guidelines: A Theory of Planned Behavior Survey. Med Decis Making 2012;32:145-153

40. Pulcini C, Gyssens IC. How to educate prescribers in antimicrobial stewardship practices. Virulence 2013;4:192–202.

41. Duguid M, Cruickshank M. Antimicrobial stewardship in Australian hospitals,Australian Commission on Safety and Quality in Health Care, Sydney.Antimicrobial Stewardship. 2010 ISBN 978-0-9870617-0-6

7. Research aims and overview of the different chapters

The first aim of this research was to develop indicators for evaluating antimicrobial stewardship programs in a hospital setting (Chapter 2 and 3). The second aim was to evaluate components of an antimicrobial stewardship program in a hospital setting (Chapter 3,4,5,7).

Indicators for evaluating antimicrobial stewardship programs in a hospital setting

After a general introduction in Chapter 1, we describe the development of quality of care indicators towards antimicrobial stewardship programs (Chapter 2 and 3).

In chapter 2, a prospective multicenter feasibility study of a quality of care indicator for intravenous to oral switch therapy with highly bioavailable antibiotics was performed in five university hospitals in Austria, Belgium and Germany.

Research question:
- Is it feasible to implement a quality of care indicator for intravenous to oral switch therapy with highly bioavailable antibiotics?
- Is there heterogeneity of the performance gap considering intravenous to oral switch therapy in five European hospitals?

Chapter 3 describes the development and validation of potential structure indicators for evaluating antimicrobial stewardship programmes in European hospitals.

Research question:
- Which structure indicators for hospital antimicrobial stewardship programmes could be used according different professionals (infectious disease specialists, clinical microbiologists, hospital pharmacists, and quality and health care scientists) from four countries?
- Is it feasible to implement the selected indicators in eleven European hospitals?
- Is there a heterogeneity among participating centers with regard to their score for structural components?

Components of an antimicrobial stewardship program in a hospital setting

In chapter 4, the results of a survey of beta-lactam antibiotics and vancomycin dosing strategies on intensive care units and general wards in Belgian hospitals are described. Optimization of antimicrobial dosing based on pharmacokinetic and pharmacodynamic characteristics of the drug is a part of an antimicrobial stewardship program. This survey not only describes the implementation of prolonged and continuous infusions in Belgian hospitals but also reveals the pitfalls in implementing such dosing regimens.

In chapter 5, the time to the first antibiotic administration for adult patients admitted to the emergency department was assessed before and after the implementation of corrective interventions. The time to first antibiotic dose was evaluated as it can be considered as a marker of optimal care in patients treated with antimicrobials for an infection. Factors predicting delays in time to first antibiotic dose were evaluated.

Chapter 6, presents the implementation of guidelines for sequential therapy with fluoroquinolones in a Belgian hospital. One can presume that one of the simplest cost-savings stewardship initiatives is the recommendation to switch select antimicrobials from intravenous-to-oral therapy. This study describes the results of three different interventions on patient outcome and on fluoroquinolone consumption.

Chapter 7, describes the type and acceptance rate of interventions provided by a multidisciplinary infectious diseases team (MIT) in a tertiary hospital. Prospective audit with persuasive intervention, i.e. intervention and feedback, is considered as a core antimicrobial stewardship strategy.

CHAPTER 2: PROSPECTIVE MULTICENTER FEASIBILITY STUDY OF A QUALITY OF CARE INDICATOR FOR INTRAVENOUS TO ORAL SWITCH THERAPY WITH HIGHLY BIOAVAILABLE ANTIBIOTICS

Prospective multicenter feasibility study of a quality of care indicator for intravenous to oral switch therapy with highly bioavailable antibiotics

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Abstract

Background

Enhanced oral (po) bioavailability of antimicrobial drugs allows conversion to po therapy once a patient meets defined clinical criteria. This can reduce length of hospital stay, healthcare costs and risk of complications related to intravenous (iv) access. We developed a quality indicator for assessing the appropriate iv-to- po switch of bioavailable antibiotics and evaluated its feasibility and clinical relevance across acute healthcare systems.

Methods

The study was designed as a multicenter, multinational observational audit. The indicator was the proportion of inappropriate iv treatments at any point in time in adult patients treated with fluoroquinolones, clindamycin, linezolid or metronidazole. Treatments were prospectively evaluated by a trained physician or clinical pharmacist using predefined clinical criteria. The feasibility of the indicator was evaluated by measuring data availability, data collection workload and sensitivity to improvement

Results

Data were collected over a 3 month period in five university hospitals in Austria, Belgium and Germany and iv treatment was assessed in 211 patients. The indicator was measurable in 99.1% of cases. By intention to- treat analysis, 37.0% (95% CI 30.5–43.9) of treatments were inappropriate, ranging from 17.5% to 53.8% across hospitals. The median time needed for case assessment and documentation was 29 min.

Conclusions

This quality indicator was found to be generally feasible in hospitals across three European countries, and informative about the local need for clinical quality improvement.

Introduction

The project 'ABS International—Implementing antibiotic strategies for appropriate use of antibiotics in hospitals in member states of the European Union' (co-financed by the European Commission) started in September 2006. The objectives were to develop and evaluate the feasibility of quality indicators for hospital antibiotic use.

Quality indicators can be defined as 'a measurable aspect of care provided for which there is evidence and/or consensus that it represents quality on the grounds of scientific research or consensus among experts'(1). As part of the ABS project, quality indicators of antimicrobial therapy were developed by expert consensus and evaluated in an international sample of acute care hospitals.

Antimicrobial stewardship programmes promote the appropriate use of antimicrobials by selecting the appropriate drug, dose, duration and route of administration (2). High oral (po) bioavailability of antimicrobial drugs, like fluoroquinolones, linezolid, metronidazole, clindamycin, fluconazole and voriconazole, allows conversion to po therapy once a patient meets defined clinical criteria. This can result in reduced length of hospital stay, healthcare costs, potential complications due to intravenous (iv) access and a lower work burden for nursing staff. Many studies show a significant delay in switching from iv to po antibiotic therapy after criteria for the po route are met (3–9).

By considering the evidence relating to iv-to-po switch, an indicator for measuring the performance of hospitals was tested.

Methods

The objective of this multicentre, multinational prospective observational audit was to evaluate the feasibility and clinical relevance of measuring an indicator of appropriate iv use of highly bioavailable antibiotics in acute care hospitals across European countries. The indicator rate (%) was calculated using the following formula: the number of patients with inappropriate fluoroquinolone, clindamycin, linezolid or metronidazole treatment by iv route divided by the number of patients treated with iv fluoroquinolones, clindamycin, linezolid or metronidazole multiplied by 100.

Data were collected from 1 February 2008 to 30 April 2008 in five university hospitals: two in Austria, two in Belgium and one in Germany. Treatments in inpatients (>18 years) were identified based on daily review of prescriptions. The appropriateness of the iv administration route was evaluated by a physician or pharmacist trained in infectious diseases and antibiotic stewardship. The following criteria were used to define the inappropriate iv route: body temperature <38°C during the previous 24h, decreasing or normal blood leucocyte count, absence of unexplained tachycardia,

functional gastrointestinal tract (patient is able to eat or has a functional gastric feeding tube), no vomiting, no diarrhea and no severe sepsis.

Consecutive cases were audited until 40 treatment courses were included or the study completion date was reached. Data collected were patient's age and gender, infection type, antimicrobial treatment, indication and type of care (medical, surgical or intensive care) using a standardized case record paper form (CRF). The feasibility of the indicator was evaluated by measuring data availability (%), data collection workload (min/case) and baseline rate of the indicator (% inappropriate care). The minimum value of 80% cases with available data was predefined as the threshold of general feasibility. The average time spent by the data assessor per assessed case for collecting and reviewing the data, and filling the CRF was used as the workload parameter. The baseline indicator rate, expressed as the proportion of cases with nonadherence to recommended practice, reflects the 'performance gap' or sensitivity to improvement in the process of care by antimicrobial stewardship interventions. No pre-set value was assigned to this endpoint as the performance level achieved was expected to vary by hospital according to previous or ongoing local quality intervention programmes.

Case-mix stability of the indicator was explored by comparing indicator rates by type of care, infection, age group, antibiotic used, gender and availability of an iv-to-po switch improvement programme in the previous 2 years.

The protocol was approved by the Ethics Committees of Ghent University Hospital and Erasme University Hospital. Ethics Committee approval in the participating German hospital was available for general hospital wide antibiotic prescription point prevalence surveys covering the present investigation. The Austrian Ethics Committee did not see the necessity for an ethics review as actual patient treatment was not part of the project and we only dealt with retrospective and anonymous data collection.

Each investigator completed a questionnaire including the implementation of an improvement programme for iv-to-po switch in the previous 2 years.

Data were analysed using the PASW.v18 software package (SPSS Inc., Chicago, IL, USA). The x^2 test was used to assess differences in inappropriateness of prescribing and was performed with two-sided probability of type 1 error at a significance level of P=0.05. A logistic regression model was built to identify factors associated with the inappropriateness of prescribing.

Results

The size of the five participating hospitals ranged from 835 to 1600 beds. Infectious disease specialists (n=4), microbiologists (n=3) and pharmacists (n=3) were involved in data collection. Two hundred and eleven patients with an iv treatment with fluoroquinolones, clindamycin, linezolid or metronidazole were included in the study (Table 1). Four hospitals collected data on 40 treatment courses and one on 51 courses. The mean age of the patients was 59 years and 56% were female. Respectively, 45.9%, 31.2% and 20.8% of the patients were admitted to a surgical, medical and intensive care ward. The most frequent site of infection was the respiratory tract (24.6%), followed by skin, soft tissue, bone or joint (22.7%), urinary or genital tract (18.0%) and intra-abdominal cavity (17.0%). Fluoroquinolones were the most frequently administered drug class.

Table 1. Percentage inappropriate IV antibiotic treatments by indication, type of care, antibiotics used, participating center and the availability of an iv-po improvement program.

	Number of treatments (%) (N=211)	Number of inappropriate treatments	Percentage of inappropriate iv treatments	P value
Indication				
skin, soft tissue, bone or joint infection	48 (22.7)	33	68.8	<0.001
respiratory tract infection	52 (24.6)	20	38.5	
urinary/genital tract infection	38 (18.0)	14	36.8	
intra-abdominal infection	36 (17.0)	7	19.4	
other/unknown	19 (9.0)	2	10.5	
treatments 1 day before a planned operation	18 (8.5)	2	11.1	
Type of care[a]				
surgical care	97 (45.9)	36	37.1	0.007
medical care	66 (31.2)	32	48.5	
intensive care	44 (20.8)	8	18.2	
Antibiotics[b]				
fluoroquinolones	89 (42.1)	28	31.5	0.008
metronidazole	55 (26.0)	16	29.1	
clindamycin	37 (17.5)	23	62.2	
combinations	19 (9.0)	6	31.6	
linezolid	8 (3.7)	5	62.5	
Participating centre				
A	40 (18.9)	18	45.0	0.001
B	40 (18.9)	21[c]	53.8	
C	40 (18.9)	7	17.5	
D	51 (24.2)	12	23.5	
E	40 (18.9)	20[d]	51.3	
Availability of an improvement programme for iv-to-po switch during the last 2 years[e]				
yes (two hospitals)	91 (43.1)	19	20.9	0.001
no (three hospitals)	118 (55.9)	59	50.0	

[a] 4 not documented; [b] 3 not documented; [c] 1 not documented; [d] 1 not documented; [e] 2 not documented

In two hospitals one treatment could not be evaluated because of missing data, resulting in availability for this indicator of 99.1%. The median time needed to assess the case and fill in the CRF was 29 min (range 20–37 min).

The intention-to-treat analysis showed that 37.0% (95% CI 30.5–43.9) of the patients were inappropriately treated with iv antibiotics.

The reasons for inappropriate iv administration were the ability to eat (90%) and the availability of a functioning gastric feeding tube (10%). Among patients who were appropriately receiving iv therapy, a non-functioning gastrointestinal tract (24.6%), inability to swallow (23.7%), vomiting (17.5%), diarrhoea (13.2%) or severe sepsis (5.3%) rendered parenteral administration necessary. Appropriate iv therapy was given to 15.8% of the patients based on a written medical order to switch to po therapy the next day.

Comparing inappropriateness by indication, the indicator rate ranged from 11.1% inappropriate treatments 1 day before a planned operation to 68.8% for skin, soft tissue, bone or joint infection (P< 0.001). The highest proportion of inappropriate iv therapy was found in the medical wards (48.5%), followed by surgical (37.1%) and intensive care (18.2%) wards (P=0.007).

The percentage of inappropriate iv treatments by centre ranged from 17.5% to 53.8% (P=0.001). The average proportion of inappropriate iv administration was 20.9% in the hospitals (C and D) with an improvement programme versus 50.0% in the other hospitals (P=0.001).

After adjusting for type of care and type of infection, absence of an iv-to-po switch programme was associated with more inappropriate prescribing (OR 6.78; 95% CI 3.02–15.23; P<0.001). Age group (P=0.442) and gender (P=0.131) were not significantly related to inappropriateness of prescribing.

Discussion

This study evaluated the feasibility and clinical usefulness of an iv-to-po switch indicator in five acute care hospitals from three European countries. Importantly, two participants reported that, in the 2 years preceding the study, local quality improvement programmes were in place to improve the process of care under study. Therefore, the results observed do not reflect 'baseline' practice.

More than 99% of the required data proved available, which is higher than the pre-set threshold value of 80%. On average, the workload required for collecting, reviewing the data and filling the CRF was 29 min per assessed case. Significant inter-hospital variation suggests that the efficiency of data extraction depends on the quality and accessibility of clinical and pharmacy data sources. Opportunities for automated data extraction from computerized patient records should enhance the efficiency of monitoring such indicators (10).

The indicator revealed a substantial heterogeneity of the performance gap, with a range of 17.5%–53.8% of antibiotic iv administrations considered avoidable. Hospitals with an iv-to-po switch improvement programme scored significantly better for this indicator, although this study did not aim to test this hypothesis. This indicator suggests substantial sensitivity to improvement in this sample of hospitals and may be selected as the target for local quality improvement efforts. The iv-to-po switch improvement programme in the two hospitals consisted of yearly educational letters, poster campaigns and support by clinical pharmacists and infectious disease physicians.

For this indicator, results can preferably be reported by type of care and type of infection, as these characteristics were associated with significant differences in the rate of appropriate use. Medical patients were more often inappropriately treated iv compared with surgical patients. Skin, soft tissue, bone or joint infection had the highest proportion of inappropriate iv treatments, which could reflect physicians' reluctance to treat this type of infection po. For bone and joint infection it is important to emphasize that in the acute phase of the illness iv therapy is the standard administration route. The high proportion of inappropriate iv treatments can be explained by the limited evidence that suggests that the route of administration does not affect the rate of disease remission in the treatment of acute osteomyelitis (11,12). Each center used a standardized CRF to collect the data. As skin, soft tissue, bone or joint infections were grouped as one type of infection it was not possible to specify retrospectively which patients were treated for a bone or joint infection, which is a limitation of this study.

It is important to mention that fluoroquinolones and voriconazole administered by a gastric feeding tube should not be given simultaneously with enteral feeding. A common practice is to withhold enteral feeding for at least 1 h before and 2 h after fluoroquinolone and voriconazole dosing (13).

In conclusion, the results of this study indicate that the ABS iv-to-po quality indicator is widely applicable to acute care hospitals. Hospital antibiotic management teams can consider adopting it as a tool to evaluate compliance with iv-to-po switch guidelines.

References

1 Lawrence M, Olesen F. Indicators of quality in health care. Eur J Gen Pract 1997; 3: 103–8.

2 Dellit TH, Owens RC, McGowan JE Jr 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: 159–77.

3 Nathawani D, Tillotson G, Davey P. Sequential antimicrobial therapy— the role of quinolones. J Antimicrob Chemother 1997; 39: 441–6.

4 Sevinç F, Prins J, Koopmans R et al. Early switch from intravenous to oral antibiotics: guidelines and implementation in a large teaching hospital. J Antimicrob Chemother 1999; 43: 601–6.

5 Kuti J, Le T, Nightindale C et al. Pharmacoeconomics of a pharmacistmanaged program for automatically converting levofloxacin route from IV to oral. Am J Health Syst Pharm 2002; 59: 2209–15.

6 Jensen K, Paladino J. Cost-effectiveness of abbreviating the duration of intravenous antibacterial therapy with oral fluoroquinolones. Pharmacoeconomics 1997; 11: 64–74.

7 Vogel F. Intravenous/oral sequential therapy in patients hospitalised with community-acquired pneumonia. Drugs 2002; 62: 309–17.

8 Ramirez J, Bordon J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-acquired Streptococcus pneumoniae pneumonia. Arch Intern Med 2001; 161: 848–50.

9 Oosterheert JJ, Bonten MJ, Schneider MM et al. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. BMJ 2006; 333: 1193–5.

10 Fischer MA, Solomon DH, Teich JM et al. Conversion from intravenous to oral medications: assessment of a computerized intervention for hospitalized patients. Arch Intern Med 2003; 163: 2585–9.

11 Stevens DL, Bisno AL, Chambers HF et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 2005; 41: 1373–6.

12 Conterno LO, da Silva Filho CR. Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev 2009; issue 3: CD004439.

13 Williams NT. Medication administration through enteral feeding tubes. Am J Health Syst Pharm 2008; 65: 2347–57.

CHAPTER 3: DEVELOPMENT AND VALIDATION OF POTENTIAL STRUCTURE INDICATORS FOR EVALUATING ANTIMICROBIAL STEWARDSHIP PROGRAMMES IN EUROPEAN HOSPITALS

Development and validation of potential structure indicators for evaluating antimicrobial stewardship programmes in European hospitals

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Abstract

This study describes the development of structure indicators for hospital antimicrobial stewardship programmes and pilot validation across European hospitals.

A multidisciplinary panel from four European countries developed structure indicators in three steps: identification and listing of indicators, remote ranking of indicators using multi-criteria scoring, selection of indicators in a face-to-face consensus meeting. Additionally, the top-ten indicators were identified as a minimal set of key indicators. A survey was sent to the directors of antimicrobial stewardship programmes in European hospitals. The yes/no answers for the indicators were transformed into numbers in order to calculate the total scores.

A list of 58 indicators was selected and categorised into the following topics: antimicrobial stewardship services (12 items), tools (16 items), human resources and mandate (6 items), health care personnel development (4 items), basic diagnostic capabilities (6 items), microbiological rapid tests (2 items), evaluation of microbiological drug resistance data (3 items), antibiotic consumption control (5 items) and drug use monitoring (4 items).

The indicator scores, reported by 11 pilot hospitals from five European countries, ranged from 32 to 50 (maximum score=58) and from 5 to 10 points (maximum score= 10) for, respectively, the complete and the top-ten list. An international panel selected 58 potential structure indicators, among which was a minimal set of ten key structure indicators, that could be useful for assessment of the comprehensiveness and resource-intensity of antimicrobial stewardship programmes.

There was significant heterogeneity among participating centres with regard to their score for structural components of effective antimicrobial stewardship.

Background

The increasing incidence of antibiotic resistance represents a serious worldwide problem. In November 2001, the European Council adopted a recommendation on the prudent use of antimicrobial agents in human medicine (2002/77/EC), with a focus on the surveillance of antimicrobial resistance, surveillance of antimicrobial use, control and preventive measures, education and training, and research [1].

The project proposal "Implementing antibiotic strategies (ABS) for appropriate use of antibiotics in hospitals in member states of the European Union—ABS International" was presented to the EU Commission in 2005. The project started in September 2006 and was implemented in nine Member States of the EU: Austria, Germany, Belgium, Italy, Poland, Hungary, Czech Republic, Slovenia and Slovakia [2, 3].

As part of the project, structure and process indicators for evaluating activities of antimicrobial stewardship committees were developed in order to provide antimicrobial stewardship committees or antimicrobial management teams (AMTs) with quality assessment tools for evaluating their activities [4]. Structural indicators describe the organisation and resources as well as communication and evaluation tools available at the hospital level for implementing a multi-modal, multi-disciplinary antibiotic stewardship programme [5–7]. These indicators should focus on the appropriateness of antimicrobial drug prescribing and administration in hospital care, with reference to national standards and international, national or local practice guidelines. In addition to optimising individual patient care outcome, the quality objective for antibiotic use is also an important ecological dimension, namely, to minimise the risk of antibacterial resistance selection and spread associated with individual and population antibiotic exposure.

Finally, in a general setting of budgetary limitations, the efficient use of financial and human resources should also be considered in recommending any interventions to modify or monitor antimicrobial drug use. Antibacterial drugs are among the most frequently administered drugs in hospital care and a significant driver of drug acquisition, administration and bio-monitoring costs.

This study describes the development of structure indicators for antimicrobial stewardship and antibiotic use in a hospital setting by a multi-national expert panel. Furthermore, it reports on the results of a validation survey based on the selected indicators across a pilot sample of European hospitals.

Methodology

Development of structure indicators

A multi-disciplinary team composed of five infectious disease specialists, two clinical microbiologists, three hospital pharmacists and three quality of health care experts from four countries (Austria, Germany, Belgium, USA) developed and selected structure indicators on hospital organisation and resources, as well as drug use. This team was composed on an ad hoc basis with experts participating in the ABS International project. The development of structure indicators was achieved in three steps. In the first step, candidate quality indicators were identified based on the scientific literature and a structured list was compiled by all team members. The second step was to score and rank the listed quality indicators using multi-criteria scoring based on their perceived scientific value and applicability. Finally, quality indicators were selected by consensus during a general discussion in a face-to-face meeting.

The identification of potential quality indicators was based on effective interventions and programme components identified in recent reviews of the literature, quality indicators as proposed in national/international guidelines and standards, as well as ABS/BAPCOC (The Belgian Antibiotic Policy Coordination Committee) questionnaires used in Austria and Belgium for auditing the quality of antibiotic stewardship programmes [8–16].

Multi-criteria decision analysis was used to score and rank the quality indicators based on scientific value and applicability. Multi-criteria decision analysis is a procedure aimed at supporting decision makers who need to assess a number of options against potentially conflicting criteria, combining those evaluations into an overall evaluation of relative value through a transparent and traceable process. It provides a clear audit trail for reporting the decision-making process.

The methodology for scoring and ranking the potential quality indicators was adapted from the procedure described by Schouten et al. [17]. After discussion in the consensus group, two sets of criteria were agreed upon; a first set of four criteria was used for ranking the potential value of all proposed indicators and a second set of two criteria was scored to assess the assumed applicability across health care centres in Europe.

For both sets of criteria, a scoring scale of 0 (lowest value) to 5 (maximum value) was used for scoring by each of the 13 team members to remotely and independently assess each proposed quality indicator; the sum of rates for each criterion provided the final mean score (maximum of 20 for value ranking) for each quality indicator. This ranking score was used to prioritise the options in descending order within the structure indicators. The applicability score was used during a group discussion to

decide upon suitability for inclusion in the field validation phase. Scoring criteria for ranking score was based on clinical relevance, ecological relevance, economic relevance and scientific validity (Table 1).

Table 1. Scoring criteria for ranking and applicability score

Scoring criteria for ranking	
Clinical relevance:	Is the quality indicator likely to predict a health benefit for the patient and if so, how big a benefit to expect?
Ecological relevance:	Is the quality indicator likely to predict an effect on reducing/minimising the development of antibiotic resistance, and if so how big a benefit to expect?
Economic relevance:	Is the quality indicator likely to predict more efficient use of hospital care resources, including drug acquisition, delivery and monitoring costs?
Scientific validity:	What is the strength and volume of scientific evidence from published studies linking the quality indicator to either a health benefit or ecological benefit for reducing resistance or improved cost-effectiveness of care?
Criteria for applicability score	
Generalisability:	How widely applicable is the quality indicator across hospitals and healthcare systems?
Assumed feasibility:	How easy will be the data collection for measuring the quality indicator from routinely available administrative and clinical records?

Previous systematic reviews, evidence-based guidelines and meta-analyses were used as the main sources for ranking this dimension. Scoring criteria for calculating the applicability score were generalisability and assumed feasibility based on the expert experience (Table 1). Finally, a consensus meeting was organised to discuss the ranking results and select the quality indicators. Additionally, based on the highest score for ranking and applicability, the top ten indicators were identified as the minimal set of key structure indicators.

Structured questionnaire survey

To pilot the feasibility and validate the discriminatory power of the selected indicators, a structured questionnaire survey comprising hospital information [hospital affiliation, number of beds, number of intensive care unit (ICU) beds] and questions to score indicators was developed. The survey was administered by email (April 2008) to the director of the antimicrobial stewardship programme in 11 volunteer acute care hospitals participating in the ABS project: five in Austria, two in Belgium, one in the Czech Republic, two in Germany and one in Slovenia. The respondents could send back the filled in questionnaire by email or post to a central data manager. For further analysis, the yes/no answers for the indicators were transformed into numbers in order to calculate the total scores for each dimension of structure. One point was given in the case of a "yes" answer and zero points in the case of a "no" answer. This calculation was made for both the extensive list of structure indicators and the top-ten key indicators

Results

Development of indicators

A list of 74 potential quality indicators was identified based on a literature review and national quality indicators implemented in the countries participating in the project. Each indicator was scored, resulting in a ranking and applicability score. The scores were used during the consensus meeting to select and clarify the final indicators.

Based on the initial list of 74 structure indicators, and after screening for redundancy, a final list of 58 indicators were selected and categorised in the following topics: antimicrobial stewardship services (n=12), tools (n=16), human resources and mandate (n=6), health care personnel development (n=4), basic diagnostic capabilities (n=6), microbiological rapid tests (n=2), evaluation of microbiological data on antibiotic resistance (n=3), antibiotic consumption control (n=5) and drug use monitoring (n=4) (Table 2). The top-ten structure indicators with the highest score for ranking and applicability are identified with an asterisk (*) and were considered to be key elements of an effective antibiotic stewardship programme.

Validation survey

Eleven hospitals, including seven university and four general hospitals, participated in the pilot study. The size of the hospitals ranged from 280 to 2,392 beds, with the number of ICU beds ranging from 9 to 132.

As shown in Table 3, the total score of individual hospitals ranged from 32 to 50 points. The maximum possible score of 58 was not reached by any hospital. When only the ten indicators of key elements of an effective antibiotic stewardship programme were listed for the hospitals, the score ranged from 5 to 10 points (maximum possible score=10).

Table 2 Value ranking and applicability scores for selected potential indicators. The highest scores are indicated in **bold**

Dimension	Item	Value ranking score					Applicability score		
		Clinical relevance 0 to 5	Ecological relevance 0 to 5	Economic relevance 0 to 5	Validity 0 to 5	Total score /20	Generalisability 0 to 5	Assumed feasibility 0 to 5	Total score /10
Services	*Bedside expert consultant advice regarding antibiotics by microbiologist/infectious disease specialist/antibiotic officer on request available on the same day	4.7	3.9	4.3	4.3	**17.2**	3.8	4.4	8.2
	*Regular ward rounds by members of the AMT (multi-disciplinary antibiotic management team) performed (at least weekly)	4.5	3.9	4.2	4.3	**16.8**	3.8	4.5	8.3
	AMT (multi-disciplinary antibiotic management team) meetings performed at least bi-monthly	2.8	2.8	3.0	3.2	11.8	3.9	4.4	8.3
	AB policy and progress report disseminated to medical director by AMT/AB officer	3.1	3.0	3.2	3.3	12.5	3.9	4.3	8.3
	AB policy and progress report disseminated to infection control committee/hygiene team by AMT/AB officer	3.1	3.2	2.8	2.9	12.0	3.7	4.3	7.9
	AB policy and progress report disseminated to drugs and therapeutics committee by AMT/AB officer	2.8	2.8	3.4	2.8	11.8	3.6	4.3	7.8
	AB policy plan with quantitative objectives for performance indicators published annually by AMT/AB officer	3.1	3.1	3.4	3.1	12.7	3.4	4.0	7.4
	*Clinical audit of prescribers' compliance with local clinical guidelines/guide performed annually by AMT/AB officer	4.3	3.7	4.1	4.0	**16.1**	3.9	3.8	7.8
	ABS-related formal exchange of experiences (e.g. meeting) of AMT with general practitioners min. 1×/year performed	3.1	2.6	2.6	2.8	11.2	3.5	4.4	7.9
	ABS-related formal exchange (e.g. meeting) of experiences of AMT with other hospitals min. 1×/year performed	2.7	2.8	2.6	2.9	11.1	3.4	4.3	7.6
	Clinical audit by AB officer for evaluation of prescribers' compliance with streamlining drugs on days 2–3	4.0	3.5	4.0	3.8	15.3	3.5	3.9	7.4
	Concurrent review by AB officer for evaluation of prescribers' compliance with streamlining drugs on days 2–3	4.0	3.5	4.0	3.8	15.3	3.5	3.9	7.4
Tools	**AB formulary/list available	4.3	4.1	4.3	4.2	**16.9**	4.5	4.9	9.4
	*AB formulary/list biannually updated	4.3	4.1	4.3	4.2	**16.9**	4.5	4.9	9.4
	List of reserve antibiotics with authorisation system for delivery available	3.8	3.9	4.3	4.0	15.9	4.2	4.8	8.9
	Computerised antibiotic prescription/order form/system available	3.9	3.7	4.1	3.8	15.5	3.5	4.5	8.0
	Time-limited drug delivery/automatic stop order available	3.6	3.4	3.8	3.7	14.5	3.4	4.3	7.8
	Local clinical practice guidelines/guide for microbiologically documented therapy available	3.6	3.4	3.8	3.7	14.5	3.4	4.3	7.8
	*Local clinical practice guidelines/guide for microbiologically documented therapy updated biannually	4.5	4.1	4.3	4.3	**17.2**	4.1	4.7	8.8
	*Local clinical practice guidelines/guide for empirical therapy available	4.5	4.1	4.3	4.3	**17.2**	4.1	4.7	8.8
	**Local clinical practice guidelines/guides for empirical therapy updated biannually	4.7	4.2	3.8	4.3	**16.9**	4.2	4.6	8.8

Table 2 (continued)

Dimension	Item	Value ranking score					Applicability score		
		Clinical relevance 0 to 5	Ecological relevance 0 to 5	Economic relevance 0 to 5	Validity 0 to 5	Total score /20	Generalisability 0 to 5	Assumed feasibility 0 to 5	Total score /10
	*Local clinical practice guidelines/guide for surgical antibiotic prophylaxis available	4.6	3.9	4.1	4.1	**16.7**	4.2	4.8	8.9
	Local clinical practice guidelines/guide for surgical antibiotic prophylaxis updated biannually	4.3	3.5	4.0	3.8	15.2	4.3	5.0	9.3
	Guidelines/guides for iv–oral switch available	3.7	3.1	4.6	4.2	15.5	4.4	4.8	9.2
	Guidelines/guides for iv–oral switch updated biannually	3.5	2.5	4	3	13	3	4	7
	AB pocket guidebook or PDA (personal digital assistant) available	3.0	3.5	2.5	3.5	12.5	2.5	3.5	6
	Computer-based clinical decision support for antibiotic prescribing available	3.5	3.2	3.8	3.7	14.1	2.8	3.6	6.4
	Special request/order form for (selected) antimicrobial drugs available	3.6	3.3	3.8	3.7	14.3	3.7	4.8	8.4
Human resources and mandate	*Formal mandate for hospital multi-disciplinary antibiotic management team (AMT) existing	4.5	4.0	4.0	4.4	**16.9**	4.4	4.8	9.2
	Formal mandate for AB officer existing	4.0	3.4	4.0	4.0	15.4	4.0	3.5	7.5
	Time resources for AMT defined	4.0	3.2	4.0	3.8	15	3.0	4.0	7.0
	Time resources for AB officer defined	4.0	3.2	4.0	3.8	15	3.0	4.0	7.0
	*AB officer or AMT member is member of the drugs and therapeutics committee	4.0	4.1	4.0	3.9	**16**	4.0	4.0	8.0
	All experts (infectiologist, microbiologist, pharmacist) involved in the guideline/guide development process	4.5	3.6	3.8	3.7	14.4	4.3	4.5	8.0
Personnel development	Participation of AB officer or members of AMT in AB-related symposia, congresses, seminars at least 1×/year	3.8	4.0	3.9	4.0	15.7	4.0	3.9	7.9
	Prescriber education by passive methods (bulletin, intranet) performed	2.7	2.5	2.6	2.8	10.5	3.5	4.0	7.5
	*Prescriber education by personalised interactive methods (like daily ward rounds) performed	4.6	4.0	4.2	4.1	**16.8**	3.8	4.4	8.2
	Visits by industry representatives with health care providers inside the hospital are regulated by the hospital	3.5	3.0	3.5	3.0	13.0	3.5	4.0	7.5
Basic diagnostic	Working relationship by regular meetings once a week between microbiologists and practitioners	4.0	3.9	4.0	3.8	15.7	4.0	4.0	8.0
	Transport time of clinical material to the microbiological laboratory during the week possible within 2 h	4.0	2.6	2.7	3.4	11.5	3.9	4.0	7.2
	Microbiological laboratory: written directives concerning specimen storage available	3.4	2.4	2.8	3.3	11.8	3.7	4.5	8.2
	Microbiological laboratory: written directives concerning rejection criteria on clinical specimens (e.g. culturing of sputa but not saliva) available	3.4	2.4	2.8	3.3	11.8	3.7	4.5	8.2
	Quality management of the microbiological laboratory: certified (according to ISO)	3.8	2.9	3.1	3.4	13.2	4.2	4.8	9.0
	Quality management of the microbiological laboratory: accredited (by government)+B41	3.8	2.9	3.1	3.4	13.2	4.2	4.8	9.0

Table 2 (continued)

Dimension	Item	Value ranking score					Applicability score		
		Clinical relevance 0 to 5	Ecological relevance 0 to 5	Economic relevance 0 to 5	Validity 0 to 5	Total score /20	Generalisability 0 to 5	Assumed feasibility 0 to 5	Total score /10
Microbiological rapid tests	*Clostridium difficile* toxin test available within 18 h	4.4	3.5	3.5	3.9	15.3	4.1	4.8	8.9
	Legionella urinary antigen test available within 18 h	4.1	2.8	3.1	3.5	13.5	3.9	4.8	8.7
Microbiological data evaluation	Antibiotic resistance data regarding MRSA analysed and written report provided at least 1×/year	3.6	4.0	3.2	3.5	14.4	4.4	4.7	9.1
	Antibiotic resistance data regarding ESBL analysed at least 1×/year	3.6	4.0	3.2	3.4	14.2	4.2	4.7	8.9
	Antibiotic resistance data (other than MRSA and ESBL) analysed at least 1×/year	3.6	4.2	3.3	3.5	14.6	4.2	4.7	8.9
Antibiotic consumption controlling	Annual analysis of AB consumption data (in DDD or RDD) available on hospital level by drug/drug class	2.8	3.3	3.8	3.4	13.3	4.3	4.7	8.7
	Annual analysis of AB consumption data (in DDD or RDD) available on department level (i.e. by discipline)	2.9	2.8	3.1	3.2	12.0	3.6	3.7	7.4
	Annual analysis of AB consumption data (in DDD or RDD) available on ward level	2.8	2.5	3.0	3.1	11.4	3.8	3.5	7.3
	AB consumption feedback to the ward at least 1×/year	3.3	3.3	3.8	3.3	13.7	3.5	3.7	7.2
	Prospective drug use evaluation on the wards by AB officer at least 1 drug/annually	3.8	3.5	3.9	3.5	14.7	3.5	4.1	7.6
Drug use	Total annual antibacterial (ATC J01) consumption for monitoring local temporal trend	2.7	3.9	4.4	3.8	14.8	4.4	4.7	9.1
	Cumulative incidence of surgical interventions with postoperative surgical site infection	4.2	2.8	3.6	3.7	14.2	3.6	2.9	6.5
	Percentage of consumption IV versus IV + oral	3.1	2.6	4.6	3.8	14.1	4.1	3.9	8.0
	Ratio between broad-spectrum beta-lactam versus non-broad-spectrum beta-lactams per discipline	2.9	3.4	3.8	3.5	13.7	3.6	3.7	7.3

*Indicators with the highest value ranking scores considered as key elements of an antimicrobial stewardship programme

**Indicators with high value ranking scores but redundant compared with similar indicators

Table 3 Overview of scores for the 11 acute hospitals in the structural indicator survey

Dimension	Score for all potential indicators (=58) per hospital											Max. total score	Score for key indicators (=10) per hospital											Max. key indicator score
	A	B	C	D	E	F	G	H	I	J	K		A	B	C	D	E	F	G	H	I	J	K	
Services	5	6	6	6	9	10	10	6	4	6	10	12	1	2	1	2	3	3	3	2	2	2	2	3
Tools	13	14	11	10	8	10	14	8	8	8	7	16	4	4	3	3	4	3	4	2	3	1	1	4
Human resources and mandate	4	6	3	6	6	5	6	4	2	3	2	6	2	2	1	2	2	2	2	1	1	2	1	2
Personnel development	2	4	4	3	3	4	3	3	2	3	4	4	0	1	1	1	1	1	1	1	0	1	1	1
Basic diagnostic	4	5	3	3	2	6	5	4	4	3	5	6												—
Microbiological rapid tests	1	2	2	2	2	2	2	2	2	2	2	2												—
Microbiological data evaluation	3	3	3	3	3	3	3	3	3	3	3	3												—
Antibiotic consumption controlling	4	5	5	0	5	5	4	5	5	4	5	5												—
Drug use	3	2	3	0	1	2	3	3	3	0	3	4												—
Total	39	47	40	33	39	47	50	39	33	32	41	58	7	9	6	8	10	9	10	6	6	6	5	10

Discussion

An extensive list of 58 potential structure quality indicators was selected as being useful for the assessment of the comprehensiveness and resource-intensity of antibiotic stewardship programmes. The extensive list offers hospitals a tool to characterise and evaluate the activities and resources of the local programme. As we were aware that indicators ought to be few and simple to be used in practice, we have identified a set of ten key indicators as recommended for monitoring the effective deployment of antimicrobial stewardship programmes in acute care hospitals. The top-ten key structure indicators focus on the availability of an antibiotic formulary and guidelines for the provision of a formal mandate for a multi-disciplinary AMT which would be able to deliver bedside antibiotic advice, educate prescribers and audit compliance with local clinical guidelines. To strengthen the AMT decisions, one of the team members should also be present on the drugs and therapeutics committee.

One can presume that the selected indicators seem to be already implemented in most hospitals, but the literature shows the opposite. A survey in 32 European hospitals showed that 52 % of the hospitals had no antibiotic committee and 23 % had no antibiotic formulary [18]. A survey of infectious diseases physician members of the Infectious Diseases Society of America Emerging Infections Network (IDSA EIN) revealed that 27 % of respondents reported that their institutions did not have or were not planning an antibiotic stewardship programme. Lack of funding and lack of personnel were reported as major barriers to implement a programme. A recent Policy Statement on Antimicrobial Stewardship by the Society for Healthcare Epidemiology of America (SHEA), the IDSA and the Pediatric Infectious Diseases Society (PIDS) outlines recommendations for the mandatory implementation of antimicrobial stewardship throughout health care, suggests process and outcome measures to monitor these interventions, and addresses deficiencies in education [19]. Another survey in Belgium demonstrated a well-developed structure of AMTs in hospitals and a broad range of services provided [16]. The Belgian experience showed that the mandatory implementation of antimicrobial stewardship programmes in hospitals and the yearly mandatory review of structure indicators was the key to the extensive implementation of antimicrobial stewardship programmes across the national hospital care system. Also, the Scottish Antimicrobial Prescribing Group (SAPG) has demonstrated that the implementation of regularly reviewed national prescribing indicators, acceptable to clinicians, implemented through regular systematic measurement, can drive improvement in the quality of antibiotic use in key clinical areas [20].

In this article, we describe the development of structure indicators for assessing antimicrobial stewardship programmes. The project "Implementing antibiotic strategies (ABS) for appropriate use of antibiotics in hospitals in member states of the European Union—ABS International" validated also process indicators for evaluating surgical antibiotic prophylaxis (indication, drug choice, timing

and duration of administration) and process indicators for antibiotic therapy: (1) management of community-acquired pneumonia (blood culture and *Legionella* antigen tests and drug choice for empirical treatment); (2) management of *Staphylococcus aureus* bacteraemia (echocardiography, IV catheter removal and duration of effective therapy) and (3) IV-PO switch for treatment with fully bio-available antibiotics [4, 21, 22].

Less focus was given on outcome indicators which were perceived to fall outside the scope of the validation in the ABS feasibility study. Nathwani et al. noted that "measurement for improvement is not focussed on judging whether data meet a compliance threshold or target but rather is a means of determining whether the changes we make to improve are effective and to what degree" [20]. Outcome indicators are, indeed, necessary to measure this. Recently, McGowan Jr et al. stated that antimicrobial stewardship programmes are associated with desirable outcomes for clinical care and cost reduction, but that less evidence exists for reduction in antibiotic resistance as a result of antimicrobial stewardship programmes and for their costeffectiveness [23]. They also focussed on the methodological problems in assessing outcomes, which are barriers in developing evidence-based outcome indicators.

Since the performance of the ABS study, other studies on indicators for assessing antimicrobial stewardship programmes have been published. The SAPG has developed prescribing indicators for hospital and primary care [24]. Improvement in compliance with the indicators has been demonstrated with resultant reductions in *Clostridium* difficile infection rates. In 2007, New South Wales Therapeutic Advisory Group (NSWTAG) developed a set of process indicators to measure the quality use of medicines (QUM) in Australian hospitals in collaboration with the NSW Clinical Excellence Commission (CEC) [25]. As part of the European Commission concerted action Antibiotic Resistance Prevention and Control (ARPAC) Project, data on antibiotic stewardship were collected and relationships investigated by antibiotic consumption in European hospitals using antibiotic stewardship indicators with focus on the structure, design and content of written hospital antibiotic policies and formularies [18]. Policies and practices relating to antibiotic stewardship varied considerably across European hospitals. A ten-member expert panel from Canada and the United States defined five quality metrics for antimicrobial stewardship programmes with focus on process and outcome indicators from three domains including antimicrobial consumption, antimicrobial resistance and clinical effectiveness [26].

Participants of the pilot validation survey had developed a local antibiotic stewardship programme with dedicated resources and provided a wide range of education, evaluation and regulation tools for local prescribers. In particular, 10 out of the 11 centres had local multi-disciplinary practice guidelines for antibiotic prophylaxis and therapy, and seven centres had already performed clinical audit of these

guidelines. There was significant heterogeneity among participating centres with regard to their scoring for structural components of effective antibiotic stewardship, which ranged from 32 to 50 out of the maximum score of 58. Hospitals with a lower score for the complete set of indicators also performed poorly for the top-ten key indicators. These findings confirm the results of the previously mentioned surveys in Europe and United States revealing heterogeneity among participating hospitals when considering the implementation of antimicrobial stewardship programmes [18, 27].

Our study has several limitations. The selected indicators were developed by consensus of a multi-disciplinary team of professionals (infectious disease specialists, clinical microbiologists, hospital pharmacists, and quality and health care scientists) from four countries. Although this composition reflects the range of expertise considered to be optimal for the composition of an antibiotic policy group for hospital care, no attempt was made to extend its composition beyond the ABS project group to represent all stakeholders (e.g. government authorities, policy makers, patient platforms) in the field due to the timelines of the project. Therefore, it only reflects the subjective opinion and knowledge of a selfselected group of experts. Here we can also mention that no indicator in the dimension of microbiological rapid test has achieved high ranking which could be explained by the low number of microbiologist participating to the study and the lack of evidence in literature. A second limitation was the methodology used for scoring the scientific validity of quality indicators based on the secondary literature and personal knowledge of the primary literature of the ABS quality indicator team members. A third limitation could be the use of multi-criteria decision analysis to score and rank the quality indicators. Although this methodology was recently also used by Rello et al. for the development of a European care bundle for the prevention of ventilator-associated pneumonia, most studies developing indicators in human medicine used a modified Delphi method [26, 28]. Nevertheless, we can conclude that the different stages are more or less the same comparing the multi-criteria decision analysis and the modified Delphi method like for instance used by Morris et al . Each expert scored each indicator in regard to the chosen items (taken from the literature) and the next stage was to send the individual ranking scores to all experts. Everybody scored the indicators again and, afterwards, there was discussion in the experts' consensus group.

Benchmarking by comparisons between hospitals can be an important stimulus to quality improvement [18, 29]. Variations may reflect real and important variations in actual health care quality, e.g. inappropriate antibiotic use, that merit further investigation and action, but some apparent variation may also arise because of other misleading factors. such as the lack of adjustment for case-mix differences.

We suggest that a selection among the potential structure indicators examined in this study, with focus on the top-ten indicators proposed by the ABS International group, could be used for regular assessment of the extent and strength of hospital antimicrobial stewardship programmes. This can be done by administering questionnaire surveys on a national or international basis. These organisational elements should be seen as part of the hospital patient safety and quality of care system. In order to operate, they should be adequately supported and empowered and funded by health authorities and hospital management. Verification of the actual implementation of these structure indicators may be considered by national or regional health authorities responsible for hospital accreditation.

Conclusion

An international multi-disciplinary team developed and tested 58 potential structure indicators for feasibility across health care settings, of which a minimal set of ten key structure indicators were selected, that may be used for antibiotic stewardship programme monitoring and comparing efforts by health institutions to improve antimicrobial prescribing quality. In this pilot survey in five European countries, there was significant heterogeneity with both the extensive and key indicator results among participating centres.

Transparency declarations

None to declare.

References

1. Council of the European Union (2002) Council recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC). OJEU 45:13–16

2. Allerberger F, Gareis R, Jindrák V, Struelens MJ (2009) Antibiotic stewardship implementation in the EU: the way forward. Expert Rev Anti Infect Ther 7:1175–1183

3. Allerberger F, Lechner A, Wechsler-Fördös A, Gareis R; on behalf of ABS International (2008) Optimization of antibiotic use in hospitals—antimicrobial stewardship and the EU project ABS international. Chemotherapy 54:260–267

4. Buyle FM, Metz-Gercek S, Mechtler R, Kern WV, Robays H, Vogelaers D, Struelens MJ; Antibiotic Strategy International— ABS Quality Indicators Team (2012) Prospective multicentre feasibility study of a quality of care indicator for intravenous to oral switch therapy with highly bioavailable antibiotics. J Antimicrob Chemother 67:2043–2046

5. Donabedian A (1988) The quality of care. How can it be assessed? JAMA 260:1743–1748

6. Lawrence M, Olesen F (1997) Indicators of quality in health care. Eur J Gen Pract 3:103–108

7. Hoven JL, Haaijer-Ruskamp FM, Vander Stichele RH; DURQUIM Scientific Committee (2005) Indicators of prescribing quality in drug utilisation research: report of a European meeting (DURQUIM, 13-15 May 2004). Eur J Clin Pharmacol 60:831–834

8. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America (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 44:159–177

9. MacDougall C, Polk RE (2005) Antimicrobial stewardship programs in health care systems. Clin Microb Rev 18:638–656

10. Sourdeau L, Struelens MJ, Peetermans WE, Costers M, Suetens C; Hospital Care Working Group of Belgian Antibiotic Policy Coordination Committee (BAPCOC) (2006) Implementation of antibiotic management teams in Belgian hospitals. Acta Clin Belg 61:58–63

11. Davey P, Brown E, Fenelon L, Finch R, Gould I, Hartman G, Holmes A, Ramsay C, Taylor E, Wilcox M, Wiffen P (2005) Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 19(4):CD003543

12. Knox K, Lawson W, Holmes A (2005) Multidisciplinary antimicrobial management teams and the role of the pharmacist in management of infection. In: Gould IM, van der Meer JWM (eds) Antibiotic policies: theory and practice. Springer US, New York,pp 227–249

13. Nathwani D (1999) How do you measure the impact of an antibiotic policy? J Hosp Infect 43:S265–S268

14. Nathwani D, Gray K, Borland H (2002) Quality indicators for antibiotic control programmes. J Hosp Infect 50:165–169

15. Struelens MJ, Costers M; Belgian Antibiotic Policy Coordination Committee (BAPCOC)-Hospital Care Working Group (2008) Hospital antibiotic management in Belgium—results of the ABS maturity survey of the ABS International group. Wien Klin Wochenschr 120:284–288

16. Van Gastel E, Costers M, Peetermans WE, Struelens MJ; Hospital Medicine Working Group of the Belgian Antibiotic Policy Coordination Committee (2010) Nationwide implementation of antibiotic management teams in Belgian hospitals: a selfreporting survey. J Antimicrob Chemother 65:576–580

17. Schouten JA, Hulscher ME, Wollersheim H, Braspennning J, Kullberg BJ, van der Meer JW, Grol RP (2005) Quality of antibiotic use for lower respiratory tract infections at hospitals: (how) can we measure it? Clin Infect Dis 41:450–460

18. Bruce J, MacKenzie FM, Cookson B, Mollison J, van der Meer JW, Krcmery V, Gould IM; ARPAC Steering Group (2009) Antibiotic stewardship and consumption: findings from a pan-European hospital study. J Antimicrob Chemother 64:853–860

19. Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; Pediatric Infectious Diseases Society (2012) Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol 33:322–327

20. Nathwani D, Sneddon J, Malcolm W, Wiuff C, Patton A, Hurding S, Eastaway A, Seaton R, Watson E, Gillies G; Scottish Antimicrobial Prescribing Group (2011) Scottish Antimicrobial Prescribing Group (SAPG): development and impact of the Scottish National Antimicrobial Stewardship Programme. Int J Antimicrob Agents 38:16–26

21. Kern WV, Metz-Gercek S, Buyle F, Jindrak V, Lechner A, Mittermayer H, Seifert H, Wechsler-Fördös A, Wenisch C, Zupanc-Leijko T, Mechtler R, Struelens M (2009) Staphylococcus aureus bloodstream infection management indicators as quality indicators for hospital antibiotic stewardship: feasibility study by the ABS International Quality Indicators (ABS QI) team. Abstract of the 19th European Congress of Clinical Microbiology and Infectious Diseases, Helsinki, Finland, May 2009. Abstract number P764

22. ABS International Quality Indicators. Available online at: http://www.abs-international.eu/ fileadmin/abs-international/Final Conference_Presentations/6_ABS_International_Quality_indicators_ Struelens.pdf. Accessed 1st December 2012

23. McGowan JE Jr (2012) Antimicrobial stewardship—the state of the art in 2011: focus on outcome and methods. Infect Control Hosp Epidemiol 33(4):331–337

24. Malcolm W, Nathwani D, Davey P, Cromwell T, Patton A, Reilly J, Cairns S, Bennie M (2013) From intermittent antibiotic point prevalence surveys to quality improvement: experience in Scottish hospitals. Antimicrob Resist Infect Control 2(1):3

25. NSW Therapeutic Advisory Group Inc., Clinical Excellence Commission. Indicators for quality use of medicines in Australian hospitals, Version 1, 2007. Available online at: http:// www.ciap.health.nsw.gov.au/nswtag/reviews/indicators.html

26. Morris AM, Brener S, Dresser L, Daneman N, Dellit TH, Avdic E, Bell CM (2012) Use of a structured panel process to define quality metrics for antimicrobial stewardship programs. Infect Control Hosp Epidemiol 33:500–506

27. Dumartin C, Rogues AM, Amadeo B, Pefau M, Venier AG, Parneix P, Maurain C (2011) Antibiotic stewardship programmes: legal framework and structure and process indicator in Southwestern French hospitals, 2005–2008. J Hosp Infect 77:123–128

28. Rello J, Lode H, Cornaglia G, Masterton R; VAP Care Bundle Contributors (2010) A European care bundle for prevention of ventilator-associated pneumonia. Intensive Care Med 36:773–780

29. Pope SD, Dellit TH, Owens RC, Hooton TM; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America (2009) Results of survey on implementation of Infectious Diseases Society of America and Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Infect Control Hosp Epidemiol 30:97–98

CHAPTER 4: A SURVEY OF BETA-LACTAM ANTIBIOTICS AND VANCOMYCIN DOSING STRATEGIES IN INTENSIVE CARE UNITS AND GENERAL WARDS IN BELGIAN HOSPITALS

A survey of beta-lactam antibiotics and vancomycin dosing strategies in intensive care units and general wards in Belgian hospitals

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Abstract

Extended and continuous infusions with betalactam antibiotics have been suggested as a means of pharmacokinetic and pharmacodynamic optimisation of antimicrobial therapy. Vancomycin is also frequently administered in continuous infusion, although more for practical reasons.

A survey was undertaken to investigate the recommendations by the local antibiotic management teams (AMTs) in Belgian acute hospitals concerning the administration (intermittent, extended or continuous infusion) and therapeutic drug monitoring of four beta-lactam antibiotics (ceftazidime, cefepime, piperacillin–tazobactam, meropenem) and vancomycin for adult patients with a normal kidney function.

A structured questionnaire survey comprising three domains was developed and approved by the members of the Belgian Antibiotic Policy Coordination Committee (BAPCOC). The questionnaire was sent by e-mail to the official AMT correspondents of 105 Belgian hospitals, followed by two reminders.

The response rate was 32 %, with 94 %, 59 %, 100 %, 100 % and 100 % of the participating Belgian hospitals using ceftazidime, cefepime, piperacillin tazobactam, meropenem and vancomycin, respectively. Comparing intensive care unit (ICU) with non-ICU wards showed a higher implementation of extended or continuous infusions for ceftazidime (81 % vs. 41 %), cefepime (35 % vs. 10 %), piperacillin–tazobactam (38 % vs. 12 %), meropenem (68 % vs. 35 %) and vancomycin (79 % vs. 44 %) on the ICU wards. A majority of the hospitals recommended a loading dose prior to the first dose. For vancomycin, the loading dose and the trough target concentration were too low based on the current literature.

This survey shows that extended and continuous infusions with beta-lactams and vancomycin are widely implemented in Belgian hospitals.

Introduction

Beta-lactam antibiotics and vancomycin are commonly used to treat severe infections. Beta-lactams exhibit timedependent killing, with minimal or no persistent effects. The time during which the free concentration remains above the minimum inhibitory concentration (MIC) (fT >MIC) is their main pharmacokinetic/pharmacodynamic (PK/PD) index of efficacy. Vancomycin also has timedependent killing, but shows moderate to prolonged persistent effects, which makes the area under the concentration– time curve (AUC)/MIC ratio its main PK/PD index for efficacy [1].

Time-dependent killing antibiotics would, theoretically, benefit from continuous administration, and animal as well as in vitro studies have shown improved efficacy when using extended or continuous infusions [1]. A systematic review concluded that the continuous administration of beta-lactam antibiotics is not associated with an improvement in clinical cure or in decreased mortality, but the authors pointed out that the wide confidence intervals observed in this analysis did not allow excluding true differences between both forms of administration [2]. A systematic review focusing on continuous versus intermittent infusion of vancomycin showed that continuous infusion is not associated with differences in mortality but with a significantly lesser risk of nephrotoxicity [3]. Wysocki et al. also found that target concentrations were reached faster with continuous infusion and that there was lesser variability in the AUC24h values [4].

In this context, a survey was undertaken in Belgium to gain knowledge about which recommendations were made by the local Antibiotic Management Teams (AMTs) regarding dosing strategy (intermittent, extended or continuous infusion) and therapeutic drug monitoring of four betalactam antibiotics (ceftazidime, cefepime, piperacillin–tazobactam, meropenem) and vancomycin in adult patients with a normal kidney function.

Methods

A structured questionnaire survey covering three domains was developed: (1) hospital and contact information; (2) a form for each antibiotic about the dosing regimen, indications, use of therapeutic drug monitoring (TDM), type of administration (roller clamp, volumetric pump, syringe pump) and volume of infusion; (3) literature references or other information on which these regimens were based. The respondents could enter the AMT's recommendations for each antibiotic's (intermittent, extended or continuous infusion) unit doses (for intermittent administration) and loading (if applicable) and maintenance doses (for extended and continuous infusion); type of patients involved (all patients, intensive care patients, patients with a specific pathogen); therapeutic drug monitoring and the corresponding target concentration(s).

The study questionnaire was revised through pilot testing and was approved by the Belgian Antibiotic Policy Coordination Committee (BAPCOC) [5]. The questionnaire was sent by email to the official AMT correspondent of each involved Belgian hospital (n=105) on March 25th 2011, with reminders on April 21st and May 9th 2011. The respondents could send back the questionnaire by e-mail or post.

Results

Thirty-four (32 %) responses were received, of which 27 (79 %) were from general and 7 (21 %) were from university hospitals. Ten (29 %) hospitals indicated to have less than 300 beds, 13 (38 %) had between 300 and 600, and 11 (32 %) had more than 600. The numbers of intensive care unit (ICU) beds ranged from 6 to 96. The questionnaires were completed by medical specialists in infectiology, pneumology or intensive care medicine (n=16), in clinical microbiology (n=10) or by clinical pharmacists (n=11) on behalf of the AMT.

The recommendations for the administration of betalactams and vancomycin are shown in Table 1. Ceftazidime, piperacillin–tazobactam, meropenem and vancomycin were used in almost all hospitals.

Table 1. Recommendations for administration of four betalactam antibiotics and vancomycin: ICU versus non-ICU

		Non ICU				ICU			
		Intermittent infusions	Prolonged infusions		Combination	Intermittent infusions	Prolonged infusions		Combination
	N	II (%)	EC (%)	CI (%)	II/CI (%)	II (%)	EC (%)	CI (%)	II/CI (%)
ceftazidime	32	19 (59)	0 (0)	13 (41)	0 (0)	6 (19)	0 (0)	26 (81)	0 (0)
cefepime	20	18 (90)	1 (5)	1 (5)	0 (0)	13 (65)	5 (25)	2 (10)	0 (0)
piperacillin-tazobactam	34	30 (88)	4 (12)	0 (0)	0 (0)	21 (62)	12 (35)	1 (3)	0 (0)
meropenem	34	22 (65)	11 (32)	1 (3)	0 (0)	11 (32)	22 (65)	1 (3)	0 (0)
vancomycin	34	19 (56)	0 (0)	12 (35)	3 (9)	7 (20)	0 (0)	24 (71)	3 (9)

II: intermittent infusion; EC: extended infusion; CI: continuous infusion

Considering the non-ICU wards, the main recommendations were: (i) for ceftazidime: almost equal distribution between intermittent administration or continuous infusion (no hospital used extended infusion); (ii) for piperacillin–tazobactam and meropenem: mainly by intermittent infusion and, if not, by extended infusion only (meropenem was used by continuous infusion in one hospital only); (iii) for cefepime: mainly by intermittent infusion and, if not, by continuous infusion only; (iv) for vancomycin: about two-thirds by intermittent infusion and one-third by continuous infusion. Moving now to ICU wards, we see that: (i) continuous infusion was the predominant mode of administration

for ceftazidime and vancomycin; (ii) extended infusion was most often recommended for meropenem (four hospitals mentioning that it was for infections with multidrug-resistant pathogens; one hospital recommended continuous infusion); (iii) intermittent administration remained predominant for cefepime and piperacillin–tazobactam, with extended infusion being the next most popular recommendation (continuous infusion was also recommended by several hospitals for cefepime, but by only one hospital for piperacillin–tazobactam).

The recommended dosing regimens for each mode of administration of each antibiotic are shown in Table 2.

Table 2. Recommended dosing regimens for intermittent, prolonged and continuous infusions.

	Intermittent	Prolonged	Continuous
ceftazidime	2 g q8h/30 min		2 g/30min loading dose + 6 g q24h/24h
cefepime	1 g q8h/30 min 2 g q8h/30 min	2 g q8h/3h	2 g/30min loading dose + 2 g q8/8h 2 g/30min loading dose + 6 g q24/24h
piperacilline tazobactam	4/0.5 g q8h/30 min 4/0.5 g q6h/30 min	4/0.5 g q6h/3h 4 g/0.5g /30min loading dose + 4/0.5 g q6h/3h	16g/2g q24h/24h
meropenem	0.5 q6h/30min 1 g q8h/30 min 1 g/30 min loading dose + 0.5 g q4h/30 min 2 g q8h/30 min	1 g q8h/3h 1 g/30 min loading dose + 1 g q8h/3h 2 g/30 min loading dose + 1 g q8h/3h 2 g q8h/3h 2 g/30 min loading dose + 2 g q8h/3h	1 g/30 min loading dose + 1 g q6h/6h
vancomycin	15 mg/kg q12h/1h 20 mg/kg q12h/1h		15 mg/kg /2h loading dose + 30 mg/kg q24h/24h 20 mg/kg /2h loading dose + 30 mg/kg q24h/24h

For the intermittent administration of beta-lactams, the most recommended daily doses were rather fixed for ceftazidime (6 g) and piperacillin–tazobactam (12–16 g), but variable for cefepime (3 to 6 g) and meropenem (2 to 6 g). For prolonged infusion (always limited to 3 h), similar daily doses as in the intermittent mode of administration were recommended for cefepime, piperacillin–tazobactam and meropenem, with a loading dose recommended only for the latter two antibiotics. For continuous infusion, a loading dose (usually corresponding to the normal unit dose of an intermittent administration) was recommended for ceftazidime, cefepime and meropenem, but not for piperacillin–tazobactam, while the maintenance dose corresponded, essentially, to the total daily dose of the

intermittent administration mode. For vancomycin, the dose recommended was 15 to 20 mg/kg for its intermittent mode of administration and 30 mg/kg over 24 h preceded by a loading dose corresponding to what was recommended for intermittent administration for its continuous administration.

With respect to practical aspects of continuous infusion administration of cefepime and meropenem, one hospital prepared syringes with 2 g of cefepime to be administered over an 8-h period, but another hospital prepared syringes with 6 g cefepime for use over 24 h, whereas meropenem was usually prepared in a syringe containing 1 g of antibiotic to be administered over 6 h.

Concerning monitoring, all hospitals assayed vancomycin, recommending trough serum levels between 5 and 20 mg/L for intermittent administration and stable serum levels between 15 and 25 mg/L (two hospitals) and 20–30 mg/L (19 hospitals) for continuous infusion. One hospital was measuring the serum concentrations of meropenem.

Most of the participants did not provide data concerning the devices used for administration or infusion volumes. One hospital, however, mentioned a switch from an extended to an intermittent (loading dose of 1 g followed by 500 mg q6h) meropenem infusion after the observation of 40 % loss of the antibiotic dose due to line dead space [6, 7].

The hospitals based their recommendations on the scientific literature (65%), an opinion leader (59%), information from a university hospital (53%), the "Sanford guide to antimicrobial therapy" (35%) or summaries of product characteristics (SmPCs) (4%) [8–10].

Discussion

To our knowledge, this survey represents the first attempt to describe the implementation of extended and continuous infusions in hospitals at a national level in Europe. The adoption of continuous and extended infusion regimens for beta-lactams was variable and largely depended on the antibiotic, but it is remarkable that the implementation of these modes of administration was between 10 % and 44 % for the non-ICU wards and between 35 % and 81 % for the ICU wards. These modes of administration can, therefore, no longer be ignored. Actually, continuous infusion is included as an accepted mode of administration for both ceftazidime and vancomycin in the SmPCs of the corresponding branded products in Belgium (Glazidim® and Vancocin®), as well as in the Belgian edition of the "Sanford guide to antimicrobial therapy" [8–10]. The higher level of adoption in ICUs is consistent with the literature, suggesting that prolonged beta-lactam infusions are advantageous for infections with more resistant pathogens, in critically ill and immunocompromised patients, and in patients with unreliable pharmacokinetics [11].

A loading dose prior to the initiation of the extended or continuous infusion is essential to shorten the time needed for obtaining a steady-state concentration at the targeted level [12, 13]. This was not always recommended for betalactams, which is most unfortunate, because a simple but effective approach is simply to use the normal initial dose recommended for intermittent dosing. Studies have stressed the importance of using a sufficiently large loading dose of vancomycin when using continuous infusion to avoid insufficiënt drug concentrations in the early phase of therapy [14–16]. Even for the intermittent mode of administration, the Infectious Diseases Society of America (IDSA) consensus recommendations suggest a loading dose of 25–30 mg/ kg in order to rapidly reach the desired target serum concentration [17]. Of note, this loading dose should be administered over at least 1 h (or even 2 h if the dose is 2 g) to avoid a "red man" syndrome. This was taken into account by all hospitals recommending continuous infusion, but not by those recommending intermittent administration.

Serum concentrations for beta-lactam antibiotics were not measured (except in one hospital). A recent study shows that standard dosing regimens for piperacillin–tazobactam, ceftazidime and cefepime may lead to serum concentrations insufficient to cover less susceptible pathogens in the early phase of severe sepsis and septic shock [18]. But optimal targets for beta-lactam therapy remain controversial [19]. Low trough drug concentrations in critically ill patients seem to be associated with increased renal clearance, suggesting that TDM could be useful for this type of patient [20]. For vancomycin, the trough serum levels (5–20 mg/L) recommended by the participating hospitals are too low to achieve an AUC/MIC ratio of ≥400 in most patients if the MIC of vancomycin for the target organism is ≥1 mg/L [17]. For continuous infusion, optimal serum levels are less clearly defined, with targets of 15–20, 20–25 and 25–30 mg/L mentioned in the literature [4, 17, 21, 22]. These should cover organisms with a vancomycin MIC up to 1 and 2 mg/ L for the lowest and largest targets, respectively. Should organisms with a vancomycin MIC > 2 mg/L become frequent [these organisms should be reported as resistant according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretative criteria], we may face a severe limitation in our therapeutic approach with this antibiotic, because stable concentrations > 28 mg/L (needed to obtain a satisfactory AUC/MIC ratio) have been associated with a significant increase in renal toxicity [23]. Nevertheless, a meta-analysis shows that continuous vancomycin infusion is associated with a significantly lower risk of drug-related nephrotoxicity compared with intermittent infusions with the same daily dose [3]. As there is a tendency to use higher vancomycin dosages, it is important to determine their impact on drug-related toxicity [24, 25].

Antibiotic stability and incompatibility with other drugs are important considerations in the implementation of prolonged infusions. Piperacillin–tazobactam, ceftazidime and vancomycin are stable for at least 24 h at 25 °C, but concentrated solutions of cefepime quickly change in colour [26]

and meropenem is unstable [27, 28]. Several drugs incompatibilities have been described [9]. Vancomycin is incompatible with all beta-lactams, and both beta-lactams and vancomycin are incompatible with propofol [9]. In ICU wards, the problem can easily be avoided, as most patients have multiple-lumen catheters, but this may not be the case in non-ICU wards, where most patients have single-lumen catheters.

A first limitation of the study is the low response rate (32 %), which questions the generalisability of our conclusions. However, all hospital types, based on the number of beds and academic profile, were represented. A second limitation is that no valid information was obtained on the mode of administration or infusion volume. Implementing prolonged infusions can have important practical implications, such as the availability of syringe pumps, multi-lumen catheters (to avoid direct drug interferences) and appropriate control of the amount of antibiotic effectively delivered.

It is clear that the Belgian AMTs are in favour of prolonged infusions. However, there is much variation in the recommended dosing regimens, especially for meropenem, which reflects the variability in the literature data (Table 2). It is important to emphasise that AMTs have the responsibilities to support their recommendations for continuous and/or extended infusions of antibiotics with clear guidelines for appropriate administration (doses, schedules, stability, incompatibility) to allow their safe and easy implementation by physicians, nurses and clinical pharmacists.

Conclusion

This survey showed that extended and continuous infusion of ceftazidime, cefepime, piperacillin–tazobactam, meropenem and vancomycin are widely implemented in Belgian hospitals. For intensive care unit (ICU) wards, a majority of the hospitals recommended ceftazidime and vancomycin in continuous and meropenem in prolonged infusions. For non-ICU wards, ceftazidime, meropenem and vancomycin were frequently used in continuous and/or prolonged infusions, despite the lack of evidence of clinical advantage for non-critical patients. Conversely, cefepime and piperacillin–tazobactam are mostly used as intermittent administration. A majority of the hospitals recommended a loading dose prior to the first dose. For vancomycin, the recommended loading dose and trough target serum concentrations were too low if considering the current literature data.

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Conflict of interest

The authors declare that they have no conflict of interest.

Transparency declarations

None to declare.

References

1. Craig WA (2003) Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am 17:479–501

2. Roberts JA, Webb S, Paterson D, Ho KM, Lipman J (2009) A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics. Crit Care Med 37:2071–2078

3. Cataldo MA, Tacconelli E, Grilli E, Pea F, Petrosillo N (2012) Continuous versus intermittent infusion of vancomycin for the treatment of Gram-positive infections: systematic review and meta-analysis. J Antimicrob Chemother 67:17–24

4. Wysocki M, Delatour F, Faurisson F, Rauss A, Pean Y, Misset B, Thomas F, Timsit JF, Similowski T, Mentec H, Mier L, Dreyfuss D (2001) Continuous versus intermittent infusion of vancomycin in severe staphylococcal infections: prospective multicenter randomized

study. Antimicrob Agents Chemother 45:2460–2467

5. Van Gastel E, Costers M, Peetermans WE, Struelens MJ; Hospital Medicine Working Group of the Belgian Antibiotic Policy Coordination Committee (2010) Nationwide implementation of antibiotic management teams in Belgian hospitals: a selfreporting survey. J Antimicrob Chemother 65:576–580

6. Claus B, Buyle F, Robays H, Vogelaers D (2010) Importance of infusion volume and pump characteristics in extended administration of β-lactam antibiotics. Antimicrob Agents Chemother 54:4950

7. Geggie D, Moore D (2007) Peripheral line dead space: an unrecognised phenomenon? Emerg Med J 24:558–559

8. Sanford JP, Gilbert D, Chambers H, Eliopoulos GM, Moellering R, Saag M (2010) The Sanford guide to antimicrobial therapy, 2010–2011, 22nd edn. Belgian/Luxembourg version. Belgian/Luxembourg Working Party on Antimicrobial Therapy. ISBN 978-1-930808-63-3

9. Federal Agency for Medicines and Health Products (FAMHP) Summary of product characteristics (SPC) for vancocin. Available online at: http://bijsluiters.fagg-afmps.be/. Accessed 1 Oct 2012

10. Federal Agency for Medicines and Health Products (FAMHP) Summary of product characteristics (SPC) for glazidim. Available online at: http://bijsluiters.fagg-afmps.be/. Accessed 1 Oct 2012

11. Van Herendael B, Jeurissen A, Tulkens PM, Vlieghe E, Verbrugghe W, Jorens PG, Ieven M (2012) Continuous infusion of antibiotics in the critically ill: the new holy grail for betalactams and vancomycin? Ann Intensive Care 2:22

12. Mouton JW, Vinks AA (2007) Continuous infusion of betalactams. Curr Opin Crit Care 13:598–606

13. Roberts JA, Kirkpatrick CM, Roberts MS, Dalley AJ, Lipman J (2010) First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis. Int J Antimicrob Agents 35:156–163

14. Ocampos-Martinez E, Penaccini L, Scolletta S, Abdelhadii A, Devigili A, Cianferoni S, de Backer D, Jacobs F, Cotton F, Vincent JL, Taccone FS (2012) Determinants of early inadequate vancomycin concentrations during continuous infusion in septic patients. Int J Antimicrob Agents 39:332–337

15. Truong J, Levkovich BJ, Padiglione AA (2012) Simple approach to improving vancomycin dosing in intensive care: a standardised loading dose results in earlier therapeutic levels. Intern Med J 42:23–29

16. Li J, Udy AA, Kirkpatrick CM, Lipman J, Roberts JA (2012) Improving vancomycin prescription in critical illness through a drug use evaluation process: a weight-based dosing intervention study. Int J Antimicrob Agents 39:69–72

17. Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr, Craig W, Billeter M, Dalovisio JR, Levine DP (2009) Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 66:82–98

18. Taccone FS, Laterre PF, Dugernier T, Spapen H, Delattre I, Wittebole X, De Backer D, Layeux B, Wallemacq P, Vincent JL, Jacobs F (2010) Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. Crit Care 14:R126

19. Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, Lipman J (2010) Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents 36:332–339

20. Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BC, Ungerer JP, Lipman J, Roberts JA (2012) Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 142:30–39

21. Pea F, Furlanut M, Negri C, Pavan F, Crapis M, Cristini F, Viale P (2009) Prospectively validated dosing nomograms for maximizing the pharmacodynamics of vancomycin administered by continuous infusion in critically ill patients. Antimicrob Agents Chemother 53:1863–1867

22. Carricajo A, Forgeot A, Morel J, Auboyer C, Zeni F, Aubert G (2010) Dosage adjustment of vancomycin in continuous infusion in critically-ill patients. Ann Fr Anesth Reanim 29:55–57

23. Spapen HD, Janssen van Doorn K, DiltoerM, VerbruggheW, Jacobs R, Dobbeleir N, Honoré PM, Jorens PG (2011) Retrospective evaluation of possible renal toxicity associated with continuous infusion of vancomycin in critically ill patients. Ann Intensive Care 19:26

24. Ingram PR, Lye DC, Tambyah PA, Goh WP, Tam VH, Fisher DA (2008) Risk factors for nephrotoxicity associated with continuous vancomycin infusion in outpatient parenteral antibiotic therapy. J Antimicrob Chemother 62:168–171

25. Gupta A, Biyani M, Khaira A (2011) Vancomycin nephrotoxicity: myths and facts. Neth J Med 69:379–383

26. Baririan N, Chanteux H, Viaene E, Servais H, Tulkens PM (2003) Stability and compatibility study of cefepime in comparison with ceftazidime for potential administration by continuous infusion under conditions pertinent to ambulatory treatment of cystic fibrosis patients and to administration in intensive care units. J Antimicrob Chemother 51:651–658

27. Kuti JL, Nightingale CH, Knauft RF, Nicolau DP (2004) Pharmacokinetic properties and stability of continuous-infusion meropenem in adults with cystic fibrosis. Clin Ther 26:493–501

28. Berthoin K, Le Duff CS, Marchand-Brynaert J, Carryn S, Tulkens PM (2010) Stability of meropenem and doripenem solutions for administration by continuous infusion. J Antimicrob Chemother 65:1073–1075

CHAPTER 5: TIME TO FIRST ANTIBIOTIC DOSE FOR ADULT PATIENTS ADMITTED TO THE EMERGENCY DEPARTMENT BEFORE AND AFTER TARGETED INTERVENTIONS

Time to first antibiotic dose for adult patients admitted to the emergency department before and after targeted interventions

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Abstract

Background

The time to first antibiotic dose (TFAD) defined as the time in hours from arrival of the patient at the emergency department (ED) to the administration of the first antibiotic dose is described in the literature as a quality indicator for the treatment of infections. This indicator was evaluated in our institution followed by educational interventions in order to optimize TFAD.

Methods

In this retrospective observational single hospital study, the TFAD for adult patients with a diagnosis of an infection in the ED for which an antibiotic treatment was prescribed and who stayed for at least 2 days in hospital were compared before and after the implementation of corrective interventions (period A versus B) .

A multivariate model was set up to detect key factors associated with TFAD. The following factors were entered in the model: age, gender, LOS, CRP, APACHE II score, place of first administration, type of infection.

Results

Sixty-five patients were included in period A and 114 patients in period B. In period A, 46 (71%) patients received the first dose in the ED, versus 91 (80%) patients in group B (p=0.200). The other patients received the first dose after transfer to the ward.

The univariate analysis showed that the median TFAD in period A was 2.44 hours (IQR 1.78-4.19) versus 3.30 hours (IQR 2.40-4.50) in period B (p=0.034). The median TFAD when the first dose was administered in the ED was 2.14 hours in period A versus 3.2 hours in period B (p<0.001). When the first dose was administered on the ward the TFAD was 4.56 hours in period A and 4.26 hours in period B (p=0.535)

The multivariate analysis showed no difference for TFAD between period A and B but showed that the place of the first antibiotic dose and type of infection were significantly associated with TFAD.

Conclusion

In conclusion we demonstrated significant persistent room for improvement for TFAD in infections in patients admitted to the ED, in spite of a targeted intervention.

Introduction

For critically ill patients with septic shock and meningitis data suggest that early administration of antibiotics is associated with higher survival rates (1, 2, 3). Community acquired pneumonia (CAP), usually is less rapidly progressive compared to septic shock and meningitis. There has been a debate over the use of the time to first antibiotic dose (TFAD) as a performance measure.

For severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation) administration of broad-spectrum antimicrobials therapy within 1 hour of recognition is recommended (4). For bacterial meningitis, administration of antimicrobial therapy should be initiated as soon as possible after the diagnosis of bacterial meningitis is suspected or proven. This may include administration prior to hospital admission if the patient initially presents outside the hospital (5).

For pneumonia data are not so straightforwarded. Recently a cross-sectional analysis of 95,704 adult ED admissions with a diagnosis of pneumonia in 530 hospitals in the USA showed no association between the publicly reported TFAD quality measure performance and pneumonia inpatient mortality (6). However in a study of 529 patients with community-acquired pneumonia admitted to the intensive care unit in 33 hospitals, early oxygenation assessment was associated with more rapid antibiotic delivery and better intensive care unit survival reflecting the importance of prompt management, including antibiotic delivery (7).

For CAP the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission or JC) has instituted in 2002, a quality of care standard that evaluates whether pneumonia patients receive their first dose of antibiotics within four hours of hospital arrival (8). In 2006, it became part of a measure set linked to additional payments under several pilot pay-for performance programs in USA hospitals. This standard has been criticized as a quality standard because it put pressure on clinicians to rapidly administer antibiotics despite diagnostic uncertainty at the time of patients' initial presentation. In 2007, the allowed time window was extended to 6 hours in response to this criticism (8).

In 2005 the local Antibiotic Management Group of the Ghent University Hospital evaluated in cooperation with the emergency department (ED) theTFAD for patients with suspected or proven infections admitted to the ED and transferred to a ward for further treatment. Following this evaluation, organizational interventions were implemented to improve timely drug administration. A didactic presentation was once provided in 2006 by an ED physician towards ED physicians and ED nurses, during a regular staff meeting, to emphasize the importance of timely antibiotic administration. Pharmacy collaborators were also educated (once in 2006, 2008 and 2010) by a pharmacist with focus on the clinical impact of delays in pharmacy logistics. This topic is part of a hospital wide training

program on antibiotic skills towards nurses which is provided twice a year by an infectious disease physician and a clinical pharmacist. Another measure consisted of the extension of the ED stock of some frequently prescribed antibiotics as lack of immediate availability of these antibiotics could result in a delayed administration. In 2008-2009 a second study was performed to re-evaluate the TFAD and to analyse the factors that could explain variation in TFAD. In this study we report the retrospective evaluation of this process.

Methods

In this retrospective observational single hospital study, all medical records of patients admitted to the ED between February 28, 2005 and March 22, 2005 (period A) and between December 1, 2008 and January 31, 2009 (period B) were screened. Adult patients (>18 years old) with a diagnosis of an infection on the ED for which an antibiotic treatment was prescribed and who stayed for at least 2 days in hospital were included. Patients who had received antibiotics within 24h before ED arrival were excluded.

TFAD was defined as the time from arrival of the patient at the ED to the administration of the first antibiotic dose. Medical and pharmaceutical charts were reviewed and the data were extracted using a standardized case record paper form (CRF). The following data were collected: gender, type of infection, type of antibiotic, length of stay (LOS), age, APACHE II score, C-reactive protein, place of first antibiotic dose (ED versus ward) and hour of admission on ED.

The APACHE (Acute Physiology And Chronic Health Evaluation) II score or modified APACHE II score (in those patients were not all data were available) were calculated based on clinical parameters.

For period B also the availability of the prescribed antibiotic on ED and the workload on ED was collected. The workload was defined as the number of patients on ED, 4 hours before each admission.

On the ED, antibiotics are stocked in an electronic automated dispensing system (Pyxis Medsystem® station) which allows to register the exact time when the nurse or physician takes out the medication. The time of taking out the antibiotic was used as time point of administration, as the nurse normally administers immediately the antibiotic after removal from the electronic automated dispensing system.

An emergency physician reviewed all medical charts of patients in period B with a TFAD of 6 hours or more in order to assess the reason for the delay.

Data analysis was performed using the Statistical Package for Social Science (SPSS version 20.0 Inc., Chicago, IL, USA). Variables were compared between period A and period B. The categorical variables were compared using the Chi-square test, continuous variables with the Mann–Whitney U-test. The significance level was set at $p < 0.05$.

A multivariate model was set up to detect key factors associated with TFAD. The following factors were entered in the model: age, gender, LOS, CRP, APACHE II score, place of first administration, and type of infection.

The protocol was approved (approval number: B67020095783) by the Ethical Committee of Ghent University Hospital.

Results

Sixty-five patients were included in period A and 114 patients in period B. The patient characteristics for the two study periods were similar except for the APACHE II score (Table 1).
In period A, 46 (71%) patients received the first dose in the ED, versus 91 (80%) patients in group B (p=0.20).

Table 1. Patients characteristics

	Period A (n=65)	Period B (n=114)	P-value
Age, years (median, IQR)	66 (54-74)	66 (52-76)	.842
Sex (male), N (%)	32 (49%)	61 (54%)	.642
Type of infection			
Pulmonary infection, N (%)	45 (69%)	71 (62%)	
Skin infection and others, N (%)	7 (11%)	9 (8%)	.069
Intra-abdominal infections, N (%)	10 (15%)	13 (12%)	
Urinary tract infections, N (%)	3 (5%)	21 (18%)	
LOS	8 (5-13)	8 (6-12)	.269
First antibiotic administration on the ER, N (%)	46 (71%)	91 (80%)	,200
CRP mg/dL on admission (median, IQR)	11 (4-23)	9 (3-17)	.435
APACHE II score (median, IQR)	12 (8-17)	11 (7-13)[a]	.038

a: 19 missing data

The univariate analysis showed that the median TFAD in period A was 2.44 hours (IQR 1.78-4.19) versus 3.30 hours (IQR 2.40-4.50) in period B (p=0.034) (Table 2). The TFAD 95-percentile was in period A respectively 12.76 hours versus 8.25 hours in period B.
The median TFAD when the first dose was administered in the ED was 2.14 hours (IQR 1.41-2.56) in period A versus 3.20 hours (IQR 2.36-4.33) in period B (p<0.001). When the first dose was

administered on the ward the TFAD was 4.56 hours (IQR 4.18-9.39) in period A and 4.26 (IQR 2.60-7.35) hours in period B (p=0.535)

Table 2. Time to first antibiotic dose comparing period A en period B (univariate analysis)

Median TFAD (in hours)	Period A	Period B	p value
Overall (median, IQR)	n=65 2.44 (1.78-4.19)	n=114 3.30 (2.40-4.50)	0.034
first dose in the ED (median, IQR)	n=46 2.14 (1.41-2.56)	n=91 3.20 (2.36-4.33)	<0.001
first dose on the ward (median, IQR)	n=19 4.56 (4.18-9.39)	n=23 4.26 (2.60-7.35)	0.535

After adjustment for age, gender, LOS, CRP, APACHE II score, type of infection and place of first antibiotic administration and period of evaluation, two factors were identified as being associated with TFAD (Table 3). Patients receiving the first antibiotic dose on the ED had a lower TFAD compared with those who received the first dose on a ward. Patients with a pulmonary infection had a lower TFAD compared with patients with an abdominal infection. TFAD was not associated with the period of registration (A and B) and with parameters reflecting the severity of illness (APACHE II score, CRP and LOS). R squared of this multivariable model was 0.276.

In period B, the median workload, expressed as the number of patients on ED 4 hours before each admission, was 6.0 patients (range 0 - 15) which was not statistically correlated with TFAD in an univariate analysis. This variable was not assessed in period A.

For patients receiving the first dose in the ED in period B (n=91), median TFAD was 3.5 hours (range 0.41-7.6 hours) when the antibiotic was available in the ED (n=82) compared to 3.0 hours (range 1.6-5.4 hours) when the antibiotic was not available in the ED (n=9). There was no statistical difference between these two subgroups (p=0.386).

For the patients receiving the first dose on the ward in period B, in 11 (47.8%) patients the antibiotic was available in the ward stock with 4.9 hours as median TFAD (range 2.08-10.9 hours). For 12 (53.3%) patients the antibiotic was not available on the ward with 8.12 hours as median TFAD (range 0.26- 16.75 hours). There was no statistically significant difference between these two subgroups (p=0.193).

For the majority (85%) of the patients in period B the first antibiotic dose was prescribed to be administered intravenously. Amoxicillin/clavulanic acid IV (53.2%), piperacillin/tazobactam IV (10.3%), moxifloxacin PO (8.7%), levofloxacin IV (7.9%), ciprofloxacin PO (6.3%) and moxifloxacin IV (5.5%) were the most frequently prescribed antibiotics.

Thirteen medical charts of patients in period B with a TFAD exceeding 6 hours were reviewed by an emergency physician. In two patients the higher TFAD was linked to diagnostic complexity. In another two patients the initial diagnosis was not clear and antibiotics were only administered after a final diagnosis on the ward. In one patient a referring physician did not order antibiotics in the ED although the patient had a urinary tract infection with a history of sepsis . For 2 patients a written order was found to give the first dose on the ward. For 6 patients, it was not possible to evaluate retrospectively the reason for a higher TFAD.

Table 3. Linear regression model[a] for TFAD

	Estimate	95% CI lower bound	95% CI upper bound	P
Intercept	7.958	5.895	10.002	.000
Period A	-.309	-1.260	.642	.521
Period B	0 [b]	.	.	.
First dose on ER	-3.252	-4.267	-2.236	.000
First dose on ward	0 [b]			
Sex, male	-.219	-1.115	.677	.630
Sex, female	0 [b]	.	.	.
Infection type				
Pulmonary infection	-1.401	-2.798	-.005	.049
Skin infection and others	-.976	-3.147	1.194	.375
Intra-abdominal	0 [b]	.	.	.
Urinary tract	-1.607	-3.359	.145	.072
Age	.005	-.021	.032	.699
LOS	.020	-.046	.086	.559
CRP	.016	-.023	.055	.413
APACHE II score	-.087	-.184	.011	.080

[a] R squared = .276

[b] this parameter is set to zero because it is redundant

Discussion

In this retrospective observational study, the TFAD for adult patients with a diagnosis of an infection in the ED for which an antibiotic treatment was prescribed and who stayed for at least 2 days in hospital were compared before and after the implementation of interventions (period A versus B) .

The study showed that 75% of the patients received their first antibiotic dose within 4.19 hours in period A and within 4.50 hours in period B after admission on the ED. In 5 % of the patients TFAD exceeded 12.7 hours in period A and 8.25 hours in period B which is unacceptable.

Although the univariate analysis suggested that the TFAD was higher in period B versus period A for patients receiving this first dose on the ED, the multivariate analysis showed no difference between the two periods. We can conclude that the interventions in our study did not result in any long term improvement.

In a similar study performed in a Dutch hospital the TFAD was 5.0 h before and 3.2 h after an intervention including the development of guidelines, educational programs (lectures to the medical and nursing staff) and improvement of the availability of antibiotics in the ED in a readily accessible place (9). In another study in the USA, evaluating the TFAD for 2.076 patients with pneumonia admitted in the ED, 78.6% of the patients received antibiotic therapy within 4 hours which is comparable with our results (10).

Even after a teaching intervention, which resulted in a modest increase of antibiotics being delivered in the ED, still one fifth of the patients received the first antibiotic dose only after transfer to a ward in period B. This was not related to the workload in the ED. This is in contradiction with two retrospective studies performed in the USA. In one study including 334 patients, the emergency department occupancy rate was associated with increased time to antibiotic treatment for patients admitted with pneumonia (11). In another retrospective study of 694 patients with pneumonia treated in an ED crowding on ED resulted in more frequent and longer delays in delivering antibiotics (12).
The lack of association between workload and TFAD in our study could be the result of the limited number of patients. Unfortunately the workload on the ED was not measured in period A.

The longer TFAD for patients receiving the first dose on the ward can be the result of a combination of factors. One of the reasons for this delay could be the time needed to transfer the patient from the ED to the ward, but this was not measured in this study. In general nurses administer medication at scheduled times. When the physician not emphasized to administer the first antibiotic dose sooner,

then this could lead to a higher TFAD. A Dutch study showed that more than half of the patients received indeed their first dose at scheduled times (13).

Although there was no significant correlation between TFAD and availability of the prescribed antibiotic on the ward, the TFAD is considerably longer for those patients for whom the antibiotic was not in stock on the ward. One of the reasons for this delay could be the delivery time from the pharmacy to the ward. To limit this delay physicians and nurses were asked to mention the targeted time of administration on the prescription form which allows the pharmacy to give priority to these shipments. Dee et al showed indeed that the main reason for delay in antibiotic administration was failure to label antibiotic orders as first dose (14).

For the patients receiving the first dose in the ED, the availability of the antibiotic in the ED was not linked to a lower TFAD. We can presume that in those cases where the antibiotic was not available in the ED there was a good communication between ED and pharmacy about the emergency for delivery.

The multivariate analysis showed that TFAD was considerably longer for intra-abdominal compared to pulmonary infections. This could be explained by more complex and time consuming diagnostic procedures (i.e. CT scan). The same multivariate analysis did not demonstrate shorter TFAD with higher severity of illness, although this may have been due to the limited sample size.

All frequently prescribed antibiotics, except for piperacillin/tazobactam IV and ciprofloxacin PO, were available in the electronic automated dispensing system on the ED. After the discussion of the results of period B piperacillin/tazobactam IV was also stocked on the ED. Ciprofloxacin PO was not added because levofloxacin PO, being a valid alternative, was already available.

The experience in the USA with a public quality indicator for TFAD of 4 hours in CAP resulted in too rapid administration of antibiotics despite diagnostic uncertainty which illustrates the unintended consequences of the introduction of an indicator linked to accreditation programs. Although the link between early TFAD and clinical outcome is not clear for all type of infections, we agree with Bordon et al that early TFAD should be considered as an important marker of optimal care of patients rather than as a factor predicting outcomes for patients (15).

The results of this study show that further corrective actions are necessary to optimise the number of patients that receive the first antibiotic dose on the ED. This is also recommended in the Infectious Diseases Society of America/American Thoracic Society consensus CAP guideline (16). This was also supported by a Dutch study where the administration of antibiotics in the ED was strongly associated with antibiotic administration within 4 h (17). We emphasize here that the first antibiotic should be

given in the ED as several properties of the ED environment like manpower, the presence of physicians and the availability of antibiotics ensure timely administration.

In order to enhance the number of patients that receive the first antibiotic dose on the ED, we will continue to provide education to nurses, physicians and pharmacy collaborators. For physicians it is important to communicate clearly the time frame of administration of antimicrobials towards (with) the nurses. Performing a structured interview with the key players on the ED could provide information on the barriers to administer timely the first antibiotic dose.

The most frequently used antimicrobial agents on ED are available in the electronic automated dispensing system on the ED. In case other antimicrobial agents are necessary outside the opening hours of the pharmacy (10 pm – 8 am), all antimicrobial agents are available in an emergency cabinet which is 24h/24h accessible for all nurses and physicians. Furthermore the implementation of the computerized physician order entry (CPOE) system will probably optimise the TFAD as there will be no delay in forwarding the antibiotic prescription to the pharmacy. The effect of this intervention could not be assessed in our study due to the limited number of wards that were already using the CPOE system during the study period in our hospital. Actually CPOE is implemented for 90% of the wards which allows the pharmacist to check the hour of administration of each antimicrobial agent prescribed and to give priority for shipment to the ward.

The first limitation of this study is the retrospective design. The hours of administering the antibiotics are based on the time the nurse took the antibiotic out of the Pyxis Medstation which allows us to register the time at the level of minutes. We presume here that this time correlates with the administration of the antibiotic. On the wards we used the nursing file where a cross is placed in an hour time table which is likely to result in a margin error. In this study the delays in diagnostic testing and in consultant advice were not evaluated which is a second limitation for this study. Thirdly it was not possible to evaluate the time between the arrival of the prescription in the pharmacy and the delivery of the antibiotic on the ward which could be one of the reasons for a high TFAD on the wards. The review of the patient files by the emergency physician showed that for 50 % of the patients it was not possible to detect retrospectively reasons for a long TFAD which suggest to perform such evaluations in the future prospectively in order to identify causes for delays. Fourthly most confounders used in the multivariate analysis were linked to the outcome of the patient (age, LOS, CRP, APACHE II score, place of first administration, and type of infection). Ideally also the factor working hours/night was included as Natsch et al showed that the TFAD was significantly shorter in patients admitted at night than in patients admitted during office hours (3.7 vs. 6.0 h) (13).

Fifthly the evaluation of the appropriateness of the antibiotic administration according the guidelines should have been helpful to interpret the relevance of a shorter TFAD. Sixthly in this study we only evaluated the long term improvement. Ideally we performed also a short term evaluation.

In the future we should asses TFAD in a bundle approach including other process indicators like timely oxygenation, obtaining of blood and sputum samples and choice of empiric systemic antimicrobial therapy according local guidelines (17,18).

Conclusion

Seventy five percent of the patients received their first antibiotic dose within 4.19 hours in period A and within 4.50 hours in period B after admission on the ED. Even after a teaching intervention, still 20% of the patients received the first dose only after transfer to a ward. This underscores the need for further interventions aiming at long term improvement.

Conflict of interest

The authors declare that they have no conflict of interest.

Transparency declarations

None to declare.

References

1. Pines JM. Timing of antibiotics for acute severe infections. Emerg Med Clin N Am 2008;26:245-257.

2. Lepur D.; Baršić B. (2007). Communtiy acquired bacterial meningitis in adults: antibiotic timing in disease course and outcome. Infection 2007;35: 225-231

3. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589-96

4. Dellinger P, Levy M, Rhodes et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 Crit Care Med 2013; 41:580–637

5. Tunkel A,Hartman B,Kaplan S, Kaufman B,Roos K,Scheld M,Whitley R, Practice Guidelines for the Management of Bacterial Meningitis. Clin Infect Dis 2004;39:1267–84

6. Quattromani E, Powell ES, Khare RK, Cheema N, Sauser K, Periyanayagam U, Pirotte MJ, Feinglass J, Mark Courtney D. Hospital-reported data on the pneumonia quality measure "Time to First Antibiotic Dose" are not associated with inpatient mortality: results of a nationwide cross-sectional analysis. Acad Emerg Med 2011;18:496-503

7. Blot S, Rodriguez A,Solé-Violán J , Blanquer J, , Almirall J, Rello J, for the Community-Acquired Pneumonia Intensive Care Units (CAPUCI) Study Investigators Effects of delayed oxygenation assessment on time to antibiotic delivery and mortality in patients with severe community-acquired pneumonia. Crit Care Med 2007;35:

8. Wachter RM, Flanders SA, Fee C, Pronovost PJ. Public reporting of antibiotic timing in patients with pneumonia: lessons from a flawed performance measure. Ann Intern Med 2008;149:29-32

9. Natsch S, Kullberg BJ, Meis J, van der Meer J. Earlier initiation of antibiotic treatment for severe infections after interventions to improve the organization and specific guidelines in the emergency department. Arch Intern Med. 2000;160:1317-1320

10. Hsu DJ, Stone RA, Obrosky DS, Yealy DM, Meehan TP, Fine JM, Graff LG, Fine MJ. Predictors of timely antibiotic administration for patients hospitalized with community-acquired pneumonia from the cluster-randomized EDCAP trial. Am J Med Sci. 2010;339:307-13

11. Sikka R, Mehta S, Kaucky C, Kulstad EB ED crowding is associated with an increased time to pneumonia treatment Am J Emerg Med. 2010;28:809-12

12. *Pines JM, Localio AR, Hollander JE, Baxt WG, Lee H, P*hillips C, Metlay JP. The Impact of Emergency Department Crowding Measures on Time to Antibiotics for Patients With Community-Acquired Pneumonia. Ann Emerg Med. 2007;50:510-516.

13. Natsch, S.,Kullberg B., van der Meer J.,Meis J.. Delay in administering the first dose of antibiotics in patients admitted to the hospital with serious infections. Eur. J. Clin. Microbiol. Infect. Dis. 1998;17:681-684

14. Dee A, Kelly B, Hampp C. Root Cause Analysis and Subsequent Intervention to improve first dose antibiotic turnaround time for hospitalized pediatric patients. J Pediatr Pharmacol Ther 2010;15:182–188

15. Bordon J, Aliberti S, Duvvuri P, Wiemken T, Peyrani P, Natividad I, Caceres-Lara A, Delapenha R, Blasi F, Ramirez Early administration of the first antimicrobials should be considered a marker of optimal care of patients with community-acquired pneumonia rather than a predictor of outcomes. J. Int J Infect Dis. 2013;17:293-8

16. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:S27–72

17. Schouten JA, Hulscher ME, Kullberg B, Cox A, Gyssens I, van der Meer JW, Grol RP. Understanding variation in quality of antibiotic use for community-acquired pneumonia: effect of patient, professional and hospital factors. JAC 2005;56:575–582

18. van den Bosch C, Hulscher M, Natsch S, Gyssens IC, Prins JM, Geerlings SE. Development of quality indicators for antimicrobial treatment in adults with sepsis. BMC Infectious Diseases 2014, 14:345

CHAPTER 6: IMPLEMENTATION OF GUIDELINES FOR SEQUENTIAL THERAPY WITH FLUOROQUINOLONES IN A BELGIAN HOSPITAL

Implementation of guidelines for sequential therapy with fluoroquinolones in a Belgian hospital

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Abstract

Objective

This study measured the impact of three interventions for physicians, in order to implement guidelines for sequential therapy (intravenous to oral conversion) with fluoroquinolones.

Setting

A Belgian university hospital with 1.065 beds.

Method

The first intervention consisted of the hospital-wide publication of guidelines in the local drug letter towards all prescribers. The consumption of fluoroquinolones was measured by means of an interrupted time-series (ITS) analysis 21 months before (period A) and 24 months after publication (period B). The second intervention was an educational interactive session, by infectious disease specialists, to the medical staff of orthopaedics and endocrinology. The third intervention comprised a proactive conversion programme on the abdominal surgery, gastro-enterology and plastic surgery wards, where pharmacists attached a pre-printed note with a suggestion to switch to an oral treatment every time a patient met the criteria for switching. The second and third intervention took place 6 months after the first intervention. Fluoroquinolone treatments were evaluated during a 2 month period before (group 1) and after the introduction of the second (group 2) and third (group 3) intervention.

Main outcome measure

The monthly ratio of intravenous versus total fluoroquinolone consumption (daily defined doses per 1,000 bed days) was measured to assess the impact of the first intervention. The impact of the second and third intervention was measured in relation to the number of days that intravenous therapy continued beyond the day that the patient fulfilled the criteria for sequential therapy and the antibiotic cost.

Results

The ITS demonstrated a reduction of 3.3% in the ratio of intravenous versus total consumption after the publication of the guidelines (P = 0.011). In group 1, patients were treated intravenously for 4.1 days longer than necessary. This parameter decreased in group 2 to 3.5 days and in group 3 to 1.0 day (P = 0.006). The mean additional cost for longer intravenous treatment decreased from 188.0€ in group 1, to 103.0€ in group 2 and 44.0€ in group 3 (P = 0.037)

Conclusion

This study demonstrated that active implementation of guidelines is necessary. A proactive conversion programme by a pharmacist resulted in a reduction in the duration of the intravenous treatment, and the treatment cost.

Introduction

Efficient treatment of infection involves selecting the most appropriate drug at its optimal dosage and duration in order to eradicate the infection while minimizing side effects and selection of resistant strains [1]. In addition, the route of administration of the drug is an important factor. ''Intravenous (IV) to oral'' switch or sequential therapy is considered as a method to achieve a more efficient utilisation of antibiotics. Sequential therapy is defined as conversion from intravenous to oral formulation of the same medication while maintaining equivalent potency [2]. Several advantages have been associated with this strategy: less preparation time, easier drug administration, patient comfort, lower risk of bacteraemia and thrombophlebitis, savings in antibiotic costs and potential shortening of the length of hospital stay [2–14]. Several clinical trials have demonstrated the efficacy of sequential therapy [11–14].

The main obstacle to sequential therapy is the perception by physicians that IV antibiotics are better than oral. One erroneous concept is that all patients with an infectious disease need IV treatment. Anti-infective treatment should be evaluated regardless of route of administration. If orally administered medications are well absorbed and provide blood and tissue levels that are the same as those attained by IV administration, then the therapeutic outcome is comparable [15].

Antibiotic costs represent a significant proportion of a hospital's budget. In the Ghent University Hospital, a Belgian tertiary hospital with 1065 beds, the antibiotics for systemic use represent 12% of yearly drug budget for hospitalised patients, and fluoroquinolones (FQ) are responsible for 16% of this total.

Most FQ show excellent bioavailability, which makes them ideal for intravenous-to-oral antibiotic switches in hospitalised patients. They are also characterised by excellent penetration into most tissues and body fluids. Studies showed that FQ, like aminoglycosides but in contrast to b-lactams, work mainly in a concentration-dependent manner and exert a marked post-antibiotic effect [16].

Considering the impact on the drug budget and the excellent bioavailability of FQ and the evidence for sequential therapy for this antibiotic group found in the literature, a programme to implement sequential therapy was started.

Considering these figures and the excellent bioavailability of FQ and the evidence for sequential therapy for this antibiotic group found in the literature, a programme to implement sequential therapy was started.

Aim of the study

The objective of this study was to assess the impact of three professional interventions for physicians, in order to implement sequential therapy for FQ; namely: publication and dissemination of guidelines in the local drug letter, educational interactive sessions by an infectious disease specialist to the medical staff of orthopaedics and endocrinology and a proactive conversion programme by a pharmacist on the abdominal surgery, gastro-enterology, and plastic surgery ward.

The monthly ratio of intravenous versus total fluoroquinolone consumption, in daily defined doses per 1,000 bed days, was measured to assess the impact of the first intervention. The impact of the second and third intervention was measured in relation to the number of days that intravenous therapy continued beyond the day that the patient fulfilled the criteria for sequential therapy and the antibiotic cost.

Method

Interventions

The local Antibiotic Work Group, composed of infectious disease specialists, microbiologists, intensive care physicians and pharmacists, developed guidelines for sequential therapy based on literature data [3, 7, 14].

The guidelines were approved by the Pharmacotherapeutic Committee. The activities of the Antibiotic Work Group and Pharmacotherapeutic Committee are explicitly defined in Belgian legislation and the development of guidelines for rational drug use is mentioned as one of their key activities [17]. The criteria proposed for sequential therapy were: body temperature $<38°C$ for 24 h, decreasing or normal leukocyte count, no unexplained tachycardia, patient tolerance of oral dosing or feeding, no malabsorption (vomiting, diarrhoea), no planned surgery within 24 h [7] (Table 1).

Table 1 Criteria for sequential therapy with fluoroquinolones

Body temperature $< 38°C$ for 24 h
Decreasing or normal leukocyte count
No unexplained tachycardia
Patient tolerance of oral dosing or feeding
No malabsorption (vomiting, diarrhoea)
No planned surgery within 24 h

The first intervention consisted of the publication and dissemination of guidelines in the local drug letter [period A (before intervention) versus B (after intervention)] in October 2003. The drug letter is

the official letter of the Pharmacotherapeutic Committee, where new recommendations are published and disseminated. This intervention was oriented towards all physicians (approximately 650) in the hospital. The sequence of the interventions is illustrated in Fig. 1.

Figure 1. Sequence of the interventions
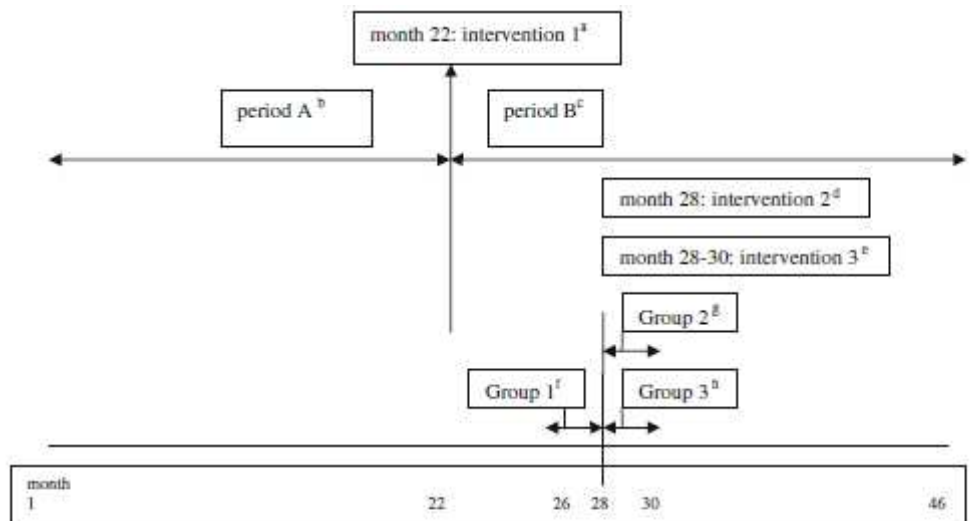
a. intervention 1 (month 22): hospital wide publication of guidelines for promoting sequential therapy for all physicians in the drug letter
b. period A (month 1 – 21): hospital wide fluoroquinolone consumption before intervention 1
c. period B (month 22- 46): hospital wide fluoroquinolone consumption after intervention 1
d. intervention 2 (month 28): an educational interactive session given by two infectious disease specialists to the medical staff of orthopaedics and endocrinology
e. intervention 3 (month 28-30): clinical pharmacists reinforced the guidelines every time a patient treated with intravenously fluoroquinolones met the criteria for sequential therapy
f. group 1 (month 26 – 28): evaluation of 36 intravenous fluoroquinolone treatments before intervention 2 and 3 on the orthopaedics, endocrinology, abdominal and plastic surgery and gastro-enterology wards
g. group 2 (month 28 – 30): evaluation of 21 intravenous fluoroquinolone treatments after intervention 2 on the orthopaedics and endocrinology wards
h. group 3 (month 28 – 30): evaluation of 24 intravenous fluoroquinolone treatments after intervention 3 on the abdominal surgery , plastic surgery and gastro-enterology wards

The wards where the second and third intervention took place were orthopaedics, endocrinology, abdominal surgery, gastro-enterology, and plastic surgery, which were selected based on their high fluoroquinolone consumption. Orthopaedics and endocrinology were randomly assigned to the second intervention and abdominal surgery, gastroenterology, and plastic surgery to the third intervention.

The second intervention consisted of an educational interactive session given by two infectious disease specialists to the medical staff of orthopaedics and endocrinology at the end of March 2004. The rationale and advantages of implementing sequential therapy were presented and discussed with the participating physicians (approximately 15 physicians at each meeting). The main focus of this intervention was to convince the physicians that orally administered fluoroquinolones are as effective as those given intravenously if the patient's clinical status complies with the criteria for sequential therapy.

During the third intervention, clinical pharmacists reinforced the guidelines every time a patient treated with intravenously fluoroquinolones met the criteria for sequential therapy. Infectious disease specialists were consulted by the clinical pharmacists in cases where there was doubt about patient's clinical status. A pre-printed note for the prescriber was attached to the patient's chart by the clinical pharmacist, with a suggestion to switch to an oral treatment and a short summary of the advantages. The prescriber was also asked to explain the reason if the advice was not taken. The third intervention took place on the abdominal surgery, gastro-enterology, and plastic surgery wards between 1 April 2004 and 31 May 2004.

This study was approved by the Ethics Committee of Ghent University Hospital.

Interrupted time-series (ITS) analysis.

The impact of the interventions was measured at two levels, macro and micro.

At the macro level the hospital consumption of FQ (ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin) was used to evaluate the long term impact of the publication of the guidelines by performing an interrupted time-series (ITS) analysis [18, 19]. This study design is characterized by a series of measurements over time in order to detect spontaneous evolution and discriminate from the effect of an intervention, thus avoiding possible bias. Consumption data were expressed in daily defined doses (DDD) using the Anatomical Therapeutic Chemical (ATC) classification rates were expressed in DDD/1,000 bed days. The monthly oral and IV FQ consumption and the ratio of IV versus total FQ usage were counted, starting 21 months before until 24 months after the publication of the guidelines.

Pre- and post- prospective study

At a micro level, a pre- and post-prospective study was performed in order to assess the impact of the educational sessions and the proactive conversion programme. All patients treated with intravenous FQ were included for a period covering 2 months before until after the intervention. For every patient the following variables were collected: age, type of infection, co-morbidity, leukocyte level, heart rate, antibiotics used, concomitant drugs, administration route of antibiotics. In the baseline period (group 1) data were collected on the orthopaedics, endocrinology, abdominal and plastic surgery and gastroenterology wards. The impact of the educational sessions was assessed on the orthopaedics and endocrinology wards (group 2). The impact of the proactive conversion programme was assessed on the abdominal, plastic surgery and gastro-enterology wards (group 3). The data were collected by a hospital pharmacist. The severity of the underlying illness was defined for each patient by counting the case mix index [20]. The case mix index is calculated using diagnosis-related groups (DRG's), a

measure that is nowadays routinely obtained in various countries as a basis for hospital reimbursement. DRG's developed as an instrument to relate the case mix of a hospital to the costs, classify patients depending on their diagnosis, treatments, age and other information into mutually exclusive, clinically and financially homogeneous categories [21].

A panel of one hospital pharmacist and two infectious disease specialists evaluated the treatment of each patient and identified the moment the patient fulfilled the criteria to switch to oral therapy after starting intravenous treatment. The number of days that intravenous therapy continued beyond this day enables measurement of the impact of the intervention. To calculate the potential financial impact, the cost of continuing intravenous therapy when oral FQ could have been used was determined for each treatment and compared with the cost of an oral treatment. Indirect costs for preparing and administering the FQ were not considered.

At the end of the study the results were presented to all participating prescribers.

Statistical analysis

Statistical analysis was performed using R (a language and environment for statistical computing) [22]. The categorical variables were compared using the Chisquare test, continuous variables with the Mann–Whitney U-test and Kruskal–Wallis test. Segmented regression analysis was used for the two time periods. The significance level was set at a = 0.05, two-tailed.

Results

Impact publication of guidelines

An interrupted time-series analysis demonstrates a decreasing IV versus total (IV + PO)FQ consumption since the publication of the guidelines (Fig. 2). The mean ratio of IV versus total (IV + PO) FQ usage was in the 21 months before the intervention 44.5% and decreased to 41.2% in the following 24 months (P = 0.011).

Impact of educational sessions and pro-active intervention

Eighty-one patients were included, 36 in group 1, 21 in-group 2 and 24 in group 3 (Table 2). The number of type of infections was significantly different for skin and soft tissue infections and prosthetic material infections. There was no difference for urinary tract infections, gastrointestinal infections, pneumonia and osteomyelitis. The case mix index, mean age and gender ratio were similar. The case-mix index was not available for two patients in group 1 and five patients in group 2 and 3. The mean time to reach the criteria for sequential therapy was 5.2 days in group 1, 5.8 days in group 2 and 5.0 days in group 3 (P = 0,934).

Table 2 Comparison of patient characteristics in group 1 (baseline), group 2 (educational sessions by infectious disease specialist) and group 3 (proactive conversion-programme by a pharmacist)

Characteristic	Group 1 N = 36	Group 2 N = 21	Group 3 N = 24	P
Type of infection				
Urinary tract infection	11	5	12	0.117[a]
Skin and soft tissue infection	4	7	2	0.048[a]
Gastro-intestinal infections	7	0	6	0.061[a]
Pneumonia	3	1	1	0.857[a]
Prosthesis-infection	0	5	0	0.001[a]
Osteomyelitis	0	2	0	0.065[a]
Others	11	1	3	0.037[a]
Mean case mix index (SD)[c]	1.7 (1.4)	1.5 (0.9)	1.6 (1.4)	0.966[b]
Mean age, years (SD)	62 (15)	59 (16)	58 (15)	0.574[b]
Gender ratio, m/f	22/14	9/12	14/10	0.398[a]
Mean time start therapy until fulfilment of criteria (days) (SD)	5.2 (5.2)	5.8 (6.2)	5.0 (4.7)	0.934[b]

[a] Chi-square test (Fisher's exact test)
[b] Kruskal–Wallis test
[c] Data not available for two patients in group 1, five patients in group 2 and five patients in group 3
SD standard deviation

In group 1, patients were treated for a further 4.1 days after they fulfilled the criteria (Table 3). This parameter decreased in group 2 to 3.5 days and in group 3 to 1.0 day (P = 0.006). The pharmacist's advice in group 3 was accepted 22 times (91.7%). In two cases (8.3%) the physicians did not follow this advice because the patient had started vomiting.

Table 3 Comparison patient outcome group 1 (baseline), group 2 (educational sessions by infectious disease specialist) and group 3 (proactive conversion-programme by a pharmacist)

Characteristic	Group 1 N = 36	Group 2 N = 21	Group 3 N = 24	P
Mean duration of IV treatment	8.6 (6.6)	9.3 (7.9)	4.7 (4.5)	0.029[a]
Mean duration of extra IV treatment (SD)	4.1 (5.8)	3.5 (4.9)	1.0 (1.3)	0.006[a]
Mean additional cost by longer IV treatment in € (SD)[c]	188.7 (292.9)	103.6 (131.5)	44.8 (60.2)	0.037[b]

[a] Kruskal–Wallis test and Mann–Whitney U-test

[b] Difference extra IV treatment and similar oral PO treatment for an individual patient

SD standard deviation; P < 0.05 = significant

The economical impact was demonstrated by counting the difference in cost of antibiotics between an intravenous and oral treatment (difference extra IV treatment and similar oral PO treatment for an individual patient). The mean extra cost per patient by longer IV treatment decreased significantly from 188.0€ in group 1, to 103.0€ in group 2 and 44.0€ in group 3 (P = 0.037).

Figure 2. Evolution of the ratio of IV versus total (IV/ PO) FQ usage, expressed in daily defined doses per 1,000 bed days, starting 21 months before until 24 months after the publication of the guidelines in the drug letter
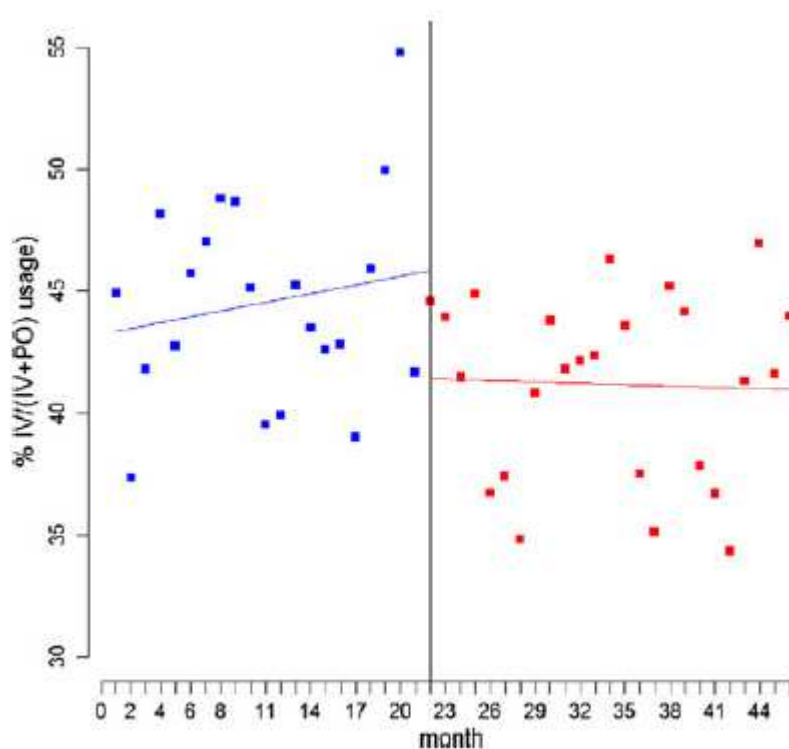
Discussion

The results of this pilot study demonstrate that the delay in switching to oral FQ therapy once the criteria for sequential therapy were met was significantly shorter during the intervention where the pharmacist provided immediate feedback to the prescriber about a specific patient. There was a limited impact of the educational interactive sessions. The long-term impact of the publication of the guidelines for all physicians, based on consumption figures, shows a small decrease in usage of intravenous FQ.

Six months after publication of the guidelines the IV/PO ratio was increasing (Fig. 2). This illustrates that such an intervention has a gradual rather than an instant effect (learning effect) which may decline over time (decay effect). The IV/PO ratio may be an indicator for implementing sequential therapy but could be biased by confounding factors. An example of a possible confounding factor is the length of stay of the patients. Patients who are switched to an oral therapy could be discharged earlier as the oral therapy can easily be continued at home. In this case the IV/PO ratio will increase as we only look at the consumption in the hospital.

In the pre and post prospective study, the mean time to reach the criteria for sequential therapy was approximately 5.0 days for the three evaluated groups. In comparable studies, this varies between 2.4 and 3.6 days [6, 13, 14]. The high figure in our study could be explained by the case mix index of the included patients.

The most important outcome was the extra IV treatment after reaching the criteria for sequential therapy. In the baseline period, patients were treated for an additional 4.1 days. This was reduced by 0.6 days after the education sessions and by 3.1 days during the proactive intervention. Studies measuring the impact of proactive interventions describe a reduction of 1.5–4.0 days [4, 13].

The impact of a once-only educational session is clear but not significant. It was remarkable during these sessions that the majority of the physicians were not aware of the bio-equivalence of intravenous and oral FQ and the difference in costs between the oral and intravenous preparations. The limited reduction in extra IV days after the educative session can possibly be explained by the fact that physicians, although being aware of the guidelines, were reluctant to initiate oral therapy in daily practice.

The impact of the pro-active programme by a pharmacist was significant. The physicians mostly accepted the advice of the pharmacist. This intervention was not considered as interference by the physicians, something that became clear during the oral presentation at the end of this study where the

results were discussed with the prescribers. The advice was well founded and difficult cases were discussed in advance with an infectious disease specialist. When the pharmacist suggested switching to an oral therapy, possible food-drug and drug–drug interactions were also taken into account. In this case the pharmacist suggested administering the interacting drug 2 h after the administration of the FQ to avoid reduced absorption of the FQ antibiotic. Physicians and nurses considered this important as they were not always aware of these potential pitfalls during oral FQ treatment.

The relation between the case mix index and the duration of an intravenous treatment is not clear. A shorter IV treatment with FQ was not associated with a shorter length of stay. Studies with more statistical power are necessary to evaluate this relationship.

The pre and post prospective study has limitations. First the small number of patients limited the statistical power of the study. More inclusions should have been possible if the study was conducted over a longer period than 2 months before and after the study. Second, a control group was not included after the second and third intervention. That's the reason why this study is not considered as a controlled before and after study but a pre-and post study. The limitation with this type of study is that, without reference to a control group, it cannot answer whether the improvement or decline would have occurred anyway, even without the intervention. The results of this study however confirms the conclusions of similar publications [13, 14]. Third, the first evaluation of patients' charts (group 1) took place 4 months after the publication of the guidelines and started 2 months before the educational sessions by the infectious disease specialist. Ideally, the same evaluation should have been done 2 months before and after the publication of the guidelines in order to evaluate the impact of this intervention based on clinical data.

It is clear that an early switch to oral treatment is linked to lower costs. In this study only the cost of the antibiotics was considered. The advantages are in reality higher, taking into account supplies for administration, labour in drug preparation and administration, and avoiding infusionrelated complications. In addition, the length of stay may be shortened if patients are able to complete their course of therapy outside the hospital. In a pharmaco-economic study evaluating a pharmacist-managed programme for automatically converting levofloxacin route from IV to oral, the total cost per patient decreased from 121 $ to 82 $. The length of stay decreased from 9.5 to 6.0 days [5].

This study will be the start of an extensive poster campaign in our hospital. The campaign will focus not only on FQ but also on clindamycin, linezolid, fluconazole and metronidazole, which are also equally bioavailable. Most educational initiatives are planned at the beginning of the medical year in

order to promote early development of optimal prescribing habits for new residents in a teaching hospital. Pro-active interventions can be integrated into an electronic prescribing programme. This will give the opportunity to develop computer-generated reminders based on an algorithm, to indicate when a patient can be treated orally instead of IV.

Conclusion

This study demonstrated that an active implementation of guidelines for sequential therapy is necessary. Several methods of implementation were compared: publication of guidelines, educative sessions by an infectious disease specialist and a pro-active intervention by a clinical pharmacist. The results show that a pro-active intervention results in a significant reduction of the duration of the intravenous treatment, and a reduction in the treatment cost.

References

1. Fishman N. Antimicrobial stewardship. Am J Med. 2006; 119:S53–61.

2. Nathawani D, Tillotson G, Davey P. Sequential antimicrobial therapy the role of quinolones. J Antimicrob Chemother. 1997;39:441–6.

3. 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: 159–77.

4. Sevinc̨ F, Prins J, Koopmans R, Langendijk P, Bossuyt P, Dankert J, et al. Early switch from intravenous to oral antibiotics: guidelines and implementation in a large teaching hospital. J Antimicrob Chemother. 1999;43:601–6.

5. Kuti J, Le T, Nightindale C, Nicolau D, Quintiliani R. Pharmacoeconomics of a pharmacist-managed program for automatically converting levofloxacin route from IV to oral. Am J Health Syst Pharm. 2002;59:2209–15.

6. Jensen K, Paladino J. Cost-effectiveness of abbreviating the duration of intravenous antibacterial therapy with oral fluoroquinolones. Pharmacoeconomics. 1997;11:64–74.

7. Vogel F. Intravenous/oral sequential therapy in patients hospitalised with community-acquired pneumonia. Drugs. 2002;62: 309–17.

8. Conort O, Gabardi S, Didier M, Hazebroucq G, Cariou A. Intravenous to oral conversion of fluoroquinolones; knowledge versus clinical practice patterns. Pharm World Sci. 2002;24: 67–70.

9. Beringer A, Nguyen K, Razeghi J. Implementing a program for switching from I.V. to oral antimicrobial therapy. Am J Health Syst Pharm. 2001;58:1146–9.

10. Ramirez J, Bordon J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic communityacquired Streptococcus pneumoniae pneumonia. Arch Intern Med. 2001;161:848–50.

11. Martinez M, Freire A, Castro I, Inaraja M, Ortega A, Del Campo V, et al. Clinical and economic impact of a pharmacist-intervention to promote sequential intravenous to oral clindamycin conversion. Pharm World Sci. 2000;22:53–8.

12. Laing R, Mackenzie A, Shaw H, Gould I, Douglas J. The effect of intravenous-to-oral switch guidelines on the use of parenteral antimicrobials in medical wards. J Antimicrob Chemother. 1998;42:107–11.

13. Zamin M, Pitre M, Conly J. Development of an intravenous-tooral route conversion program for antimicrobial therapy at a Canadian tertiary care health facility. Ann Pharmacother. 1997; 31:564–70.

14. Von Gunten V, Amos V, Sidler A, Beney J, Troillet N, Reymond J. Hospital pharmacists' reinforcement of guidelines for switching from parenteral to oral antibiotics: a pilot study. Pharm World Sci. 2003;25(2):52–5.

15. Wetzstein G. Intravenous to oral (iv:po) anti-infective conversion therapy. Cancer Control. 2000;7:170–6.

16. Van Bambeke F, Michot J, Van Eldere J, Tulkens P. Quinolones in 2005: an update. Clin Microbiol Infect. 2005;11:256–80.

17. Royal Decree of February 12, 2008 laying down the standards which a hospital pharmacy must meet in order to be approved. Brussels: Belgian Gazette; 12 Feb 2008. http://www.ejustice.just. fgov.be/doc/rech_n.htm. Accessed 14 Mar 2008.

18. Ansari F, Gray K, Nathwani D, Phillips G, Ogston S, Ramsay C, et al. Outcomes of an intervention to improve hospital antibiotic prescribing: interrupted time series with segmented regression analysis. JAC. 2003;52:842–8.

19. Matowe L, Leister C, Crivera C, Korth-Bradley J. Interrupted time series analysis in clinical research. Ann Pharmacother. 2003;37:1110–6.

20. The WHO Collaborating Centre for Drug Statistics Methodology. ATC index with DDD's. Oslo, Norway; 2003. http://www.whocc. no/atcddd/. Accessed 3 Apr 2006.

21. Kuster S, Ruef C, Bollinger A, Ledergerber B, Hintermann A, Deplazes C, et al. Correlation between case mix index and antibiotic use in hospitals. JAC. 2008;62:837–42.

22. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2007. ISBN 3-900051-07-0. http://www. R-project.org. Accessed 2 Jan 2007.

CHAPTER 7: IMPLEMENTATION OF A MULTIDISCIPLINARY INFECTIOUS DISEASES TEAM IN A TERTIARY HOSPITAL WITHIN AN ANTIMICROBIAL STEWARDSHIP PROGRAM

Implementation of a multidisciplinary infectious diseases team in a tertiary hospital within an Antimicrobial Stewardship Program

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Abstract

Background

In January 2011, as part of an antimicrobial stewardship program the Antimicrobial Management Team (AMT) at the Ghent University Hospital initiated a multidisciplinary Infectious Diseases Team (MIT) consisting of infectious diseases physicians, clinical microbiologists and clinical pharmacists. The aim of this study is to describe the type and acceptance rate of recommendations provided by the MIT.

Methods

Prospective, observational study in a tertiary care, university teaching hospital with 1062 beds in non consecutive hospitalized adult patients, excluding intensive care units and pediatrics.

Results

The MIT communicated 432 recommendations in 87 days observed. Of the 293 patients for whom a recommendation was made, the median age was 57 years (range 16–91 years) and 169 (57.7%) were male. Skin or soft tissue infections (14%), respiratory tract infections (13%), infections without known focus (11%), abdominal infections (11%) and bone infections (8%) were most common. Recommendations were made to perform additional clinical investigation(s) [N = 137 (27%)], to adjust the dose of an antimicrobial drug [N = 42 (8%)], to stop an antimicrobial drug [N = 104 (21%)], to switch from a parenteral to an oral drug [N = 39 (8%)] or to initiate an antimicrobial drug [N = 178 (36%)] with an acceptance rate of 73.0%, 83.3%, 81.7%, 76.9% and 84.0% respectively.

Conclusions

The MIT formulated about 5 recommendations a day primarily focusing on pharmacotherapy but also on clinical investigations. In both fields a high acceptance rate was observed.

Background

Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration [1]. The major objectives are to optimize the clinical outcomes related to antimicrobial use while minimizing toxicity and other adverse events and limiting the selective pressure on bacterial populations that drives the emergence of antimicrobial-resistant strains.

Infections caused by multidrug-resistant bacteria are associated with higher mortality, prolonged hospital stay and increased costs [2]. The emergence of multidrug-resistant organisms limits therapeutic choices in hospital-acquired infections.

Reducing and preventing antimicrobial resistance by enhancing the appropriate use of antimicrobials is one of the cornerstones of the European Union policy against antimicrobial resistance [3]. Antibiotic stewardship programs are proposed as a tool to optimize the prescribing of antibiotics [4]. Antimicrobial stewardship may also reduce excessive costs attributable to suboptimal antimicrobial use [1]. A recent study has shown that 38% of the antibiotic usage in European hospitals was not compliant to guidelines which need to be promoted through an antimicrobial stewardship program [5].

To influence the antimicrobial prescribing behaviour, a multidisciplinary approach which involves opinion leaders and senior clinicians is preferable. Ideally such a multidisciplinary antimicrobial stewardship team should bring different competences together, including infectious diseases (ID) physicians, clinical microbiologists and clinical pharmacists.

Since 2002, the Belgian Antibiotic Policy Coordination Committee (BAPCOC) was able to secure federal funding, provide technical guidance and offer advanced specialist training for the formal establishment and follow-up of Antimicrobial Management Teams (AMTs) in Belgian hospitals [6]. The minimal composition, mandate and tasks of hospital AMTs have been consolidated in legislation (Royal Decree of 12 February 2008) on the norms for AMTs as dedicated subgroups of the hospital Drugs and Therapeutic Committee [6].

The AMT of the Ghent University hospital provides national (The Sanford Guide To Antimicrobial Therapy - Belgian/Luxembourg Edition) and local antimicrobial guidelines to the prescribers [7]. The electronic medical record allows physicians to consult the microbiological results of the clinical laboratory, including identification and susceptibility of pathogens. Eighty percent of the wards use a computerised physician order entry (CPOE) system in which dosing regimens are incorporated in medication order sets and where current and past antimicrobial therapies can be consulted. Wards where CPOE is not yet implemented can prescribe restricted antimicrobials (voriconazol, caspofungin, anidulafungin, liposomal amphotericin B, meropenem, piperacillin/tazobactam, linezolid, tigecycline,

vancomycin, teicoplanin, colimycin, ceftazidim, levofloxacin, moxifloxacin, ciprofloxacin) with a specific antibiotic prescription form.

The AMT at our hospital initiated a multidisciplinary infectious diseases team (MIT) in January 2011, as part of an antimicrobial stewardship program, which is directed by ID physicians and also consists of clinical microbiologists and clinical pharmacists. Once a week, a haematologist joins the team. Figure 1 gives a schematic representation of the activities of the MIT. The MIT meets daily to discuss (a) requests for ID consultations reviewed by ID physicians, (b) positive blood cultures and cultures with resistant strains or with organisms requiring special attention, reviewed by microbiologists (c) presumed inappropriate therapies identified by pharmacists. The pharmacists review therapies with antifungals, meropenem, piperacillin/tazobactam, linezolid, tigecycline, vancomycin and teicoplanin, blood concentrations of antimicrobials requiring monitoring (vancomycin and teicoplanin, aminoglycosides,voriconazole) and antimicrobials with high bioavailability that may be switched from parenteral to oral administration based on the electronic medical patient record. The MIT communicates its recommendations to the physicians by phone and by notes in the electronic patient file where a specific MIT section is available. The MIT limits its interventions to adult patients hospitalized in non-critical care departments. Critical care patients are discussed weekly in a separate meeting with clinical microbiologists and intensive care physicians. The pediatric department has a dedicated pediatric ID physician.

The aim of this pilot study is to describe the type and acceptance rate of interventions provided by the MIT.

Methods

A prospective, observational study was performed in a tertiary care, teaching hospital with 1062 beds. The MIT pharmacists registered every recommendation communicated by the MIT during 87 non-consecutive days between October 2011 and May 2012.

The following data were registered in a standardised case record form: date of MIT recommendation, hospitalisation ward, type of infection and current antimicrobial treatment. Five types of recommendations can be distinguished: (a) initiating or changing an antimicrobial regimen; (b) additional clinical investigations; (c) dosing adjustments;(d) switching from parenteral to oral formulations (5) discontinuing antimicrobials. The rationale for the recommendations and the specific antimicrobials involved were registered.

Recommendations were scored as accepted when a physician implemented the recommendation(s) within 3 days after the communication. The acceptance rate was classified as "not documented" in those cases where it was not possible to document this retrospectively (e.g. patient discharged or transferred to another health care facility).

The study was approved by the local Ethics Committee.

Results

The MIT communicated 432 recommendations during 87 non-consecutive days in 293 patients The median age was 57 years (range 16–91 years) and 169 (57.7%) were male.

Skin or soft tissue infections (14%), respiratory tract infections (13%), infections without known focus (11%), abdominal infections (11%) and bone and joint infections, including prosthetic infections (8%) were most frequently involved .

In 277 (64.1%) of the recommendations the MIT proposed a modification in therapy or further clinical investigations which were accepted. In 84 (19.4%) of the recommendations the MIT suggested to continue the actual therapy which was implemented. This resulted in a total acceptance rate of 83.5%. For the other recommendations, 57 (13.2%) were not implemented and for 14 (3.2%) implementation could not be documented.

MIT recommendations originated from new electronically requested ID consultations (61%), current antimicrobial therapies provided by pharmacists (18%), follow up of earlier requested ID consultations (12%), microbiological information provided by microbiologists (4%), current therapies provided by ID physicians (3%) and haematologists (2%). The electronical ID consultations were ordered by 30 medical disciplines, ranging from 1 to 24 (median 7.5) requests per discipline.

The majority of the recommendations were made for patients on the following wards: abdominal surgery (16.2%), gastroenterology (9.3%), thoracovascular surgery (7.9%), rehabilitation medicine (5.8%) and orthopaedics (5.0%).

Some of the 432 recommendations consisted of multiple types of recommendations, which were taken into account individually in table 1. This resulted in 500 individual recommendations.

Recommendations were made to perform additional clinical investigation(s) [N = 137 (27%)], to adjust a dose of an antimicrobial drug [N = 42 (8%)], to stop an antimicrobial drug [N = 104 (21%)], to switch from a parenteral to an oral drug [N = 39 (8%)] and to initiate an antimicrobial drug [N = 178 (36%)] with an acceptation rate of respectively 73.0%, 83.3%, 81.7%, 76.9% and 84.0% (Table 1). Of the 178 initiated antimicrobials 113 (63%) were a replacement of and 26 (15%) an addition to the current therapy.

Within the accepted recommendations, vancomycin, piperacillin/tazobactam and meropenem treatments were more frequently stopped versus initiated (respectively 31 vs. 5 , 21 vs. 7 and 20 vs. 14). Considering the administration route, parenteral therapies were more frequently stopped than

initiated (148 versus 97). In general, treatments were more frequently discontinued instead of initiated (184 versus 152) after a MIT recommendation. This is not a likelihood but a frequency distribution as recommendations to continue treatments were more likely to be implemented.

Table 1. Classification of the recommendations provided by the MIT with acceptance rates.

Classification of recommendation		Number of recommendations N (%)	Accepted N (%)	Acceptance not documented N(%)	Not accepted N(%)
Additional clinical investigation		137 (27%)	100 (73%)	5 (4%)	32 (2%)
Dosing adjustment		42 (8%)	35 (83%)	3 (7%)	4 (10%)
Reason	Subtherapeutic or toxic serum concentration	15 (36%)	12 (80%)	0 (0%)	3 (20%)
	Evidence-based guidelines	15 (36%)	12 (80%)	2 (13%)	1 (7%)
	Other*	8 (19%)	7 (88%)	1 (13%)	0 (0%)
	Compromised renal function	4 (10%)	4 (100%)	0 (0%)	0 (0%)
Type of adjustment	Increase	22 (52%)	16 (73%)	2 (9%)	4 (18%)
	Reduction	11 (26%)	11 (100%)	0 (0%)	0 (0%)
	Same daily dose, other dosing regimen	9 (21%)	8 (89%)	1 (11%)	0 (0%)
Stop antimicrobial therapy		104 (21%)	85 (82%)	4 (4%)	15 (14%)
Reason	No indication to proceed	70 (67%)	57 (81%)	4 (6%)	9 (13%)
	Prolonged therapy	25 (24%)	22 (88%)	0 (0%)	3 (12%)
	Tentative	9 (9%)	6 (67%)	0 (0%)	3 (33%)
Switch parenteral to oral therapy		39 (8%)	30 (77%)	1 (3%)	8 (21%)
Initiation antimicrobial therapy		178 (36%)	150 (84%)	11 (6%)	17 (10%)
Reason	Replacement	113 (63%)	94 (83%)	7 (6%)	12 (11%)
	Untreated indication	35 (20%)	30 (86%)	1(3%)	4(11%)
	Addition	26 (15%)	23 (88%)	1 (4%)	2 (8%)
	Restart	2 (1%)	1 (50%)	0 (0%)	1 (50%)
	Reason unknown	2 (1%)	2 (100%)	0 (0%)	0 (0%)

* different length of administration, increase of dose to reach the sternum, increase of dose because of intermediate sensitivity of bacterial strain, increase of dose because of infection of vascular prosthesis, different dosing regimen because of parenteral administration in home setting, increase of dose because of high body weight, tentative.

Discussion

This study shows that an average of five recommendations per day were provided by the MIT, of which 83% were accepted This acceptance rate is comparable with numbers in similar studies performed in the USA, Brazil, Singapore and Australia, showing acceptance rates ranging from 64% to 80% [8-12].

Remarkably, the number of recommendations seems slightly higher in our study. This could be the result of the inclusion of pharmacotherapeutic as well as diagnostic recommendations, in contrast to the previously published reports. In the other studies the AMT program was performed by ID physicians together with clinical pharmacists whereas only in one study there was also participation of a clinical microbiologist [9]. The numbers of beds ranged from 60 to 1596 [8-12].

Our recommendations cover a wide range of infection types, with a majority of skin or soft tissue infections, respiratory tract infections, infections without known focus and abdominal infections.

Some of these infections can be complicated and complex, requiring a long duration of therapy, a setting in which the advice of the MIT can be important.

The majority (61%) of the recommendations originate from ID consultations. This may reflect the embedment of this clinical service within the hospital. A significant number (18%) of recommendations originate from therapies reviewed by clinical pharmacists. Pharmacists spend approximately 2 hours per day in analysing treatments with antifungals (with the exception of fluconazole), meropenem, piperacillin/tazobactam, linezolid, tigecycline, vancomycin, teicoplanin and antimicrobials with a high bioavailability that may be switched from parenteral to oral administration. Because this represents a significant workload each type of antimicrobial agent is reviewed only once a week. Data-mining software able to generate automated reports based on pharmaceutical, clinical and microbiological data could have a time-saving effect [11]. This should allow us to enhance the frequency of the actual antimicrobial agents and to evaluate additional antimicrobial agents . Furthermore, computer decision support systems could support physicians upon the initiation of a therapy [13,14]. Such a system is already applied on the intensive care unit of our hospital [14]. However, this was outside the scope of the current study.

The number of recommendations originating from positive microbiological cultures provided by clinical microbiologists is small, because during the time period of the study, most of the positive cultures were directly discussed by the clinical microbiologists with the treating physicians outside the framework of the MIT. This is a direct consequence of the different organisation of the microbiology laboratory, where the results are generated early in the morning, in contrast with the MIT meetings which are held in the late afternoon.

The majority (73%) of the recommendations focus on pharmacotherapy. All recommendations to reduce the dose of antimicrobials were accepted, while recommendations to increase the dose had a lower acceptance rate. Physicians seem to feel more confident with reducing doses considering compromised renal function or risk of side effects. They may not yet be fully aware of the concept of individualised antimicrobial therapy. This may require increasing doses e.g. in infections with less sensitive strains, in patients with significant pharmaco-kinetic changes such as increased distribution volume (burns, cirrhosis) or the phenomenon of augmented renal clearance in critically ill.[15] Recommendations that propose a tentative stop of an antimicrobial therapy and an observation of the clinical evolution imply a greater degree of uncertainty for physicians which can explain the low acceptance rate in this setting.

The acceptance rate to switch from a parenteral to an oral formulation (IV-PO switch) of the same antimicrobial is relatively low. An explanation could be that pharmacists' only source to consider

possible switches is the electronic medical record where clinical data that could support the medical decision to continue parenteral therapy (e.g. severe vomiting, diarrhea, not functional tube) were not always documented. The proportion of recommendations proposing an IV-PO switch is small, which could be the result of other and earlier initiatives towards physicians. Within the same hospital we have reported high compliance with internal guidelines on IV/PO switch [16,17]. These initiatives were developed outside the framework of the MIT but were coordinated by the AMT.

Recommendations to initiate an antimicrobial therapy have the highest overall acceptance rate with physicians. Most recommendations in this category propose to replace a current antimicrobial by an alternative. Most persuasive reasons to initiate an antimicrobial therapy were to enhance effectiveness, to narrow spectrum and to allow a switch to oral therapy. The analysis of accepted recommendations suggests that the MIT was able to de-escalate therapies, to switch to oral antimicrobials and to discontinue antimicrobials when applicable.

About 17% of the recommendations focus on additional clinical investigations with an acceptance rate of 73%, which is lower compared to pharmacotherapy oriented recommendations but comparable with a recently published similar study [18]. The lower acceptance rate on diagnostic issues suggests that physicians more readily accept recommendations on pharmacotherapy as compared to critical reflections on their diagnostic path. This is also shown by the low uptake of performing transesophageal echocardiography in patients with *Staphylococcus aureus* bacteraemia. As a result of these data, patients with a *Staphylococcus aureus* bacteraemia are now prospectively followed during their hospital stay to ensure echocardiography screening for latent infective endocarditis [19].

Establishing a culture of measurement and clinician feedback is an effective stewardship strategy [4,20]. The effectiveness can be improved by the Feedback Intervention Theory through providing specific, frequent and written suggestions for improvement [21]. This was also applied by the MIT by documenting recommendations in the CPOE system and by additional communication by phone. Another strength of the MIT is that follow up by the MIT is provided for patients with complex infections. This is strongly appreciated by the physicians. The multidisciplinary composition of the MIT reflects the recommendations in literature [2,4,22]. The MIT is directed by an infectious disease physician who is a respected authority which is a fundamental feature in marketing the MIT concept [23]. Initially the pharmacist reviewed only prolonged therapies (>10 days) of the target antimicrobial agents which has changed over time to all treatments.

Pre-authorization of restricted antimicrobial agents is not implemented in our hospital and only once a week each type of antimicrobial agents is reviewed. The combination of these two factors indicates potential for further optimization. This will increase the workload which can be in turn reduced by implementing automated reports. One study from a hospital in the USA with 513 beds described that

software-generated antimicrobial therapy reports contain information on approximately 60–80 patient cases, resulting in about 20 cases daily after evaluation by a pharmacist. These cases are then reviewed together with an ID physician. Projecting this method to our hospital, this could generate 36 cases on a daily basis to discuss within the MIT [11].

In order to support physicians during the diagnostic evaluation of the patient, some guidelines are now linked to the data of clinical chemistry (e.g. serum concentration levels of glycopeptide and aminoglycoside agents are linked to drug therapeutic monitoring guidelines) and microbiology (positive blood cultures with *Staphylococcus aureus* are linked to the *Staphylococcus aureus* bacteremia guideline).

This pilot study has some limitations. Reasons to decline a recommendation were not assessed. Recent literature on antimicrobial stewardship focuses on the behaviour of individual prescribers. This could lead to understanding the barriers to and facilitators of behavioural change [24]. This should be taken into account for further research.

No statements can be made on the cost-effectiveness, patient safety, impact on morbidity and mortality and local resistance patterns. Restricted antibiotics (e.g. vancomycin, piperacillin-tazobactam and meropenem) were more frequently stopped than initiated and oral therapies were more frequently initiated compared with parenteral therapy. This suggests that the MIT can have a positive impact on antimicrobial expenditure. In the past this was shown in our hospital for an IV-PO switch program [16]. This is in line with documented positive impact of antimicrobial stewardship programs on antimicrobial expenditure and clinical outcome [8-12,25].

Conclusion

This prospective observational pilot study showed that the multidisciplinary infectious diseases team, as part of an antimicrobial stewardship program, formulated about 5 interventions a day for non-critically ill adult patients. Recommendations were communicated by phone and by notes in the electronic patient file resulting in high acceptance rates. Acceptance rates were higher for recommendations on pharmacotherapy as compared to diagnostic issues.

References

1. Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; Pediatric Infectious Diseases Society.Policy Statement on Antimicrobial Stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS) Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; Pediatric Infectious Diseases Society. Infect Control Hosp Epidemiol 2012;33:322-327.

2. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, WilcoxM. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2013; Issue 4. Art. No.: CD003543. DOI: 10.1002/14651858.CD003543.pub3.

3. Communication from the commission to the European Parliament and the council. Action plan against the rising threats from Antimicrobial Resistance Brussels. 2011 [Cited 2013 June 28th]. Available from: http://ec.europa.eu/dgs/health_consumer/docs/ communication_amr_2011_ 748_en.pdf.

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. Zarb P, Amadeo B, Muller A, Drapier N, Vankerckhoven V, Davey P, Herman Goossens H. Identification of targets for quality improvement in antimicrobial prescribing: the web-based ESAC Point Prevalence Survey 2009. J Antimicrob Chemother 2011;66: 443-449.

6. Van Gastel E, Costers M, Peetermans WE, Struelens MJ, and on behalf of the Hospital Medicine Working Group of the Belgian Antibiotic Policy Coordination Committee. Nationwide implementation of antibiotic management teams in Belgian hospitals: a self-reporting survey. J Antimicrob Chemother 2010;65: 576-580.

7. Sanford JP, Gilbert DN, Chambers HF, Eliopoulos GM, Moellering RC, Saag MS. The Sanford Guide to Antimicrobial Therapy, 2012–2013, 23rd edn. Belgian/Luxembourg version. Belgian/Luxembourg Working Party on Antimicrobial Therapy. ISBN 978-1-930808-70-6

8. Pate PG, Storey DF, Baum DL.Implementation of an antimicrobial stewardship program at a 60-bed long-term acute care hospital. Infect Control Hosp Epidemiol 2012; 33: 405-408.

9. Liew YX, Lee W, Loh JC, Cai Y, Tang SS, Lim CL, Teo J, Ong RW, Kwa AL, Chlebicki MP. Impact of an antimicrobial stewardship programme on patient safety in Singapore General Hospital. Int J Antimicrob Agents 2012;40: 55-60.

10. Magedanz L, Silliprandi EM, dos Santos R.Impact of the pharmacist on a multidisciplinary team in an antimicrobial stewardship program: a quasi-experimental study. Int J Clin Pharm 2012; 34:290-294.

11. Nowak M, Nelson R, Breidenbach J. Clinical and economic outcomes of a prospective antimicrobial stewardship program. Am J Health-Syst Pharm 2012;69:1500-8.

12. Cairns KA, Jenney AW, Abbott IJ, Skinner MJ, Doyle JS, Dooley M, Cheng AC. Prescribing trends before and after implementation of an antimicrobial stewardship program. Med J Aust 2013;18:262-6.

13. Pestotnik SL. Expert Clinical Decision Support Systems to Enhance Antimicrobial Stewardship Programs: : insights from the society of infectious diseases pharmacists. Pharmacotherapy 2005;25:1116–1125.

14. Steurbaut K, Colpaert K, Gadeyne B, Depuydt P, Vosters P, Danneels C, Benoit D, Decruyenaere J, De Turck F.COSARA: Integrated Service Platform for Infection Surveillance and Antibiotic Management in the ICU. J Med Syst 2012; 36:3765–3775.

15. Udy AA, Roberts JA, De Waele JJ, Paterson DL, Lipman J. What's behind the failure of emerging antibiotics in the critically ill? Understanding the impact of altered pharmacokinetics and augmented renal clearance. Int J Antimicrob Agents 2012; 39:455-7.

16. Buyle F, Vogelaers D, Peleman R, Van Maele G, Robays H. Implementation of guidelines for sequential therapy with fluoroquinolones in a Belgian hospital. Pharm World Sci 2010; 32:404-10.

17. Buyle FM, Metz-Gercek S, Mechtler R, Kern WV, Robays H, Vogelaers D, Struelens MJ; Antibiotic Strategy International-ABS Quality Indicators Team. Prospective multicentre

feasibility study of a quality of care indicator for intravenous to oral switch therapy with highly bioavailable antibiotics. J Antimicrob Chemother 2012;67:2043-6.

18. Teo J, Kwa ALH, Loh J, Chlebicki MP, Lee W. The effect of a whole-system approach in an antimicrobial stewardship programme at the Singapore General Hospital. Eur J Clin Microbiol Infect Dis 2012; 31:947–955.

19. Kern WV, Metz-Gercek S, Buyle F, et al. *Staphylococcus aureus* bloodstream infection management indicators as quality indicators for hospital antibiotic stewardship: feasibility study by the ABS International Quality Indicators (ABS QI) team. Abstract of the Nineteenth European Congress of Clinical Microbiology and Infectious Diseases, Helsinki, 2009. 2009.15 p. S188. Abstract P764. Clin Microbiol Infect

20. Malcolm W, Nathwani D, Davey P, Cromwell T, Patton A, Reilly J, Cairns S and Bennie M. From intermittent antibiotic point prevalence surveys to quality improvement: experience in Scottish hospitals. Antimicrob Resist Infect Control 2013; 2:3.

21. Hysong S. Meta-Analysis Audit and Feedback Features Impact Effectiveness on Care Quality. Med Care 2009;47:356–363.

22. Buyle FM, Metz-Gercek S, Mechtler R, Kern WV, Robays H, Vogelaers D, Struelens MJ; on behalf of members of the Antibiotic Strategy International (ABS) Quality Indicators Team. Development and validation of potential structure indicators for evaluating antimicrobial stewardship programmes in European hospitals. Eur J Clin Microbiol Infect Dis 2013;32:1161-70.

23. Redelmeier DA, Cialdini B. Problems for clinical judgement:5. Principles of influence in medical practice. Can Med Assoc J 2002;166:1680-4.

24. Charani E, Edwards R, Sevdalis N, Alexandrou B, Sibley E, Mullett D, Franklin BD, and Holmes A. Behavior Change Strategies to Influence Antimicrobial Prescribing in Acute Care: A Systematic Review. Clin Infect Dis 2011;53:651–662.

25. Dryden M, Saeed K, Townsend R, Winnard C, Bourne1 S, Parker N. Antibiotic stewardship and early discharge from hospital: impact of a structured approach to antimicrobial management. J Antimicrob Chemother 2012;67: 2289–2296.
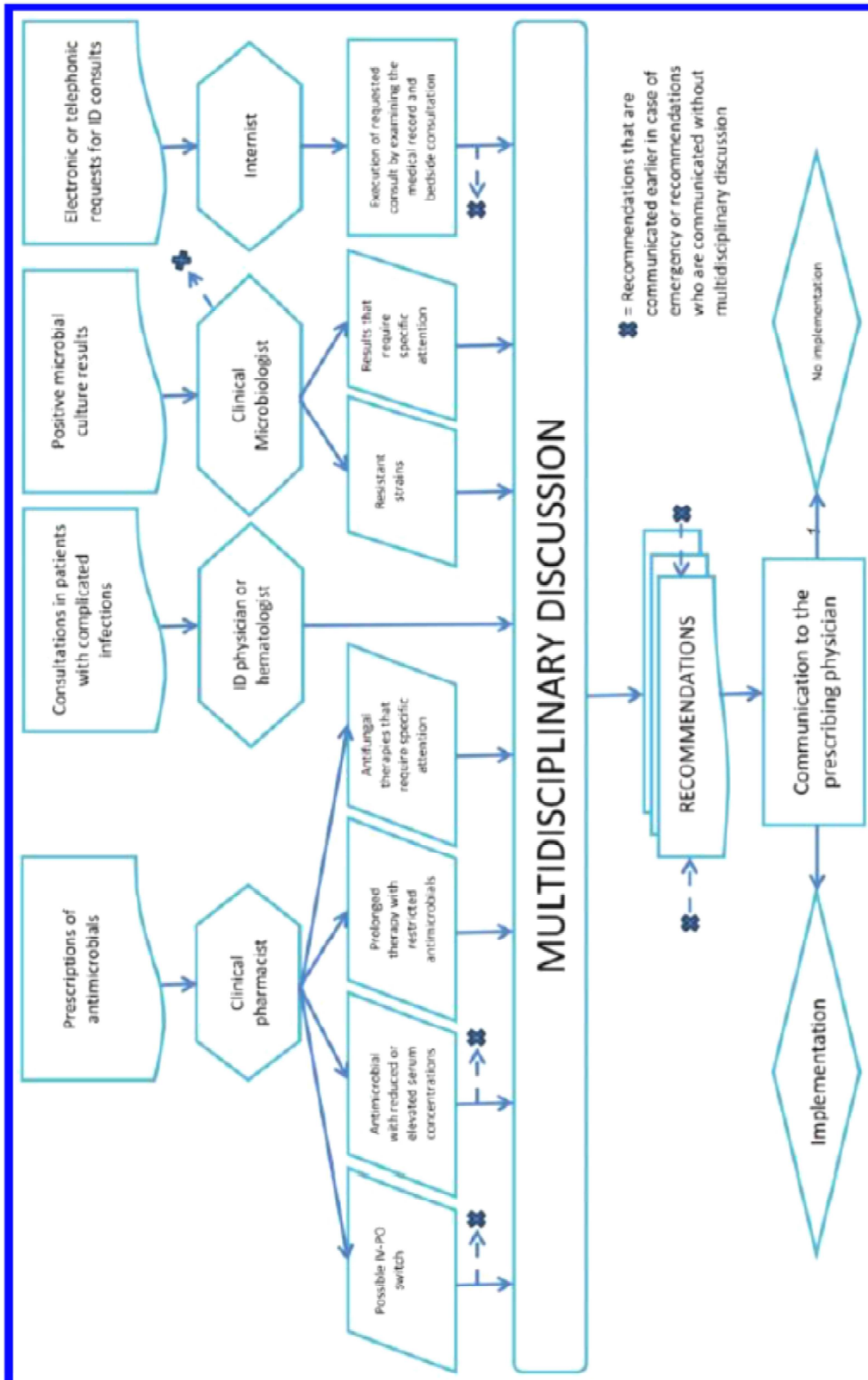
Figure 1 Flowchart activities multidisciplinary infectious diseases team.

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CHAPTER 8 DISCUSSION AND GENERAL CONCLUSION

Discussion and general conclusion

Antimicrobial stewardship stimulates the appropriate selection, dosing, route of administration, and duration of antimicrobial therapy. In conjunction with infection prevention it is a key to the prevention and control of the emergence of antimicrobial resistance.

In this thesis we describe the development and validation of quality indicators in order to monitor antimicrobial stewardship programs in a European context (Chapter 2-3). Furthermore we described elements of an antimicrobial stewardship program to optimize antimicrobial prescribing in a hospital setting (Chapter 4-5-6-7).

In the following chapter the main findings of each study will be summarized followed by a general discussion and directions for future research.

1. **Main findings**

1.1. **Development of quality indicators for evaluating antimicrobial stewardship programmes**

In the first (Chapter 2) and second study (Chapter 3) we described the development and validation of quality indicators for evaluating antimicrobial stewardship programmes in a European context.

In the first study (Chapter 2), a prospective observational study in 5 acute care hospitals in Austria, Belgium and Germany, we evaluated the feasibility and clinical relevance of measuring an indicator for intravenous to oral switch therapy with highly bioavailable antibiotics. The feasibility of the indicator was evaluated by measuring data availability, data collection workload and sensitivity to improvement. Data were collected over a 3 month period resulting in 211 patients.

Main findings

Feasibility of the indicator.

More than 99% of the required data proved available, which was higher than the pre-set threshold value of 80%. On average, the workload required for collecting, reviewing the data and filling the CRF was 29 min per assessed case. Significant inter-hospital variation suggests that the efficiency of data extraction depends on the quality and accessibility of clinical and pharmacy data sources. Opportunities for automated data extraction from computerized patient records should enhance the efficiency of monitoring such indicators.

Heterogeneity of the performance gap

By intention-to-treat analysis, 37.0% (95% CI 30.5-43.9) of treatments were inappropriate, ranging from 17.5% to 53.8% across hospitals which revealed a substantial heterogeneity of the performance.

The average proportion of inappropriate iv administration was 20.9% in the hospitals with an improvement programme versus 50.0% in the other hospitals (P=0.001).

After adjusting for type of care and type of infection, absence of an iv-to-po switch programme was associated with more inappropriate prescribing (OR 6.78; 95% CI 3.02–15.23; P<0.001).

General conclusion

The results of this study indicated that the iv-to-po quality indicator is widely applicable in acute care hospitals and could be a tool to evaluate compliance with iv-to-po switch guidelines.

In the second study (Chapter 3) we developed structure indicators for antimicrobial stewardship and antibiotic use in a hospital setting. Furthermore, we performed a validation study based on the selected indicators across a pilot sample of European hospitals.

A multidisciplinary panel from four European countries developed structure indicators in three steps: identification and listing of indicators, remote ranking of indicators using multi-criteria scoring, selection of indicators in a face-to-face consensus meeting. Additionally, the top-ten indicators were identified as a minimal set of key indicators. A survey was sent to the directors of antimicrobial stewardship programmes in eleven European hospitals. The yes/no answers for the indicators were transformed into numbers in order to calculate the total scores.

Main findings

Development of structure indicators

A final list of 58 indicators was selected and categorised in the following topics: antimicrobial stewardship services (n=12), tools (n=16), human resources and mandate (n=6), health care personnel development (n=4), basic diagnostic capabilities (n=6), microbiological rapid tests (n=2), evaluation of microbiological data on antibiotic resistance (n=3), antibiotic consumption control (n=5) and drug use monitoring (n=4). The top-ten structure indicators with the highest score for ranking and applicability were considered to be key elements of an effective antibiotic stewardship programme in a hospital setting (Table 1).

Table 1. Top ten indicators considered as key elements of an antimicrobial stewardship programme (cfr Chapter 3)

Item	Indicator description
Services	Bedside expert consultant advice regarding antibiotics by microbiologist/infectious disease specialist/antibiotic officer on request available on the same day
	Regular ward rounds by members of AMT (multidisciplinary antibiotic management team) performed (at least weekly)
	Clinical audit of prescribers' compliance with local clinical guidelines/guide performed by AMT/AB Officer
Tools	AB formulary/ list biannually updated
	Local clinical practice guidelines/guide for microbiologically documented therapy updated biannually
	Local clinical practice guidelines/guide for empirical therapy available
	Local clinical practice guidelines/guide for surgical antibiotic prophylaxis available
Human resources and mandate	Formal mandate for hospital multi-disciplinary antibiotic management team (AMT) existing
	AB officer or AMT member is member of the drugs and therapeutics committee
Personnel development	Prescriber education by personalized interactive methods (like daily ward rounds) performed

Validation survey

There was significant heterogeneity among participating centers with regard to their scoring for structural components of effective antibiotic stewardship, which ranged from 32 to 50 out of the maximum score of 58. Hospitals with a lower score for the complete set of 58 indicators were also less performant on the top-ten key indicators.

General conclusion

We concluded that a selection among the potential structure indicators examined in this study, with focus on the top-ten indicators could be used for regular assessment of the extent and strength of hospital antimicrobial stewardship programmes.

1.2. Elements of an antimicrobial stewardship program to optimize antimicrobial prescribing

In the third study (Chapter 4) we describe a national Belgian survey investigating the recommendations by the local antibiotic management teams (AMTs) in Belgian acute hospitals for the administration (intermittent, extended or continuous infusion) and therapeutic drug monitoring of four beta-lactam antibiotics (ceftazidime, cefepime, piperacillin–tazobactam, meropenem) and vancomycin

for adult patients with a normal kidney function. Thirty-four (32%) of the 105 Belgian hospitals participated to the survey.

Main findings

<u>Dosing strategies in Belgian hospitals</u>

The implementation of extended/continuous modes of administration was between 10% and 44% for non-ICU wards and between 35% and 81% for ICU wards.

For the non-ICU wards ceftazidime the intermittent administration or continuous infusion method was almost equally used. Piperacillin–tazobactam and meropenem were mainly recommended by intermittent infusion and, if not, by extended infusion. For cefepime intermittent infusion was most recommended and if not, by continuous infusion. For vancomycin about two-thirds of the ICU wards recommended intermittent infusions and one-third by continuous infusion.

For the ICU wards continuous infusion was the predominant mode of administration for ceftazidime and vancomycin. Extended infusion was most often recommended for meropenem. Intermittent administration remained predominant for cefepime and piperacillin–tazobactam, with extended infusion being the next most popular recommendation.

The higher level of adoption in ICUs is consistent with the literature, suggesting that prolonged beta-lactam infusions are advantageous for infections with more resistant pathogens, in critically ill and immunocompromised patients, and in patients with unreliable pharmacokinetics.

<u>Pitfalls</u>

For continuous infusion, a loading dose was recommended for ceftazidime, cefepime and meropenem, but not for all piperacillin–tazobactam dosing regimens. Compared with the recommendations of current literature, the loading dose and the trough target concentration for vancomycin were too low.

<u>General conclusion</u>

Belgian AMTs adopt recent literature on extended/continuous modes of administration in daily practice but more attention should be given to appropriate administration (loading dose, vancomycin target concentrations,..).

In **Chapter 5 and 6** of this thesis we describe 2 interventional studies to optimize antimicrobial prescribing with focus on appropriate timing of the initiation of an antimicrobial treatment and on parenteral to oral conversion of fluoroquinolone antibiotics. Both interventions are examples of persuasive interventions, according to The Cochrane Collaboration which combine audit and feedback.

In the fourth study (Chapter 5) the time to first antibiotic dose (TFAD), defined as the time in hours from arrival of the patient at the emergency department (ED) to the administration of the first

antibiotic dose, was investigated. This indicator, described in literature as a quality indicator for the treatment of infections, was evaluated in the Ghent University Hospital followed by educational interventions in order to optimize the TFAD.

In this retrospective observational study, the TFAD for adult patients with a diagnosis of an infection in the ED for which an antibiotic treatment was prescribed were compared before and after the implementations of an intervention (period A versus B).

A multivariate model was set up to detect key factors associated with TFAD. The following factors were entered in the model: age, gender, LOS, CRP, APACHE II score, place of first administration, type of infection. Sixty-five patients were included in period A and 114 patients in period B.

Main findings

Time to first antibiotic dose

The study showed that 75% of the patients received their first antibiotic dose within 4,19 hours in period A and within 4,50 hours in period B h after admission on the ED.

The univariate analysis showed that the median TFAD in period A was 2.44 hours (IQR 1.78-4.19) versus 3.30 hours (IQR 2.40-4.50) in period B (p=0.034). The median TFAD when the first dose was administered in the ED was 2.14 hours in period A versus 3.2 hours in period B (p<0.001). When the first dose was administered on the ward the TFAD was 4.56 hours in period A and 4.26 hours in period B (p=0.535).

Impact of an intervention to optimize the TFAD

The multivariate analysis showed no difference for TFAD between period A and B but showed that the place of the first antibiotic dose and type of infection were significantly associated with TFAD.

General conclusion

This study showed that our intervention to improve TFAD did not result in any long time improvement.

In the fifth study (Chapter 6) the implementation of guidelines for sequential therapy (intravenous to oral conversion) with fluoroquinolones (FQ) in a Belgian hospital are described. In an interventional monocentric study three persuasive interventions (hospital-wide publication of guidelines in the local drug letter, which is addressed to all physicians; educational interactive session given by infectious disease specialists to the medical staff; a proactive conversion programme initiated by a pharmacist) were implemented.

A pre- and post-prospective study was performed in order to assess the impact of the educational sessions and the proactive conversion programme. All patients treated with intravenous FQ were included for a period covering 2 months before and after the intervention.

At the macro level the hospital consumption of FQ was used to measure the long term impact of the publication of the guidelines by performing an interrupted time-series (ITS) analysis.

Main findings

Interventions

In the baseline group patients (group 1) were treated intravenously for 4.1 days longer than necessary. This parameter decreased to 3.5 days for the patients on wards where an educational interactive session (group 2) was performed and to 1.0 day (P = 0.006) on wards were a proactive conversion programme (group 3) was implemented by a clinical pharmacist.

Impact on the antibiotic treatment and consumption

The mean additional cost for a longer intravenous treatment decreased from 188.0€ in group 1, to 103.0€ in group 2 and 44.0€ in group 3 (P = 0.037).

The mean ratio of IV versus total (IV+ PO) FQ usage was in the 21 months before the intervention 44.5% and decreased to 41.2% in the following 24 months (P = 0.011).

Six months after publication of the guidelines, the IV/PO ratio was increasing. This illustrates that such an intervention has a gradual rather than an instant effect (learning effect) which may decline over time (decay effect).

General conclusion

This study demonstrated that an active implementation of guidelines for sequential therapy is necessary. Several methods of implementation were compared: publication of guidelines, educational sessions by an infectious disease specialist and a pro-active intervention by a clinical pharmacist. The results show that a pro-active intervention results in a significant reduction of the duration of the intravenous treatment, and a reduction in the treatment cost.

The sixth study (Chapter 7) describes the type and acceptance rate of interventions provided by a multidisciplinary infectious diseases team (MIT) in a tertiary hospital. This intervention is an example of educational outreach intervention (another form of persuasive intervention) and can be considered as a core antimicrobial stewardship strategy.

A prospective, observational study in a tertiary care, university teaching hospital with 1062 beds in non-consecutive hospitalized adult patients, excluding intensive care units and pediatrics was performed.

Main findings

Recommendations made by a multidisciplinary infection team

The MIT communicated 432 recommendations in 87 days. Recommendations were made to perform additional clinical investigation(s) [N = 137 (27%)], to adjust the dose of an antimicrobial drug [N = 42 (8%)], to stop an antimicrobial drug [N = 104 (21%)], to switch from a parenteral to an oral drug [N = 39 (8%)] or to initiate an antimicrobial drug [N = 178 (36%)].

Acceptance rate of the recommendations

The acceptance rate of these recommendations were 73.0% for performing additional clinical investigation, 83.3% to adjust the dose of an antimicrobial drug, 81.7% to stop an antimicrobial drug, 76.9% to switch from a parenteral to an oral drug and 84.0% to initiate an antimicrobial drug respectively.

Restricted antibiotics (e.g. vancomycin, piperacillin-tazobactam and meropenem) were more frequently stopped than initiated and oral therapies were more frequently initiated compared with parenteral therapy. This suggests that the MIT can have a positive impact on antimicrobial expenditure.

General conclusion

This prospective observational pilot study showed that the multidisciplinary infectious diseases team, as part of an antimicrobial stewardship program. Acceptance rates were higher for recommendations on pharmacotherapy as compared to diagnostic issues.

2. **Discussion**

2.1. Global perspective

In a global perspective antimicrobial resistance has become a major issue. Increasing resistance may compromise acquisitions in health care and hence affects everybody in the world (1), as infections may increasingly become more difficult to treat. Emergence and spread of new resistance mechanisms seems to outpace the development of new antimicrobials, especially in the field of Gram negative pathogen. The causes of antimicrobial resistance are complex. Some mechanisms involve human behaviour at many levels of society. These include antimicrobial prescription by caregivers both in the community and in hospital settings but also cultural attitudes and expectations within society itself and awareness of potential problems due to irrational use of antimicrobials. The future of antimicrobials and safeguarding their contribution to health improvement will hence depend on the commitment of many stakeholders, including government authorities, policy makers, university teachers, pharmaceutical companies, health-care workers and consumers.

Prevention of infection is superior to treatment of established infection. From a resistance perspective, prevention reduces antimicrobial use and the spread of resistant bacteria. At the community level, improvement of sanitation, access to clean water, poverty reduction, and vaccination will have a huge effect on infectious disease incidence and transfer of multidrug-resistant organisms (1).

When irrational use of antimicrobials is common among the public and health professionals, it becomes the norm. To break this pattern, antimicrobial stewardship programmes should focus not only on appropriate use, but also on ensuring sustainability of behavioural change and reorientation of societal norms. This is comparable with the attitude towards the relation between climate changing and pollution during the last decades around the world and, as such, implies major changes in awareness of the problem and of the shared responsibility to tackle this issue.

The lack of new antimicrobials is a threat for future treatment of infectious diseases. This empty or at the most trickling pipeline can be explained by three reasons: scientific challenges; regulatory requirements, such as the requirement of superiority or noninferiority trials; and market failure (i.e., absence of appropriate incentives to develop medicines for which use is predefined to be restricted). The Office of Health Economics has estimated that, with restrictions, the net present value of a new antimicrobial to a drug company is minus $50 million, whereas a new musculoskeletal drug, without restrictions, is worth $1 billion (1). Ten years ago antimicrobials accounted for up to 20% of the hospital pharmacy budget. Today this contribution has decreased to 5%, as drugs like antitumoral, biological and orphan drugs have moved into a leading role. Society should consider how to reintroduce or to rekindle incentives to develop relevant new antimicrobials. These could include

package deals between civil authorities and pharmaceutical industry ensuring availability and development of these niche antimicrobials in combination with guaranteed market introduction of new drugs in other pharmaceutical classes or in tender systems. Programs such as the 10 by 20 initiative in the United States calling in 2010 for the development and introduction of 10 new antimicrobials by 2020 could offer such frameworks. These should be firmly based on a long term agreement and contract between major stakeholders and, as such, not remain limited to a call or a political wish (2).

2.2. European perspective

On a European level a common strategy is necessary as resistant organisms are not constrained by national borders. Agreement on principles and key components of antimicrobial stewardship programs are necessary to support the EU member states in developing national programs. In Chapter 2 and 3 of this thesis we described two studies that were a part of the project ABS international. ABS International was one the first EU funded initiative focusing on antimicrobials stewardship programs. These studies aimed at the development of relevant indicators, of which the implementation should further be promoted by health organisations.

The Transatlantic Task Force on Antimicrobial Resistance (TATFAR) which is a cooperation between CDC and ECDC, fosters cooperation between US and EU on the issue of antimicrobial resistance. The first TATFAR recommendation refers to appropriate use of antimicrobials in human medicine through hospital antimicrobial stewardship programs and specifically, to the development of common structure and process indicators of antimicrobial stewardship programs (ASP). These consensus set of indicators is expected to be published in 2015. Hopefully this will result in further political steps in European member states to create a framework for implementing ASP. It remains to be assessed whether the Belgian model of a compulsory legal framework for antimicrobial management teams will be more widely applied throughout Europe.

2.3. Belgian perspective

On a Belgian level the BAPCOC structure mirrors the complexity of antimicrobial resistance by focusing on the different fields of community, hospital and veterinary medicine. In this thesis we focused on antimicrobial stewardship programs (ASP) in the hospital setting. These ASP are to be viewed as complementary to hospital hygiene. Both are core elements in tackling the problem of antimicrobial resistance and hence should strongly interact around the hospitalised patient.

In general, antimicrobial stewardship programs are strongly favoured and facilitated by a strong mandate by the hospital board. In the Belgian context there is a legal framework requiring the implementation of antibiotic management teams in all hospitals, with specific funding in the hospital

budget (3). However, hospital financing mechanisms in Belgium are very complex and it is not always clear if and to what extent this budget is truly allocated to the antimicrobial management team.

Undoubtedly, the human resources (both in availability and in quality of interactive communication) are key and more essential than structures in itself in achieving targets of antimicrobial stewardship. Core activities in antimicrobial stewardship programs are education, audit and feedback, surveillance of antimicrobial use and surveillance of microbial resistance and most of these areas require excellent communication skills.

2.4. Availability of guidelines

The availability of guidelines for empirical and documented infections and surgical prophylaxis is essential to support health collaborators in treating infectious diseases (4, Chapter 2-3-6). Although the availability of printed national guidelines (such as the BAPCOC guide for ambulatory use of antimicrobials and the Belgian-Luxembourg edition of the Sanford guide on Antimicrobial Therapy), antibiotic management teams spend a lot of time in developing local guidelines. It should be questioned to what degree this is efficient use of resources and whether standardized consensus approaches could not be generalized and where a balance between general and local guidelines should lie. Our third study showed that practices for extended and continuous antibiotic administration can differ substantially between hospitals in Belgium (Chapter 4). Certainly in this issue more standardisation is strongly recommended.

This objective of a set of national guidelines should ideally take the form of an electronically available and updatable tool. Such a tool should be user friendly to physicians and clinical pharmacists with no infectious disease background. BAPCOC and the Belgian Society for Infectiology and Clinical Microbiology have agreed to be key players and partners to develop and provide such guidelines. Also clinical pharmacists should be strongly involved in this process especially when pharmaceutical aspects are important such as in the administration of extended and continuous antibiotics (Chapter 4) and in screening for interactions (drug-drug, drug-food) etc.

The availability of centrally published practical guidelines should give the opportunity to the institution-based Belgian antibiotic management teams to focus more on the implementation of the guidelines and surveillance of antibiotic use than on the local development of guidelines themselves.

The guidelines of the Dutch Working Party on Antibiotic Policy are an example of guidelines for the use of antibiotics in hospitalized adult patients that have been developed at a national level and are available online (5)

2.5 Implementation of guidelines

The second step is to implement those guidelines in daily practice. First it is essential that the guidelines are easily accessible at the moment the physician prescribes antimicrobial therapies.

In this thesis we used persuasive interventions to implement guidelines. The delivery of printed educational materials, which is also a passive dissemination strategy, slightly improves healthcare professionals' practice (4). The publication of a drug letter in our fifth study showed a limited impact on the ratio of intravenous versus total fluoroquinolone consumption (Chapter 6). Also the impact of educational meetings which we used in two studies was limited when we measured the short term impact or even absent when we studied the long term impact (Chapter 4 and 5). This confirms earlier literature on the limited impact of these types of interventions and warrants an investment into proven effective strategies, such as bedside outreaching activities (4).

This "online" educational outreach however is the most labour-intensive persuasive intervention within an ASP. It combines individual patient assessment, leading to a practical recommendation, supported by motivation, to the prescriber during patient therapy (Chapter 6 and 7). Considering that the median antibiotic consumption in Belgian hospitals is 548 DDD per 1000 patient days, it is clear that it is time- consuming for ASP to identify all patients in whom antimicrobial treatment is inappropriate. It is not feasible that the whole bulk of these prescriptions can be reviewed with the limited manpower involved in AMT. Hence it needs to be assessed to what extent targeted interventions, either through limitation of the scope or restriction in time, would prove to be sufficiently effective to reach preset targets of improvement in relevant antimicrobial prescription indicators and have lasting teaching effects.

In our fifth study the proactive role of the clinical pharmacist in identifying possible IV-PO switches and in advising physicians could be clearly demonstrated (Chapter 6). This allowed us to empower clinical pharmacists to change antimicrobial prescriptions within a predefined and agreed institution-specific protocol, validated by the Antibiotic Management Team and the Medical Pharmaceutical Committee. Active participation of the clinical pharmacist in this process could be further supported by the elaboration of a legal framework defining the different validated activities of the clinical pharmacists. Such a framework, which is currently lacking, could settle the issue of liability in case of mistake and result in more legal responsibilities for clinical pharmacists in advising physicians and nurses. This framework could be similar to the legal description of autonomous or delegated nurse activities in Belgium (6). Both a general legal framework and internal institution specific protocols are especially appropriate for interventions such as IV-PO switch, dose adjustments based on the kidney functions and plasma concentrations levels.

The treatment of infectious diseases is already a significant part of the 3-year curriculum of hospital pharmacists in Belgium. In the future, a subspecialisation in infectious diseases for clinical pharmacists could be considered resulting in an infectious disease residency program comparable with that in the USA where residency graduates are equipped to participate as integral members of interdisciplinary teams caring for patients with infectious diseases, assuming responsibility for their pharmaceutical care (7). However laudable, this official recognition could be difficult to achieve in Belgium, taking into account that even clinical infectious diseases and medical microbiology have not been officially recognized as competencies or specialties in Belgium, in spite of an obvious need.

In our sixth study we described the activities of a local multidisciplinary infectious diseases team (MIT) (Chapter 7). In this MIT, ID consultation and the prescription of different types of antimicrobial agents is reviewed on a daily basis. A number of key antimicrobial classes (antifungals, carbapenems, piperacillin/tazobactam) are reviewed only once a week according the available time and resources. Each advice is motivated and hence rendered transparent and obvious to patient care. From this perspective a regular teaching effect can be assumed through this type of consultation, as antimicrobial prescriptions can be influenced. Certain aspects, such as screening of items such as IV/oral switch or of insufficient dosing of antimicrobials, such as glycopeptides, through screening of therapeutic drug monitoring (TDM) results could be facilitated through increased IT support. With this MIT structure we adapt 3 of the top ten indicators considered as key elements of an antimicrobial stewardship programme (Chapter 3). First of all we provide bedside expert consultant advice regarding antimicrobials on request, which is rendered available on the same day. Secondly we perform on daily basis a clinical audit of prescribers' compliance with local clinical guidelines. Thirdly we educate the prescribers by a personalized interactive method. Other items within the top ten listing of indicators are more generic and are developed within the AMT, of which the MIT somewhat serves as an operational arm.

More efficient identification of inappropriate antimicrobials is possible through electronic alerts which are an example of a structural intervention. Electronic alerts can notify the ASP members or directly the treating physician. Potential electronic alerts include: drug dosing (according kidney function, weight, drug plasma concentrations), dosing regimens (extended and continuous infusions), choice of antibiotic according antibiogram (de-escalation,…) duration of therapy, interactions (drug-drug, drug food), choice of administration route (IV-PO switch), allergy status, positive hemoculture (*Candidemia*, *Staphylococcus aureus* bacteraemia), etc. One of the barriers to implement such electronic alerts consists of potential "alert fatigue". Nevertheless in the future it can be a useful tool for ASP to identify targets for intervention or education and can possibly also provide prescribers with reports and evaluations of their prescribing habits (8,9).

In this thesis no restrictive interventions such as the implementation of a compulsory order form, were assessed. Nevertheless, such compulsory order forms, in which the prescriber has to complete a number of steps with essential clinical information, such as diagnosis and expected pathogens, has proven effectiveness in improving the adequacy of empiric antimicrobial choices and may be part of an antimicrobial stewardship "navigator" integrated in an electronic medical record (8 - 14).

2.6. Barriers to implement guidelines

It is important to recognize that implementing guidelines is a complex process requiring skills beyond those that can be offered by the health professionals (15).

A recent study suggested that ASPs may have more success in implementing their stewardship strategies if they focus on promoting a non-confrontational image (i.e., not a policing image), and in a face-to-face manner when possible (16).

An Australian study showed following barriers: gaps in antimicrobial prescribing knowledge (especially among interns), a lack of awareness about which antimicrobials were restricted and a reliance on senior colleagues to make antimicrobial prescribing decisions. (17). This study confirms that behaviour of physicians should be shaped starting at the undergraduate training and running through their entire professional training as juniors start to copy the behaviour of their supervisors within the first weeks in the hospital (18). Especially on the moment when new (trainee) physicians start in the hospital, clinical pharmacists should be available to make them aware of the existing guidelines and protocols.

Although medical microbiology and infectious diseases specialties are dedicated to the treatment of infections, in reality health care professionals across all specialties are required to be able to promptly diagnose and treat infections. Incentives to change behaviours in prescribing may be to acknowledge local hierarchies and include opinion leaders within different medical specialties in setting up policies and guidelines in prescribing.

In general, physicians also remain concerned about the reliability of an ASP recommendation especially when the patient had neither been seen nor examined by the ASP team stressing the importance of physical outreaching. This could probably explain partly the relative high acceptance rate of the recommendations proposed by the multidisciplinary infection team like mentioned in our sixth study (Chapter 7).

2.7. Outcome of ASP interventions

Measuring the relationship of ASPs interventions on antimicrobial resistance is complex. The time lag and relationship of changes in hospital antibiotic use to resistance patterns are inconsistent and not suited to reliably evaluate ASP interventions. There are, however, other markers of ASP success.

Measurement of antimicrobial use along with other patient-focused outcomes is critical to demonstrate impact of ASPs and should be considered (8,9).

Defining quantitative targets for evaluating antibiotic use in hospitals is difficult. The Scientific Institute of Public Health provides consumption data which allow to benchmark the Belgian hospitals. Interpretation of these data is not easy. More specific data are available on a pathology level including the severity index. But due the significant delay these data provide no clinical relevant data for the AMTs to take action.

Recent data published by the European Centre for Disease Prevention and Control (ECDC) show that the consumption of antibiotics and antimycotics in the Belgian community setting is high compared to other European countries (19). Actions need to be taken as reduction in ambulatory consumption can decrease resistance in community population and reduce import in the hospital setting. A recent study from the Belgian Scientific Institute of Public Health demonstrated the existence of a risk for acquired antimicrobial resistance in major bacterial pathogens, directly related to the consumption of antimicrobial agents at the individual patient level. When prescribing these agents, clinicians should consider that antimicrobial consumption also inherently bears an individual risk for their own patient, besides the resistance induction at the population level that has been known for a long time (20).

Actually the health care system evolves, at least partially, from a pay for service system to a pay for quality system. In order to implement this, quality indicators are necessary. In Chapter 2 and 3 we demonstrated a methodology to test the feasibility of implementing structure indicators and one process indicator in order to evaluate antimicrobial stewardship programs. In 2013, the BAPCOC organized a non- mandatory audit of 3 process indicators in antimicrobial prophylaxis in surgery. In the future other subjects for audit could be urinary tract infections, sepsis, CAP, IV PO switch, *Staphylococcus aureus* bacteremia. For the three last topics, indicators were developed and validated in the ABS international study (Chapter 2). Making these audits mandatory and defining targets could be a next step. We must however take into account that the performance level can vary by hospital according to previous or ongoing local quality intervention programmes. This was also shown in our second study where performance on IV-PO switch was higher for those hospitals with local improvement programs on this topic (Chapter 2).

The point prevalence study performed by the Scottish Antimicrobial Prescribing Group (SAPG) showed that the regular review of national prescribing indicators can drive improvement in quality of antibiotic use in key clinical areas (21). This intervention has been included in a recently developed policy statement of the Belgian Workgroup "Hospital Medicine" of the BAPCOC (22). A target of 90% is set for the indicator that evaluates the traceability of an indication for antimicrobials in the

medical file of an individual patient. Recent meta-analyses indeed suggested that the effectiveness of audit and feedback is enhanced by setting a target or behavioural goal (23,24). For sustainable clinical engagement it is important that national prescribing indicators are seen as drivers for improving clinical outcomes as opposed to being viewed as either punitive or restrictive measures (18). This is important as the experience with the TFAD indicator in the USA has led to an irrational use of antimicrobials caused by the pressure on prescribers to perform well according hospital accreditation programs linked to financial punishment.

Feedback may be more effective when baseline performance is low, the source is a supervisor or colleague, it is provided more than once, it is delivered in both verbal and written formats, and when it includes both explicit targets and an action plan (25).

3. Future research

Future research on the promotion and implementation of antimicrobial stewardship programs should focus on the evaluation of best practices to implement interventions and outcome research.

In view of the wide range of practices aimed at PK/PD optimization, the optimal choices of achieving this through standardization should be further assessed (indications, resistance levels of causative pathogens, modalities of drug administration). Clear guidelines for appropriate administration (doses, schedules, stability, and incompatibility) to allow safe and easy implementation by physicians, nurses and clinical pharmacists are here necessary.

Considering the risk of acquiring nosocomial infections and the likely increase of patients requiring long term antimicrobial therapy for infections with multidrug resistant microorganisms without oral alternatives, the active development of an outpatient parenteral antimicrobial therapy program (OPAT) should be considered. Although already developed under different formats in the USA and the UK, the practice with OPAT in Belgium remains limited and hampered by the absence of a framework for transmural distribution and follow-up. This should be ideally organized through the hospital pharmacy, in coordination with an ID service. Research on this topic should focus on the development of practical guidelines in collaboration with the infectious disease physician, hospital pharmacist, social worker, general practitioner, public pharmacist and home nurse. Clinical outcome and adverse events should be studied. Collaboration with Belgian government is necessary to create a legal framework.

It is necessary to understand the impact of antimicrobial stewardship interventions on resistance rates in hospitals but also in community. We should evaluate which interventions are most effective and cost-efficient to implement clinical guidelines in daily practice with focus on the treatment of highly prevalent infections (CAP, urinary tract infections,..), infections resulting in a high mortality figures (*Staphylococcus aureus* bacteremia, sepsis, candidemia,..) and surgical prophylaxis. In order to evaluate this, evidence based indicators should be further developed and validated by multidisciplinary panels using Delphi technique methodologies. These indicators should be oriented towards pharmacotherapy but also on diagnostic approaches (e.g. in pneumonia timely oxygenation, obtaining of blood and sputum samples).

Indicators can be used on different levels. Local AMT's can incorporate them in a checklist to review the appropriateness of antimicrobial treatments on a frequent basis. This could be used by clinical pharmacists to identify inappropriate therapies. Furthermore they can be incorporated in information technology programs to alert prescribers or AMT's when there is an opportunity to optimize therapies.

Here the implementation of structural interventions like clinical decision support tools and mobile health systems should be studied.

Finally, guidelines get poorly translated into real practice. Hence, the impact of inclusion of behavior change theory into the development and implementation of interventions should be studied, as this may prove crucial in order to achieve true change and improvement.

4. <u>Policy recommendations</u>

International and local authorities have a high responsibility in dealing with the problem of antimicrobial resistance threats. We list in this chapter policy recommendations based on the findings of this thesis oriented towards Belgian authorities.

1. Guidelines for antimicrobial therapy

The Belgian government should provide structural funding for the development and maintenance of national guidelines for empirical, documented and prophylactic antimicrobial therapy in a hospital setting.

Not only data on indications and dosages (inclusive in case of reduced kidney function) should be provided but also practical information on the administration (e.g. continuous infusion, incompatibility, stability,..) to allow safe and easy use by physicians, nurses and clinical pharmacists.

This information should be made electronically available to all health care workers with the possibility to incorporate them in the local CPOE systems. All key players like the BVIKM and VZA should be involved.

These guidelines should be used in the basic and graduated education of physicians and pharmacists to make them familiar with this format in preparation of their professional career.

2. Pay for service system

As the health care system will evolve from a pay for service system to a pay for quality system the government should progress in monitoring and steering the quality of antimicrobial stewardship programs based on predefined indicators. Here we should move from the "soft" structure indicators to the process and outcome indicators which could be measured by performing mandatory audits and defined targets.

The government should provide consumption data on a pathology level which allows benchmarking the Belgian hospitals.

Not only the hospital setting but also the ambulatory setting should evolve in the direction of a pay for service system in order to have impact on antimicrobial prescribing by general practioners.

3. Information technology

Information technology has potential for facilitating antimicrobial stewardship efforts. Here the government should support the cooperation between hospitals in the development/purchasing of new information technology systems as an encompassing project.

4. Awareness campaigns about the threat on antimicrobial resistance

Not only healthcare workers but all Belgian civilians should be aware of the threat on antimicrobial resistance. We need here the same attitude as towards the relation between climate changing and pollution. Here education should start beginning at the primary school.

5. Legal framework for healthcare workers.

As clinical pharmacists increasingly participate in clinical advice towards physicians and nurses a legal framework defining the different validated activities of the clinical pharmacists should be developed. The recognition of the function of clinical infectiology in the hospital organisation is urgently needed.

6. OPAT

Belgian government should create a framework for ambulatory parenteral antimicrobial treatment. All key players from the hospital and ambulatory setting should been involved

5. Conclusion

Antimicrobial stewardship programs can play a major role in the prudent use of antimicrobials in an environment with increasing endemicity of resistance. There is a clear need to better identify the most effective strategies to be developed by antimicrobial management teams and the mechanisms that underlie barriers to implementation. Antimicrobial stewardship is likely to be most effective through a collaborative effort, evolving away from a stand-alone function, to a part of an institution's quality- and safety-enhancing infrastructure (26). It is evident that a successful program requires a structured and systematic interaction of key players within the hospital, including clinical pharmacy, clinical infectiology, medical microbiology and hospital hygiene, not only in formal meetings but foremost in daily practice around the patient as well as a mandate from the institution itself. These activities need to be measurable through appropriate and approved indicators.

References

1. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, Greko C, So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ, Qamar FN, Mir F, Kariuki S, Bhutta ZA, Coates A, Bergstrom R, Wright GD, Brown ED, Cars O. Antibiotic resistance-the need for global solutions.Lancet Infect Dis 2013;13:1057-98

2. Infectious Diseases Society of America. The 10 '20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs. Clin Infect Dis 2010;50:1081–1083

3. Van Gastel E, Balligand E, Costers M, Magerman K, on behalf of the Hospital Medicine Working Group of the Belgian Antibiotic Policy Coordination Committee. Antibiotic management teams in Belgian hospitals: continued improvement in the period from 2007 to 2011 European Journal of Clinical Microbiology & Infectious Diseases 11/2014; DOI: 10.1007/s10096-014-2279-4

4. Giguère A, Légaré F, Grimshaw J, Turcotte S, Fiander M, Grudniewicz A, Makosso-Kallyth S, Wolf FM, Farmer AP, Gagnon MP. Educational materials: effects on professional practice and healthcare outcomes (Review). The Cochrane Library 2012, Issue 10 (accessed online October 30,2014 http://www.thecochranelibrary.com, Davey cochrane, Dellit)

5. The Dutch Working Party on Antibiotic Policy/guidelines. www.swab.nl/richtlijnen. Accessed on April 27 2015

6. Royal Decree KB 15/12/2013.

7. Jodlowski T. Infectious diseases pharmacy residency programs. Am J Health Syst Pharm. 2007;64:2330-2332

8. Hamilton K, Fishman N. Antimicrobial Stewardship Interventions. Thinking Inside and Outside the Box. Infect Dis Clin N Am 2014;28:301–313

9. Wilde A, Gross A. A new practitioner's guide to antimicrobial stewardship Am J Health-Syst Pharm 2013;70:2180-2183

10. Kullar R, Goff D, Schulz L,Fox B, Rose W. The "Epic" Challenge of Optimizing Antimicrobial Stewardship: The Role of Electronic Medical Records and Technology. Clin Infect Dis 2013;57:1005–13

11. Schulz L, Osterby K, Fox B. The Use of Best Practice Alerts with the Development of an Antimicrobial Stewardship Navigator to Promote Antibiotic De-escalation in the Electronic Medical Record Infection Control and Hospital Epidemiology 2013; 34:1259-1265

12. Gillaizeau F, Chan E, Trinquart L, Colombet I, Walton RT, Rège-Walther M, Burnand B, Durieux P. Computerized advice on drug dosage to improve prescribing practice. Cochrane Database Syst Rev. 2013 Nov 12;11:CD002894

13. Steurbaut K, Colpaert K, Gadeyne B, Depuydt P, Vosters P, Danneels C, Benoit D, Decruyenaere J, De Turck F.COSARA: Integrated Service Platform for Infection Surveillance and Antibiotic Management in the ICU. J Med Syst.2012; 36:3765-3775

14. Forrest G, Van Schooneveld T, Kullar R, Schulz L, Duong P, Postelnick M. Use of Electronic Health Records and Clinical Decision Support Systems for Antimicrobial Stewardship. Clin Infect Dis 2014;59:S122–33

15. Charani E, Castro-Sánchez E, Holmes A.The Role of Behavior Change in Antimicrobial Stewardship. Infect Dis Clin N Am 2014:28:169–175

16. Pakyz A. Moczygemba L, VanderWielen L , Edmond M, Stevens M, Kuzel A. Facilitators and barriers to implementing antimicrobial stewardshipstrategies: Results from a qualitative study American Journal of Infection Control 2014;42:S257-S263

17. Chaves N, Cheng C, Runnegar N, Kirschner J, Lee T, Buising K. Analysis of knowledge and attitude surveys to identify barriers and enablers of appropriate antimicrobial prescribing in three Australian tertiary hospitals. Intern Med J. 2014;44:568-74

18. Pulcini C, Gyssens IC. How to educate prescribers in antimicrobial stewardship practices. Virulence 2013;4:192-202.

19. http://www.ecdc.europa.eu/en/publications/Publications/antimicrobial-consumption-europe-esac-net-2012.pdf

20. Catry B et al. Verband tussen antibioticaconsumptie en microbiële resistentie bij de individuele patiënt. (https://www.riziv.fgov.be/drug/nl/statistics-scientific-information/resistance_antibiotic /pdf/study.pdf accessed 8/09/2014).

21. Malcolm W, Nathwani D, Davey P, Cromwell T, Patton A, Reilly J, Cairns S, Bennie M. From intermittent antibiotic point prevalence surveys to quality improvement: experience in Scottish hospitals. Antimicrobial Resistance and Infection Control 2013, 2:3

22. Strategic vision Belgian Antibiotic Policy Coordination Committee 2015-2019 (http://www.health.belgium.be/pdf accessed 27/01/2015)

23. Hysong SJ: Meta-analysis: audit and feedback features impact effectiveness on care quality. Medical care 2009, 47(3):356–363. 25.

24. Gardner B, Whittington C, McAteer J, Eccles MP, Michie S: Using theory to synthesise evidence from behaviour change interventions: The example of audit and feedback. Soc Sci Med 2010, 70(10):1618–1625

25. Ivers N, Jamtvedt G, Flottorp S, Young JM, Odgaard-Jensen J, French SD, O'Brien MA, Johansen M, Grimshaw J, Oxman AD. Audit and feedback: effects on professional practice and healthcare outcomes. Cochrane Database of Systematic Reviews 2012, Issue 6. Art. No.: CD000259. DOI: 10.1002/14651858.CD000259

26. Ashley E, Kaye K, DePestel D, Hermsen E. Antimicrobial stewardship: philosophy versus practice. Clin Infect Dis 2014;59:S112–21

SUMMARY

Health care is challenged by the emergence of antibiotic resistance and the slow pipeline of new antibiotics, especially against Gram negative multi-resistant bacteria. The most important cause of emergence and spread of antimicrobial resistance has been a massive overuse of antibiotics worldwide across all ecosystems over the past decades, including humans, animals, aquaculture, and agriculture. Antimicrobial resistance may lead to more difficult to treat infections and may hence be associated with increased patient mortality, longer hospital stays, and increased healthcare costs. Up to 30% of antimicrobial regimens in hospitals are considered inappropriate. An effective approach to improving antimicrobial use in hospitals is an organised antimicrobial stewardship program.

In this thesis we tried to develop and validate quality indicators in order to monitor antimicrobial stewardship programs in a hospital setting. Furthermore we evaluated key components of an antimicrobial stewardship program to optimize antimicrobial prescribing.

With a multidisciplinary panel from four European countries we developed 57 structure indicators from which ten indicators were identified as a minimal set of key indicators. A validation survey in eleven European hospitals showed a significant heterogeneity with regard to their scoring for structural components of effective antibiotic stewardship. We concluded that potential structure indicators examined in this study, with focus on the top-ten indicators, could be used for regular assessment of the extent and strength of hospital antimicrobial stewardship programs.

The feasibility and clinical relevance of measuring a process indicator for appropriate iv use of highly bioavailable antimicrobial drugs, allowing early IV to oral switch, was evaluated revealing a substantial heterogeneity of the performance gap. Absence of an iv-to-po switch programme was associated with more inappropriate prescribing. The results of this study indicated that the iv-to-po quality indicator is widely applicable and could be a tool to evaluate compliance with iv-to-po switch guidelines.

Optimizing antibiotic dosing regimens is a core activity within an antimicrobial stewardship program. Extended and continuous infusions with betalactam antibiotics have been suggested as a means of pharmacokinetic and pharmacodynamic optimisation of antimicrobial therapy. A survey was undertaken to investigate the recommendations on extended and continuous infusions of ceftazidime, cefepime, piperacillin–tazobactam, meropenem and vancomycin by the local antibiotic management teams (AMTs) in Belgian acute hospitals. This survey showed that extended and continuous infusions are widely implemented in Belgian hospitals but revealed significant variation in the recommended dosing regimens.

Two interventional studies were performed to optimize antimicrobial prescribing. These focused on appropriate timing of the initiation of an antimicrobial treatment for presumed infections in the emergency ward and on parenteral to oral conversion of fluoroquinolone antibiotics. We showed that the implementation of merely persuasive interventions such as hospital-wide publication of guidelines in the local drug letter and educational interactive sessions towards nurses and physicians only resulted in limited improvement. However, a pro-active intervention by a clinical pharmacist to stimulate parenteral to oral conversion resulted in a significant reduction of the duration of the intravenous treatment, as well as in treatment cost.

Finally we assessed the functioning of a multidisciplinary infectious diseases team (MIT), which is an example of educational outreach intervention. The MIT formulated a daily average of 5 interventions for non-critically ill adult patients in a teaching hospital. Following bedside assessment by junior staff, diagnostic and therapeutic recommendations were communicated by phone and by notes towards prescribers in the electronic patient file resulting in high acceptance rates, in particular for therapeutic recommendations.

In general this thesis provides indicators to the AMT's to evaluate their antimicrobial stewardship activities. Proactive interventions on an individual patient level are needed to optimize antimicrobial prescribing.

SAMENVATTTING

Antibiotica-resistentie en de beperkte introductie van nieuwe antibiotica, vooral tegen Gram-negatieve multiresistente bacteriën, vormen een bedreiging voor de gezondheidszorg. De belangrijkste oorzaak van ontstaan en verspreiding van antibiotica-resistentie ligt in het overgebruik van antibiotica zowel in de humane-, veterinaire- als landbouwsector. Antibiotica resistentie geeft aanleiding tot potentieel moeilijker te behandelen infecties en kan daarom gepaard gaan met een verhoogde mortaliteit, langere hospitalisatie duur voor de patiënt en toegenomen kosten voor de gezondheidszorg. Er wordt geschat dat meer dan 30% van het antibiotica gebruik in ziekenhuizen als onoordeelkundig ingeschat kan worden. 'Antimicrobial stewardship' programma's worden als een effectief instrument gezien om het antibiotica gebruik in ziekenhuizen te verbeteren.

In dit proefschrift hebben we kwaliteitsindicatoren ontwikkeld en gevalideerd die toelaten antimicrobial stewardship programma's te monitoren in het ziekenhuis. Verder hebben we elementen van een antimicrobial stewardship programma geëvalueerd met het oog op een optimalisatie van het antibioticagebruik.

In een eerste studie werden met een multidisciplinair panel afkomstig uit 4 Europese landen 57 structuur indicatoren ontwikkeld. Hiervan werden er 10 geïdentificeerd als een minimale set van indicatoren. Een validatie studie in 11 Europese ziekenhuizen toonde aan dat deze indicatoren kunnen worden gebruikt om de performantie van antimicrobial stewardship programma's in ziekenhuizen te evalueren.

In een tweede studie werd in 4 ziekenhuizen een proces indicator getest die toelaat de mogelijkheid tot omschakeling van intraveneuze naar perorale antimicrobiële geneesmiddelen met een hoge biologische beschikbaarheid te evalueren. De afwezigheid van IV-PO switch richtlijnen ging gepaard met minder performant voorschrijven. Deze studie toonde aan dat ziekenhuizen deze indicator kunnen gebruiken om de compliantie aan IV-PO richtlijnen te evalueren. .

Het optimaliseren van antibiotica doseringsschema's is een onderdeel van een antimicrobial stewardship programma. Het toedienen van beta-lactam antibiotica in verlengde of continue infusie is gebaseerd op farmacokinetische en farmacodynamische principes om antimicrobiële therapieën te optimaliseren. Met een vragenlijst gericht aan de Antibioticabeleidsgroepen van de Belgische ziekenhuizen werd gepeild naar de doseringschema's voor ceftazidim, cefepim, piperacillin–tazobactam, meropenem en vancomycine. We konden aantonen dat verlengde en continue schema's in belangrijke mate toegepast worden maar met uitgesproken variatie in de lokaal aanbevolen schema's.

Twee interventionele studies werden uitgevoerd. De eerste bestudeerde het tijdig opstarten van antibiotica bij vermoeden van infectie op de afdeling voor spoedgevallen; de tweede de optimalisatie van de overschakeling van intraveneuze naar perorale fluorochinolones. Het louter verspreiden van richtlijnen en organiseren van interactieve vorming gericht aan verpleegkundigen en artsen resulteerde in een slechts beperkte verbetering. In de tweede studie werd evenwel een duidelijk positief resultaat gedocumenteerd: een proactieve interventie door een klinisch apotheker resulteerde in een significante reductie van de duur en kost van intraveneuze fluorochinolone antibiotica.

Tenslotte werd het functioneren van een multidisciplinair infectieteam als typisch voorbeeld van een "outreach" interventie geëvalueerd. In de bestudeerde periode werden dagelijks gemiddeld 5 aanbevelingen voor volwassen patiënten op niet kritieke afdelingen in een tertiair ziekenhuis geformuleerd. Diagnostische en therapeutische aanbevelingen werden telefonisch en elektronisch via het patiëntendossier gecommuniceerd naar de voorschrijvers. Er werd een hoge aanvaardingsgraad gedocumenteerd, in het bijzonder voor therapieadviezen.

Samengevat worden met deze thesis indicatoren ter beschikking gesteld voor het evalueren van antimicrobial stewardship programma's in ziekenhuizen. Proactieve interventies gericht op de individuele patiënt zijn noodzakelijk om het antibioticagebruik te optimaliseren.

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Publications

- Bauters T, <u>Buyle F</u>, Blot S, Robays H, Vogelaers D, Van Landuyt K, Vanhove W, Claeys G. Prophylactic use of levofloxacin during medicinal leech therapy. Int J Clin Pharm. 2014;36:995-999
- <u>Buyle FM</u>, Wallaert M, Beck N, Boelens J, Callens S, Claeys G, Deryckere S, Haegeman E, Leroux-Roels I, Sermijn E, Steel E, Robays H, Vandekerckhove L, Vermis K, Vogelaers D. Implementation of a multidisciplinary infectious diseases team in a tertiary hospital within an Antimicrobial Stewardship Program. Acta Clin Belg. 2014;69:320-6
- <u>Buyle FM</u>, Metz-Gercek S, Mechtler R, Kern WV, Robays H, Vogelaers D, Struelens MJ; on behalf of members of the Antibiotic Strategy International (ABS) Quality Indicators Team. Development and validation of potential structure indicators for evaluating antimicrobial stewardship programmes in European hospitals. Eur J Clin Microbiol Infect Dis. 2013 Mar 23.
- <u>Buyle FM</u>, Decruyenaere J, De Waele J, Tulkens PM, Van Audenrode T, Depuydt P, Claeys G, Robays H, Vogelaers D. A survey of beta-lactam antibiotics and vancomycin dosing

strategies in intensive care units and general wards in Belgian hospitals. Eur J Clin Microbiol Infect Dis. 2013;32:763-8.

- Buyle FM , Metz-Gercek S, Mechtler R, Kern W V, Robays H, Vogelaers D , Struelens MJ. Prospective multicentre feasibility study of a quality of care indicator for intravenous to oral switch therapy with highly bioavailable antibiotics. JAC 2012;67: 2043-2046

- Claus B, Buyle F, Robays H, Vogelaers D. Importance of infusion volume and pump characteristics in extended administration of ß-lactam antibiotics. Antimicrob Agents Chemother. 2010;54:4950. Epub 2010 Sep 7.

- Buyle F, Vogelaers D, Peleman R, Maele G, Robays H. Implementation of guidelines for sequential therapy with fluoroquinolones in a Belgian hospital. Pharm World Sci. 2010;32:404-410

- Buyle F, Robays H. Evaluation of Belgian hospital drug formularies based on quality indicators. EJHP 2009;15:32-37

- Reynvoet E, Vandijck DM, Blot SI, Dhondt AW, De Waele JJ, Claus S, Buyle FM, Vanholder RC, Hoste EA. Epidemiology of infection in critically ill patients with acute renal failure. Crit Care Med. 2009;37:2203-9.

- Vandijck DM, Depaemelaere M, Labeau SO, Depuydt PO, Annemans L, Buyle FM, Oeyen S, Colpaert KE, Peleman RP, Blot SI, Decruyenaere JM.Daily cost of antimicrobial therapy in patients with Intensive Care Unit-acquired, laboratory-confirmed bloodstream infection.Int J Antimicrob Agents. 2008;31:161-5

- Vandijck DM, Oeyen SG, Buyle FM, Claus BO, Blot SI, Decruyenaere JM. Hyperglycaemia upon onset of ICU-acquired bloodstream infection is associated with adverse outcome in a mixed ICU population.Anaesth Intensive Care. 2008;36:25-9

- Vandijck DM, Depaemelaere M, Labeau SO, Depuydt PO, Annemans L, Buyle FM, Oeyen S, Colpaert KE, Peleman RP, Blot SI, Decruyenaere JM.Daily cost of antimicrobial therapy in patients with Intensive Care Unit-acquired, laboratory-confirmed bloodstream infection.Int J Antimicrob Agents. 2008;31:161-5

- Bauters TG, Buyle FM, Verschraegen G, Vermis K, Vogelaers D, Claeys G, Robays H.Infection risk related to the use of medicinal leeches.Pharm World Sci. 2007;29:122-5.

- Blot S, Janssens R, Claeys G, Hoste E, Buyle F, De Waele JJ, Peleman R, Vogelaers D, Vandewoude K.Effect of fluconazole consumption on long-term trends in candidal ecology.J Antimicrob Chemother. 2006;58:474-7

- Bauters TG, Nguyen BT, Buyle F, Schelstraete P, De Cock P, De Jaeger A, Verrijckt A, Robays H. Clinical pharmacy and pediatrics: why focus on antibiotics?Pharm World Sci. 2006;28:3-5

- Bauters TG, Buyle FM, Peleman R, Robays H.Antifungal drugs and rational use of antifungals in treating invasive aspergillosis: the role of the hospital pharmacist.Pharm World Sci. 2005;27:31-4

Poster presentations

- F. Buyle , A. Capiau, J. De Keulenaer, A. Somers, J. Boelens, S. Callens, D. Vogelaers, S. Commeyne. Evaluation of the treatment of Candidemia in the Ghent University hospital . Yearly symposium Flemish Association hospital pharmacists. February 3th 2015 Schelle, België.

- Boelens J, Leroux-Roels I, Callens S, Buyle F, Vogelaers D on behalf of the Multidisciplinary Infection Team of the Ghent University Hospital. Results of a stewardship program for the management of S. aureus bacteremia. 24ste ECCMID 2014, Barcelona, Spanje, 2014.

- M. Wallaert, F. Buyle, D. Vogelaers, S. Deryckere, K. Vermis, E. Haegeman, N. Beck, L. Vandekerckhove, S. Callens, E. Sermijn, F. Moerman, G. Claeys, I. Leroux-Roels, J. Boelens, A. Somers, H. Robays. Evaluation of the recommendations of an multidisciplinary infection team in the Ghent University hospital. Yearly symposium Flemish Association hospital pharmacists. February 5th 2013, Belgium

- Buyle F, Vogelaers D, Claeys G, Robays H. Evaluation of the treatment of *Staphylococcus aureus* bacteremia based on three quality indicators in a University Hospital'. ESCP International Workshop 'Patients, Infections and the Clinical Pharmacist'workshop" 30/05/2012 -1/06/2012; Leuven België

- Buyle F, Delobel C., Van Marcke A., Berkvens R., Verduyn A., Vermeir I., Robays H. Ontwikkeling en implementatie van een e-learning module "Medisch Rekenen" voor gezondheidsmedewerkers in het UZ Gent. Dag van de ziekenhuisapotheker 7 februari 2012, Schelle

- Buyle F, Delobel C., Van Marcke A., Berkvens R., Verduyn A., Vermeir I., Robays H. Ontwikkeling en implementatie van een e-learning module "Medisch Rekenen" voor gezondheidsmedewerkers in het UZ Gent. 5de Symposium Kwaliteit en patiëntveiligheid. Brussel 28 november 2011

- F. Buyle, D. Vogelaers, G. Claeys, J. De Jonghe, H. Robays. *Staphylococcus aureus* bacteriëmie (SAB): evaluatie behandeling en ontwikkeling richtlijnen. Dag van de ziekenhuisapotheker. 22 februari 2011

- F. Buyle, M. Besset, J. Decruyenaere, H. Robays, J. De Waele. Evaluation of the pharmacokinetic effect of the interaction between valproate and meropenem in critically ill patients. EAHP March 23 2010, Nice, France

- F. Buyle, S. Metz-Gercek, M. Struelens and the ABS team. Feasibility Testing of an Indicator for Intravenous to Oral Switch with Highly Bio-available Antibiotics. ICAAC September 15th 2009, San Francisco, USA (oral presentation)

- W. Kern, S. Metz-Gercek, F. Buyle, V. Jindrak, A. Lechner, H. Mittermayer, H. Seifert, A. Wechsler-Fördös, C. Wenisch, T. Zupanc-Leijko, R. Mechtler, M. Struelens and the ABS QI Team .Staphylococcus aureus bloodstream infection management indicators as quality indicators for hospital antibiotic stewardship: feasibility study by the ABS International Quality Indicators (ABS QI) team. ECCMID meeting, Helsinki from May 2009

- M. Struelens, S. Metz-Gercek, R. Mechtler, F. Buyle, A. Lechner, H. Mittermayer, F. Allerberger, W. Kern and the ABS QI Team & Feasibility Study Participants. Validation of quality indicators for hospital antibiotic use by the ABS International – Quality Indicators (QI) Project ECCMID meeting, Helsinki from May 2009

- F. Buyle, T. Verdonck, D. Vogelaers, J. Decruyenaere, L. Vandekerckhove, T. Fiers, A. Dhondt, H. Robays. Evaluation of antibiotic dosages in patients with a reduced kidney function. ESCP November 2008. Dubrovnik, Croatia

- Deryckere S, Buyle F, Van Hooreweghe M, Robays H. Maatregelen ter promotie van oraal gebruik van paracetamol in UZ Gent. Annual meeting Flemish Hospital Pharmacists, Gent, Ghent March 1st 2008

- F. Buyle, S. Deryckere, A. Clerens, D. Vogelaers, J. De Waele, J. Decruyenaere, L. Vandekerckhove, T. Fiers, H. Robays. Evaluation of administration of glycopeptide antibiotics. Annual meeting Flemish Hospital Pharmacists. Ghent March 1st 2008

- F. Buyle, S. Deryckere, A. Clerens, D. Vogelaers, J. De Waele, J. Decruyenaere, L. Vandekerckhove, T. Fiers, H. Robays. Guideline and algoritm for administration and monitoring of glycopeptide antibiotics. Annual meeting Flemish Hospital Pharmacists. Ghent March 1st 2008

- Vandijck DM, Blot SI, Depaemelaere M, Oeyen S, Colpaert KE, Annemans L, Vandewoude KH, Peleman RP, Buyle FM, Labeau SO, Decruyenaere JM. Candidemia in the Critically Ill: An Economic Analysis of Daily Antimicrobial Therapy Related Costs. 20th Annual Congress of the European Society of Intensive Care Medicine (ESICM), Berlin, Sept 24-27, 2007. *Intensive Care Med* 2007; 33, S159: 616.

- Vandijck DM, Blot SI, Depaemelaere M, Oeyen S, Colpaert KE, Annemans L, Peleman RP, Buyle FM, Labeau SO, Decruyenaere JM. Daily Cost of Antimicrobial Therapy in Critically Ill Patients with Nosocomial Sepsis. 20th Annual Congress of the European Society of Intensive Care Medicine (ESICM), Berlin, Sept 24-27, 2007. *Intensive Care Med* 2007; 33, S206, 798.

- F. Buyle, V. Bostoen, D. Vogelaers, W. Buylaert, P. De Paepe, J. Decruyenaere, H. Robays. Evaluation of the initialisation of appropriate antibiotics in patients admitted through the emergency department with suspected serious infections. December 2005, Las Vegas, VS (oral presentation)

- F. Buyle, M. Bogaert, T. Bauters, B. Claus, E. Kestens, A. Somers, M. Van Hooreweghe, H. Robays. "Evaluation of Belgian hospital drug formularies based on quality indicators" during 5th Spring conference European Symposium on Clinical Pharmacy. (25 May oktober 2005, Stockholm, Sweden)

- F. Buyle, N. Beck, T. Bauters, R. Peleman, D. Vogelaers, M. Van Hooreweghe, H. Robays. "Evaluation of the implementation of sequential therapy for fluoroquinolones" tijdens 39th Midyear meeting American Society of Health-System Pharmacists (7 december 2004, Orlando, VS)

- Buyle F, Vogelaers D, Peleman R, Schelstraete P, Verschraegen G, Claeys G, Van Hooreweghe M, Robays H. A multidisciplinary prospective interventional program to enhance appropriate prescribing of restricted anti-infectives in the Ghent University hospital. Abstract en poster tijdens 32th European Symposium on Clinical Pharmacy (30 oktober 2003, Valencia, Spain)

- Somers A, Buyle F, Robays H, Colardyn F, Verschraegen G. Evolution of antibiotic consumption and resistance patterns in the intensive care unit. Abstract en poster tijdens BESPE-symposium (23 november 2002, Gent)

- Buyle F, Vogelaers D, De Cloet J, Somers A, Kestens E, Van Hooreweghe M, Robays H. "Drug Use Evaluation of fluoroquinolones and piperacilline/tazobactam in the surgical intensive care unit of a university hospital". Abstract en poster tijdens BESPE-symposium (23 november 2002, Gent)

- Buyle F, Somers A, Van Hooreweghe M, Vander Stichele B, Bogaert M, Robays H. Quality Indicators for Pharmacotherapy and Pharmaceutical Care in Hospitals: development and feasibility". Abstract en poster tijdens BESPE-symposium (23 november 2002, Gent)

- Buyle F, Vogelaers D, De Cloet J, Somers A, Kestens E, Van Hooreweghe M, Robays H. "Drug Use Evaluation of fluoroquinolones and piperacilline/tazobactam in the surgical intensive care unit of a university hospital. Abstract en poster tijdens 33th European Symposium on Clinical Pharmacy (30 oktober 2002, Florence, Italy)

- F. Buyle, A. Somers, M. Van Hooreweghe, H. Robays. Drug use evaluation of glycopeptide antibiotics. Poster ESCP Congress (oktober 1999, Berlijn)

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