Nosocomial Intensive Care Infections

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Ziekenhuis verworven infecties op de intensive care unit

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CHAPTER 1

General introduction

THE GROWING INCIDENCE OF NOSOCOMIAL INTENSIVE CARE INFECTIONS

The advances to be made in critical care are hampered by the increasing incidence of nosocomial Intensive Care (ICU) infections. These infections are acknowledged to be a major growing clinical problem in hospitals worldwide, and within the ICU in particular.

ICU patients become more prone to develop infections as the severity of their illness increases. Modern intensive care medicine has to deal with more complex critically ill patients with a temporarily compromised immunity and a plethora of aggressive invasive diagnostics and devices that breach their host defences. These are both intrinsic and extrinsic factors that put these patients at risk. Many of these risk factors are unavoidable during ICU stay. For example, almost all ICU patients require artificial ventilation, which indeed may be a criterion for admission to the ICU. Peripheral or central venous infusions are characteristic; and total parenteral nutrition may be required. Urinary catheters are almost invariably in situ. In addition, various invasive procedures may be performed to monitor the critically ill patient. As a result, several lines of defence are broken. Thus, although these patients benefit from close monitoring with invasive devices, such care is not without hazard.

In the past few years we have seen: a rapid growth in multi-drug resistancy of ICU pathogens to the newest antimicrobial therapy, a growing emphasis on the use of technology and instrumentation, a recognition of new organisms causing infection, and an increasing focus on cost control. Today, ICU patients are more complex critically ill; they are immune-compromised patients who would previously have died of severe illness. To survive, these patients are condemned to the critical care of the ICU, and consequently, they are condemned to stay in the "lion's den of infection". To this day, we have not been successful in taming this growing problem.

THE GROWING IMPACT OF NOSOCOMIAL INTENSIVE CARE INFECTIONS

The costs of nosocomial ICU infections, in terms of added morbidity, mortality, hospital days and hospital charges, are overwhelming. However, besides this impact of nosocomial infections on morbidity, mortality and real costs, another major problem to be mentioned is the fact that these infections may continue to limit the potential advances to be made in critical care medicine. Some data from literature:

In 1981 the costs of excess hospitalization caused by nosocomial infections in the USA was estimated at $2.38 billion per year (1). In 1982 it was estimated that decreasing the nosocomial infection rate by 10-24% in Germany, would result in savings of DM 63 to 800 million per year (2). According to the SENIC Project (Study on the Efficacy of Nosocomial Infection Control) in 1974 in US hospitals: nosocomial infections added over 7.5 million extra hospital days and over 1 billion dollars to the charges for hospital care per year. Hospitals with effective

programs reduced their infection rate by 32%. Among hospitals without effective programs there was an increasing secular trend in the nationwide infection rate of 18% from 1970 to 1976 (3). The nationwide nosocomial infection rate in the USA was estimated to be 5.7 nosocomial infections per 100 admissions to acute care hospitals between 1975 and 1976; this is more than the number of hospital admissions for either cancer or accidents and at least four times greater than admissions for acute myocardial infarction (4). In Australia, the first national nosocomial prevalence study, prompted by the need to collect data on surgical wound infection relevant to the Australian population, estimated that surgical wound infections cost about $60 million in 1984 (5). Hospital-acquired infections occur in 5.7% (incidence) and in 10% (prevalence) of patients admitted to US hospitals. These rates may be 300-400% higher in selected critical care areas (6). Data from seven single-day prevalence surveys, conducted between 1986-1989 in a hospital in Hong Kong, showed infected patients to have an excess mortality rate of 7.4%, an average excess hospital stay of 23 days and an average excess antibiotic expenditure of US $190. The annual costs of potentially avoidable nosocomial infections were calculated at 130 lives, 42,000 bed days and US $ 0.3 million of antibiotics in this hospital (7). Numerous studies have reported high rates of infection in ICU patients accounting for >20% of nosocomial infections, with increased morbidity and financial cost and a mortality exceeding 40% (8-10). Among surgical patients, surgical site infections (SSI) account for 38% of nosocomial infections. It is estimated that SSIs develop in 2-5% of the 16 million patients undergoing surgical procedures each year, i.e.; one out of every 24 patients who have inpatient surgery in the United Sates has a post-operative SSI (11,12). SSIs increase the post-operative length of hospital stay by 7 to 10 days, hospital charges increase by $2,000 to $4,500, and death is directly related to SSI in over 75% of patients with SSI who die in the post-opartive period (13,14). Ventilator associated pneumonia is a major cause of morbidity and mortality, there are approximately 250,000 cases and 23,000 deaths related to this disease each year in the United States. Crude mortality has been estimated to be as high as 70%, and attributable mortality as high as 30% (15). Although intensive care units account for fewer than 10% of total beds in most hospitals, more than 20% of all nosocomial infections are acquired in ICUs (16).

SOME EXAMPLES OF RECENT HIGHLIGHTS IN THE DAY PRESS

- In july 2005, 34 patients in a peripheral hospital in the Netherlands acquired an infection with the intestinal bacterium 'Clostridium difficile' and developed nosocomial diarrhoea. Three patients died because of, or with this infection. The origin was probably the abuse of one type of antibiotic, which already has been removed from the medication list of the hospital.

- Whereas the occurrence of a MRSA (Methicillin-resistant *Staphylococcus aureus*) infection in a hospital in the Netherlands creates frontpage news; elsewhere in Europe (mainly the southern part of Europe) most types of *Staphylococcus aureus* infections are methicillin-resistant, which is now considered to be undergoing an epidemic increase. Hence the designation EMRSA for epidemic MRSA.

- In 1999; almost 250 visitors to the "Floriade" – an indoor flower and garden show – in the northern part of the Netherlands developed Legionnaire's disease and eventually 32 people died. During the following months; ventilator-associated pneumonia caused by Legionnella was observed in several ICUs in the Netherlands, whereas hospital-acquired Legionnaire's isease had not been observed in the decades prior to this outbreak.

- New sources of exogenous infection for nosocomial Intensive Care infections have been reported, including bedside computer keyboards from digital data systems in the newer ICUs, artificial nails of hospital personnel, and piercings (especially through mucous membranes) in patients or hospital personnel.

OUTLINE OF THE THESIS

To evaluate the scale of the problem of nosocomial ICU infections, a European-wide study was conducted: the 'European Prevalence of Infection in Intensive Care' (EPIIC) Study, including 10,038 ICU patients in 17 European countries.

Nosocomial ICU infections are divided in the following categories: 1) ICU-acquired infections, defined as infections clinically manifest or under treatment during ICU stay, but not clinically manifest or incubating at the moment of admission of the patient to the ICU. 2) Hospital-acquired infections, defined as infections clinically manifest or incubating at the moment of admission to the ICU, and apparently related to the preceding hospital stay. 3) Externally-acquired infections, defined as infections clinically manifest or incubating at the moment of admission to the hospital or ICU, and not related to another preceding hospital stay.

The aims of this thesis are 1) to determine the scope and magnitude of nosocomial ICU infections in Europe, and to compare this landscape with the situation in the USA (***chapter 2***), 2) to determine the scope and magnitude of nosocomial ICU infections in the Netherlands, and to compare this landscape with the situation in Europe (***chapter 3* and *4***), 3) to determine the scope and magnitude of nosocomial ICU infections for the surgical ICU patients (***chapter 5***), 4) to determine the scope and magnitude of MRSA (Methicillin-Resistant *Staphylococcus Aureus*) ICU infections, compared with MSSA (Methicillin-Sensitive *Staphylococcus Aureus)* infections (***chapter 6***), and 5) to review the problem of *Candida* ICU infections, called 'the emerging pathogens'(***chapter 7***).

In search for solutions to the candidiasis problem in the ICU setting, we performed a risk analysis of *Candida* peritonitis in the surgical ICU, in order to identify high risk subgroups and to target antifungal prophylaxis or early empirical therapy (***chapter 8***). Furthermore, we evaluated a new, rapid identification method of *Candida* species by Raman spectroscopy, in comparison to the relatively time-consuming conventional microbiological identification (***chapter 9***). Finally, we discuss the future challenges of infection control (***chapter 10***).

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CHAPTER 2

Scope and magnitude of nosocomial ICU infections; European perspective

INTRODUCTION

The scope and magnitude of nosocomial (ICU) infections is overwhelming, with a negative impact on both the added morbidity and the mortality, and as a consequence on the overall hospital charges and economic costs. Many studies come to similar results (1-6). This is not a special European, but also acknowledged to be a worldwide problem. It is special for the ICU, with considerably higher rates of nosocomial infection than in other hospital wards (2, 7-10). Aggressive invasive diagnostics, multiple therapies and a plethora of invasive devices in combination with a temporarily compromised immunity renders the ICU patient population uniquely susceptible to nosocomial infections (11-14). Overall, intrinsic risk together with extrinsic factors make the ICU patient extremely vulnerable to nosocomial infections. As stated by Meakins et al. 'Infection is their Achilles heel' (15). With the continuous recognition, the past few years, of new and more virulent organisms and with a rapid growth in antimicrobial resistance, the problem becomes even worse. Towards the year 2000 the medical profession will face the challenge of infections against which none of the current antimicrobial agents are effective; many clinicians unfortunately are not aware of this impending crisis (16).

The problem of the nosocomial ICU infections will continue to limit the potential advances to be made in critical care medicine. It is therefore of paramount concern to reduce this impact. There is still room for improvement in the control of these ICU infections. Results of the study on the Efficacy of Nosocomial Infection Control (SENIC) have suggested that up to one third of nosocomial infections to which the modern hospital is prone should be preventable (17). An epidemiological database is needed to make a quantification of the scale of the ICU infection problem and to identificate the factors, both intrinsic and extrinsic, that affect it, highlighting the risks to which the ICU patient is exposed. Awareness of the problem of these risks has already been shown to be an important factor in successful implementation of infection control policies (17,18). Investigation of this entity of infection risk must lead to targeted surveillance programmes and the subsequent initiation of appropriate infection control measures, better prevention and appropriate therapy, hopefully resulting in lower infection rates, morbidity, mortality and substantial savings for the hospital budget.

There is a remarkable difference in the knowledge of the magnitude of the infection problem between the USA and Europe. In the United States systematized information concerning the rates of nosocomial infections, ethiological organisms and risk factors are available due to the development of various national formalized systems for ongoing surveillance. In the 1960s, the Centers for Disease Control (CDC) in Georgia began recommending that hospitals conduct surveillance over the occurrence of nosocomial infections to obtain epidemiological evidence on which to base rational control measures (19,20). After an international conference on nosocomial infections in Chicago in 1970 (21) and diverse publications (22) a nationwide movement toward the establishment of organized infection surveillance ensued, and by the end of the 1970s the majority of US nation's hospitals had jumped on the 'surveillance

Table 1. Studies before 1992 of nosocomial infection rates in Europe

Reference	Year	Country	Type of study	Infection rate (%)	No. of ICUs surveyed	No.of patients Included
Bernander *et al.* (26)	1978	Sweden	Point prevalence	72	3	29
Daschner (27)	1982	Germany, Switzerland	3-year incidence	12,5 7,2 total:3-27	5 4	5374 1578
Moro *et al.* (28)	1986	Italy	Prevalence	6,8-12,4 (hosp-ICU)	130	34577
Constantini *et al.* (29)	1987	Italy	1-year incidence	26,9	4	859
Mertens *et al.* (30)	1987	Belgium	Point prevalence	9,3	106	8723
EPINCAT Working Group (31)	1990	Spain	Prevalence	26,8-46,6 (hosp-ICU)	33	7434

bandwagon' (23). In January 1974, CDC initiated the SENIC Project (Study on the Efficacy of Nosocomial Infection Control, 24) to determine whether and, if so, to what extent, this control program approach was effective in reducing nosocomial infection risks (17). Of more recent date the National Nosocomial Infection Surveillance (NNIS) study was generated by 80 medical centers in the USA from 1980-1992 (25). In Europe, no such formalized systems exist, and there has been no large international study to determine the nosocomial infection rates throughout the continent, up to 1992. Only a few studies have been undertaken in individual countries (Table 1, 26-31). With relatively few hospitals taking part in each country and with very low numbers of patients, so examining only hospital-limited rates of infections. Besides, the design of the protocol of these studies differed widely (prevalence opposite incidence studies (32). Consequently it is thus absolutely inappropriate to extrapolate the data from these studies to overall, European, epidemiological ICU settings.

THE EPIIC STUDY

It was against this background that in 1992 the European Prevalence of Infection in Intensive Care (EPIIC) study was undertaken, - the largest ever study of this type, conducted throughout Europe- to deal with the relative lack of information concerning nosocomial ICU infections, providing a new perspective on the scale of the problem in Europe.

The aims of the study

The primary aim of the EPIIC study was to determine, during exactly one day, the prevalence of ICU-acquired infections in patients on ICUs in 17 European countries. In addition, the study

had a number of subsidiary aims: to differentiate the prevalence rates of specific types of nosocomial infections, to establish the microbiology and thus determining those pathogens considered to be causal of these infections, including their patterns of antimicrobial susceptibility (or resistance) to particular antibiotics, to assess the pattern of antimicrobial prescribing, to identify risk factors for infection and to establish the relative importance of these factors by correlating them with the rates and types of infection, to correlate rates of infection with the patients clinical status on admission and with their outcome (death or survival) at a predefined end point in a 6 week follow-up period, and finally to compare infection rates in different types of ICUs and to gauge the variations in infection rates between units in the 17 different countries throughout Europe. The overall key aim of the EPIIC Study was to raise awareness of the problems of nosocomial infection in the ICU and to stimulate discussion, hopefully leading to better prevention, appropriate therapy and improving infection control programs.

The protocol of the study

This point prevalence study was conducted on a 24-hour period, 29 April 1992. On the study day, information was collected for later analysis on 10038 patients in 1417 adult, non-coronary care ICUs in 17 Western European countries, by questionnaire. Nosocomial infections in ICU were classified according to standard definitions of the Centers for Disease Control, CDC (33). Assessment of the patient's status on admission was made on the basis of his/her APACHE II score (Acute Physiology and Chronic Health Evaluation, 34,35). A logistic regression analysis was done to estimate the effects of possible risk factors, measured as odds ratios (OR, comparing relative risks), together with their 95% confidence intervals (CI). In addition multiple logistic regression analysis was done to assess which independent factors affected the overall risks of infection and death, and to investigate the relationship between these different risk factors. The complete methods have been described elsewhere (36,37). The most important reservation of the study to be mentioned, is the difficulty of identifying pathogens, who may have only reflected possible contamination or colonization in stead of represented the cause of the infection.

THE EPIIC RESULTS: EUROPE OVERALL

Participation and demographics of ICUs in Europe

Data from 1417 participating Intensive Care Units, in 17 European countries, were entered in to the study database providing a total of 10038 completed case report forms suitable for analysis. Half of these ICUs were situated in community-based hospitals (51%), 35% in university hospitals, and 14% in university-affiliated hospitals. Most units (74%) were mixed medical/surgical ICUs. The majority of ICUs (57%) were of intermediate size, consisting of

6-10 beds, though 25% were large, having 11 or more beds. Most ICUs (74%) admitted up to 14 patients per week, although a substantial number (11%) had a high admission rate of 22 or more patients per week. There was an average bed occupancy rate on the study day of 79%. The great majority of ICUs had a full-time director (67%) and/or 24-hour physician cover (72%), with consequently up to a quarter having only part-time cover. Other staff regularly joining the ICU teams included a microbiologist (overall 43%), an infection control nurse (24%), a pharmacist (20%) and an infectious diseases specialist (15%). Half of the ICUs (58%) used a written infection control policy (the others having only an informal policy), only a quarter (25%) used a written antibiotic policy, and 66% used regular bacteriological surveillance on the ICU.

Patient demographics

The EPIIC Study population was largely male (62%), and overall predominantly aged over 40 years (83%), 30% was even older than 70 years. Female patients tended to be older than men

Table 2. Patient demography: prevalence of underlying conditions

Organ failure (all types)	56.5%
Impaired respiratory reflex	21.5%
Chronic respiratory insufficiency	14.4%
Carcinoma	13.6%
Diabetes mellitus	12.6%
Multiple trauma with head injury	8.1%
Multiple trauma without head injury	4.4%
AIDS	0.8%

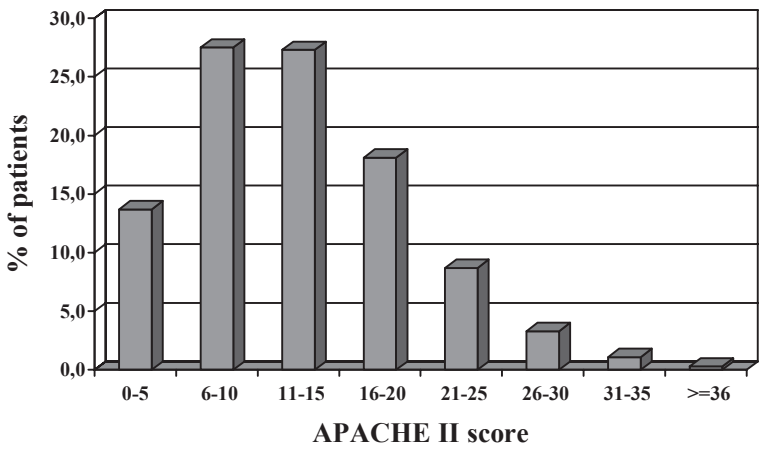

Figure 1. APACHE II scores (% of patients)

Table 3. Prevalence (% patients) of reported potential risk factors for nosocomial ICU- infection, scored in the week preceding the study day.

Length of ICU stay (days)	
0-1	17.8
1-3	28.9
3-5	8.4
5-6	8.6
7-13	13.8
14-20	8.0
>20	14.5
Diagnostic intervention	
Intravenous catheter	78.3
Urinary catheter	75.2
Central venous pressure line	63.9
Mechanical ventilation	63.0
Intubation	62.2
Arterial catheter	44.2
Central iv nutrition	36.5
Wound drain	30.6
Chest drain	14.7
Pulmonary artery catheter	12.8
Tracheostomy	12.6
Peripheral iv nutrition	9.2
Hemodialysis	5.2
Atrial/ventricular pacing	4.8
Intracranial pressure line	2.2
Peritoneal dialysis	0.5
Therapeutic intervention	
Sedation	51.2
Stress ulcer prophylaxis	
H2 receptor antagonist	39.0
Sucralfate	23.5
Antacids	9.2
Omeprazole & others	9.0
Prophylactic antibiotics	19.4
Longterm/ high dose steroids	12.9
SDD	6.3
Immunosupressive therapy	2.7
Radiotherapy	0.3

(mean age 61 and 51 years respectively). From the scored underlying conditions organ failure (of one type or another) was mostly present, in over half of the study population (57%) (Table 2). Half of the patients had undergone surgery in the month prior to the study.; 32% elective surgery and 23% emergency surgery. The site of surgery most frequently performed was ab-

dominal surgery (19%). Organ systems cited as being the most important reason for admission to the ICU were the respiratory (37%), cardiovascular (30%) and central nervous systems (23%). Of the patients 39% were admitted to the ICU for postsurgical control or surveillance. The mean APACHE II score calculated on admission was 12.7 (Figure 1). The prevalence of potential risk factors for nosocomial infection relating to the length of ICU stay prior to 29-04-92 and certain procedural or therapeutic interventions (scored in the week prior to the study) is shown in Table 3 (SDD = selective digestive decontamination).

Prevalence of nosocomial infection and the key infection types

On the study day a total of 4501 patients (45% of the total patient population) had one or more infections. Almost half were ICU acquired infections (21% of the total). Hospital-acquired infections were recorded in 10%, and community-acquired infections in 14%. Of those patients reported as having an ICU-acquired infection, the majority had only one such an infection, although 25% had two or more infections. Figure 2 gives the prevalence of the types of the most frequently reported ICU-acquired infections (incidence > 4.0%).

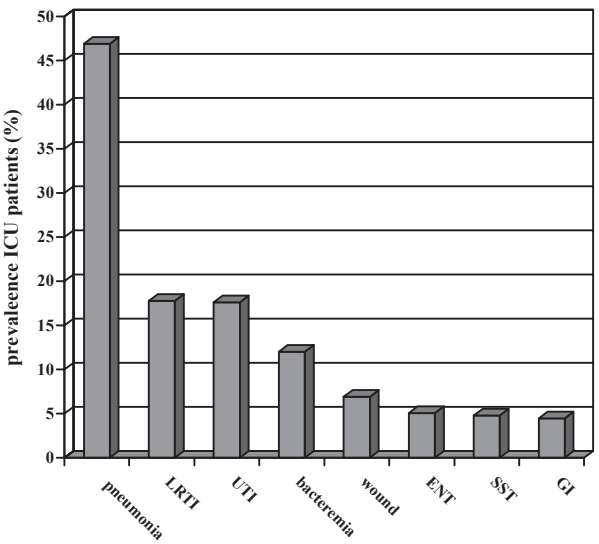

Figure 2. Key infection types. prevalence in ICU patients (%)
Lrti = lower respiratory tract infection, Uti = urinary tract infection, Ent = ear, nose and throat, Sst = skin and soft tissue, Gi = gastrointestinal

The key types of pathogens, isolated from patients with ICU-acquired infections

Overall, 55% of the ICU-acquired infections were polymicrobial. *Staphylococcus aureus* was the 'key pathogen' most frequently isolated (30%). Only the Enterobacteriaceae were reported more often (34%), but as a class. The most commonly reported isolates acquired in the ICU infections are shown in Table 4.

From the Enterobacteriaceae, as a class within the gram-negative organisms, *E.coli* was the most commonly scored pathogen, followed by *Klebsiella spp., and Enterobacter spp.* The Enterobacteriaceae were cultured from a substantial proportion of urinary isolates, particularly *E.coli:* the most common cause of urinary tract infection –both symptomatic and asymptomatic (colonization?)- cultured in 22% of these urinary isolates. In addition, the Enterobacteriaceae were reported in 28% of the lower respiratory tract infections other than pneumonia.

As noted, *S. aureus* was the most commonly reported bacterial isolate overall. Particularly causing skin and soft tissue infections (cultured in 36% of total isolates from this type of infection), pneumonia (cultured in 32%), other lower respiratory tract infections (in 31%), wound infections (in 27%), and laboratory-confirmed bloodstream infections (in 22%).

P. aeruginosa was of substantial importance in pulmonary infections: both in pneumonia (cultured in 30% of the total pneumoniae-isolates), and in the other lower respiratory tract infections (cultured in 35%). Besides, *P. aeruginosa* was also frequently cultured from skin and soft tissue infections (in 33% of total isolates of this infection), wound infections (in 21%), and urinary tract infections (in 19%).

Coagulase-negative staphylococci (CNS) were the most frequently documented isolates in laboratory–confirmed bloodstream infections, being reported in 45% of the cultures. Overall, gram-positive organisms accounted for about 70% of the cultured isolates responsible for bacteremia: besides CNS, *S. aureus* accounted for 22% of isolates and enterococci for 11%. This result confirmed the results of other studies that have documented an increasing number of gram-positive infections, particularly CNS and enterococci in bacteremia (38). This is most probably due to the selective pressure exerted by the use of broad-spectrum antibiotics, such as the third-generation cephalosporins, which are generally more potent against gram-negative than gram-positive bacteria, and to the increasing use of intravascular devices (bearing in mind the propensity of particularly CNS to colonise vascular invasive devices). However, uncertainty exists always over whether CNS are true pathogens or merely contaminants of blood cultures, when taken from an intravascular catheter? In literature, different criteria and definitions have been used to define true bloodstream infections after isolation of CNS (39-41). The EPIIC study used the CDC definitions for laboratory-confirmed primary bloodstream infection, and clinical sepsis (33).

Candida spp. are called 'emerging pathogens', because over the past decades they established themselves as serious causes of infection. Many recent studies reported *Candida spp*. as a significant pathogen (42,43). This growing importance of fungal isolates is related presumably to an increasing use of broad-spectrum antibiotics, in an increasingly immunosuppressed patientpopulation (due to the primary disease and to treatment with corticosteroids). Also the EPIIC results highlighted the growing prevalence of fungal pathogens, with a surprisingly high frequency of 17% (despite the low number of AIDS patients). The most common site from which fungi were cultured, was the urinary tract (isolated in 18% of urine samples, making fungi together with *E. coli* the most important pathogens in urinary tract

Table 4. Prevalence of reported isolates in ICU-acquired infections

Isolate	%
Staphylococcus aureus	30.1
Pseudomonas aeruginosa	28.7
Coagulase-negative staphylococci	19.1
Fungi	17.1
Escherichia coli	12.7
Enterococci	11.7
Acinetobacter spp.	9.3
Klebsiella spp.	8.1
Streptococci (other than pneumococci)	7.1
Enterobacter spp.	6.6
Proteus spp.	5.7
Other Pseudomonas spp.	4.4

infections). In addition, fungi were the third most frequently isolated pathogens in pneumonia (isolated in 14% of the cultures). Again here the difference between infection and colonization remains uncertain, as *Candida* pneumonia is a rare event. Yet more than 50% of patients with a positive fungal isolate were receiving antifungal treatment, indicating that these isolates were thought to be of clinical significance (36).

Other so called 'emerging pathogens' are *the Acinetobacter spp*. These isolates have been cultured mostly in nosocomial pneumonia (in 10%), and in the other lower respiratory tract infections (in 11%).

With respect to the microbiological isolates reported in the EPIIC study, the results are comparable with those of the NNIS study in the USA from 1980 through 1992 (25,44). One exception, being a low prevalence of *Enterobacte*r species in the EPIIC results (6.6%), particularly for laboratory-proven bloodstream infections. In the NNIS study the most common pathogens were P. *aeruginosa* (12%), *S. aureus* (12%), CNS (10%*), Candida spp*. (10%), *Enterobacter spp*. (9%), and enterococci (9%). The data of the NNIS documented the same increasing number of gram-positive infections, particularly CNS (with a frequency of 9% in 1989, increasing to 30% in 1992). The results of all these epidemiological studies emphasizes the need for broad-spectrum antibiotics, when starting empirical antimicrobial therapy on the ICU, being equally effective against gram-positive and gram-negative bacteria, changing to smaller specified antibiotics, effective for the causal pathogens, when culture results are positive.

Pattern of antibiotic administration

In total, 6250 patients (62%) were receiving antimicrobials on the study day, prescribed either for treatment or prophylaxis. Half of these patients (49%) were receiving single antibiotic therapy, the others receiving combination therapy with multiple antibiotics. The most

Table 5. Antibiotics prescribed on the study day (% of total antibiotic use)

Antibiotic	Frequency overall (%)	Use for prophylaxis (%)	Use for treatment (%)
Cephalosporins	43.6	22.1	21.6
Aminoglycosides	23.9	5.4	18.6
Quinolones	11.9	1.6	10.4
Penicillin	10.3	4.8	5.5
Macrolides	4.4	0.8	3.6
Broad-spectrum penicillins	24.3	8.1	16.2
Imipenem	8.1	0.8	7.3
Glycopeptides	11.6	1.2	10.3
Metronidazole	17.1	7.8	9.2
Aztreonam	2.0	0.4	1.6
Other	10.3	2.6	7.7

frequently administered antimicrobials were the cephalosporins, used in 44% of all antibiotic treated patients, both for prophylaxis (particularly cefuroxime and cefazolin) and for treatment (particularly ceftazidime and cefotaxim). Table 5 shows the prescription policy of the scored antimicrobials. Only few patients were receiving treatment with antifungal drugs (6.6%), or antiviral drugs (1.1%). Also the (routinely) use of selective decontamination of the digestive tract (SDD) was rare (overall, 6.3% of ICUs used SDD in the week preceding the study, 5.6% used SDD on the study day). The majority of ICUs in Europe never use SDD.

Pattern of antibiotic resistance

Data were scored about the patterns of microbial resistance to the different types of antibiotics, of the three most frequently reported isolates in the ICU-acquired infections: *P. aeruginosa, S. aureus* and coagulase-negative staphylococci. Of the cultured *P. aeruginosa* isolates 65% were resistant to one or more antibiotics. Most common was resistance of *P. aeruginosa* to gentamicin (in 46% of resistant isolates), followed by resistance to ureidopenicillin (37%), ceftazidime (28%), ciprofloxacin (26%), and imipenem (21%). Overall, 86% of the *S. aureus* isolates were resistant to one or more antibiotics. Of these, 60% of strains of *S. aureus* were resistant to methicillin (MRSA). The most commonly recorded sites of MRSA infection were in the respiratory tract: pneumonia (52%), and lower respiratory tract infections (22%). In total 73% of the CNS isolates were resistant to one or more antibiotics. The data reported a high resistance rate of CNS to methicillin (70% of resistant isolates), cefotaxime (69%), and gentamicin (66%). Resistance of CNS to teicoplanin (9%), and vancomycin (4%) was relatively uncommon, but unfortunately does exist.

The problem of resistant pathogens is becoming worse every day, particularly in the ICU, everywhere throughout in Europe. Once we thought antibiotics to be the answer to infections, now we know they are not. The successes of the past, accomplished with the advent

of (new) antibiotics, selectively eliminating of what were considered to be pathogenic microorganisms, have proved to be an illusion. On the contrary, the emergence of extremely virulent and resistant microbial strains is certainly the result of (mis)use of these antibiotics itself (45,46).

For example, the rapidity with which *methicillin-resistant S. aureus* developed in Europe after the introduction of methicillin (and cephalosporins, as cross-resistance between penicillins and fist generation cephalosporins is a common if not ever present feature). The subsequent spread of MRSA throughout Europe have created enormous problems with consequences for therapeutics and ICU-management. According to the results of the EPIIC study, 60% of strains of *S. aureus* were resistant to methicillin. We evaluated, using the EPIIC-data, the risk of accquisition of an infection with MRSA and the risk of death, compared with patients who developed methicillin-sensitive *S. aureus* (MSSA) infection (47). The most important risk factor was the length of stay in the ICU: the longer the stay, the higher was the risk of an MRSA rather than an MSSA infection (with an odds ratio of 4.07 for a stay longer than three weeks). MRSA infection reduced the chance of survival, particularly when it was found in lower respiratory tract infections: the risk of mortality was three times higher in patients with MRSA than in those with a MSSA infection.

The key risk factors for ICU-acquired infection

Statistical analysis quantified the possible relationship between investigated risk factors and nosocomial infection. After univariate analysis 14 variables were identified as significant risk factors: organ failure of any type on admission, emergency surgery (but not elective), trauma, respiratory problems and mechanical ventilation, various invasive interventions (central venous, pulmonary artery and urinary catheterization, intubation, tracheostomy), stress ulcer prophylaxis, an APACHE II score of more than 6, and prolonged length of ICU stay. The most important risk factor was the length of ICU stay (up to 29.04.92, in days): compared with a length of stay of less than 1 day (odds ratio=1), an ICU-stay of 3-4 days increased the risk of infection nine times. Those patients who had been in the ICU for 3 weeks or more, were at 76 times the risk of the one day patient. The size of the ICU was also a risk factor: patients on greater units were significantly more at risk than those on smaller units. Interestingly, cancer, an age older than 70 years, and elective surgery apparently decreased the odds ratio for infection. Also the type of ICU (medical, surgical, or mixed) and the length of stay in hospital before admission to the ICU, did not significantly affect the risk for infection. Analysing risk factors for special types of infection, also showed the length of ICU stay to be the most important risk factor. Invasive procedures to the respiratory tract (particularly tracheostomy and assisted ventilation) increased the risk of pneumonia. These interventions also increased the risk of laboratory-confirmed bloodstream infection, together with a particular risk due to a central venous pressure line. In addition multiple logistic regression analysis was done to control for the effects of confounding variables, using all the described variables significantly associated

Table 6. Independent risk factors associated with ICU-acquired infection

Risk factor	Odds ratio	95% Confidence interval
Length of ICU stay:		
< 1 day	1	
1–2 days	2.54	1.56 - 4.13
3-4 days	8.99	5.51 - 14.70
5-6 days	15.01	9.33 - 24.14
7-13 days	30.75	19.43 - 48.67
14-20 days	60.40	37.90 - 96.25
≥ 21 days	76.06	48.18 - 120.06
Pulmonary artery catheter	1.20	1.01 - 1.43
Central venous pressure line	1.35	1.16 - 1.57
Stress ulcer prophylaxis	1.38	1.20 - 1.60
Urinary catheter	1.41	1.19 - 1.69
Mechanical ventilation	1.75	1.51 - 2.03
Trauma on admission	2.07	1.75 - 2.44

with infection. Seven variables remained as independent risk factors, shown in Table 6. The APACHE II score was no longer a significant, independent risk factor in this analysis.

Awareness of these risk factors should promote their avoidance where possible, or at the moment the inevitable interventions are not absolutely necessary any more, one should remove them as soon as possible.

Mortality among ICU patients, and the relevance of various risk factors

Data concerning the outcome of the ICU patients (expected, or in the case of death, actual), were recorded on discharge from the ICU, up to a follow-up period of 6 weeks after the study day.Of those patients 83.2% were discharged from the ICU alive, so the overall mortality rate was 16.8%. There was considerable variation in mortality rate by country and by ICU. This does not mean that these differences in mortality do reflect differences in level of care in the ICUs. But rather, these differences are more likely due to differences in the patient-population, arising from discrepancies in admission criteria, reflected in differences in the severity of illness. The patient admitted for postsurgical control or surveillance has another prognosis than the ICU patient with sepsis. Nonetheless, mortality in the EPIIC study was higher in those countries with higher ICU-acquired infection rates. A significant correlation (R^2= 0.68) was noted between the prevalence rate of ICU-acquired infection and the mortality rate. Again caution must be exercised in drawing any direct conclusions. The statement that intensive care patients die of, rather than with, infection is not proven (48). The question that arises is whether infection contributes to mortality? The answer remains unclear. As stated by Gross and van Antwerpen (49) 'In two groups, well matched by many criteria,

Table 7. Independent risk factors associated with mortality

Risk factor	Odds ratio*	95% Confidence interval
Age		
60—69 years	1.7	1.07 - 2.71
≥ 70 years	2.08	1.31 - 3.31
Organ failure on admission	1.68	1.45 - 19.5
APACHE II score ≥ 31	15.55	9.3 - 26.0
ICU stay ≥ 21 days	2.52	1.99 - 3.18
Carcinoma	1.48	1.23 - 1.79
Pneumonia	1.91	1.6 - 2.29
Clinical sepsis	3.5	1.71 - 7.18
Laboratory-confirmed bloodstream infection	1.73	1.25 - 2.41

*OR's: adjusted for age

differences in prognosis on admission probably accounted for the major differences in survival. Nosocomial infections may affect outcome in those whose condition is not terminal on admission'. Notwithstanding that differences in mortality rate cannot be directly attributed to differences in infection rates or differences in microbial resistance, univariate analysis of the EPIIC data confirmed that ICU-acquired infections are among the most important independent risk factors associated with increased mortality. According to the univariate analysis the following risk factors increased the odds of death: various ICU-acquired infection types (wound infection, laboratory-confirmed bloodstream infection, sepsis, pneumonia and lower respiratory tract infection, urinary tract infection, skin and soft tissue infection), an age older than 60 years, organ failure of any type on admission, cancer, diabetes, prolonged stay in the ICU and increasing APACHE II score. The greatest risk was associated with a high APACHE II score (which indeed reflects the risk of death), and with clinical sepsis. After using multiple logistic regression analysis, eight risk factors remained as independently associated with an increased risk of mortality (Table 7).

THE EPIIC RESULTS: EUROPEAN LANDSCAPE

There were marked variations in the results of the EPIIC data between the different European countries. Overall, there was a wide range in prevalence rates of ICU-acquired infections, from 10% in Switzerland to 32% in Italy. There tended to be a trend toward higher infection rates and higher overall ICU mortality rates in Southern Europe. Table 8 shows the prevalence of ICU-acquired infection and the ICU mortality rate for each country taking part in the EPIIC study.It is more likely that these differences are based on differences in patient selection on admission, and in intensive care practice, rather than any real differences in quality and abso-

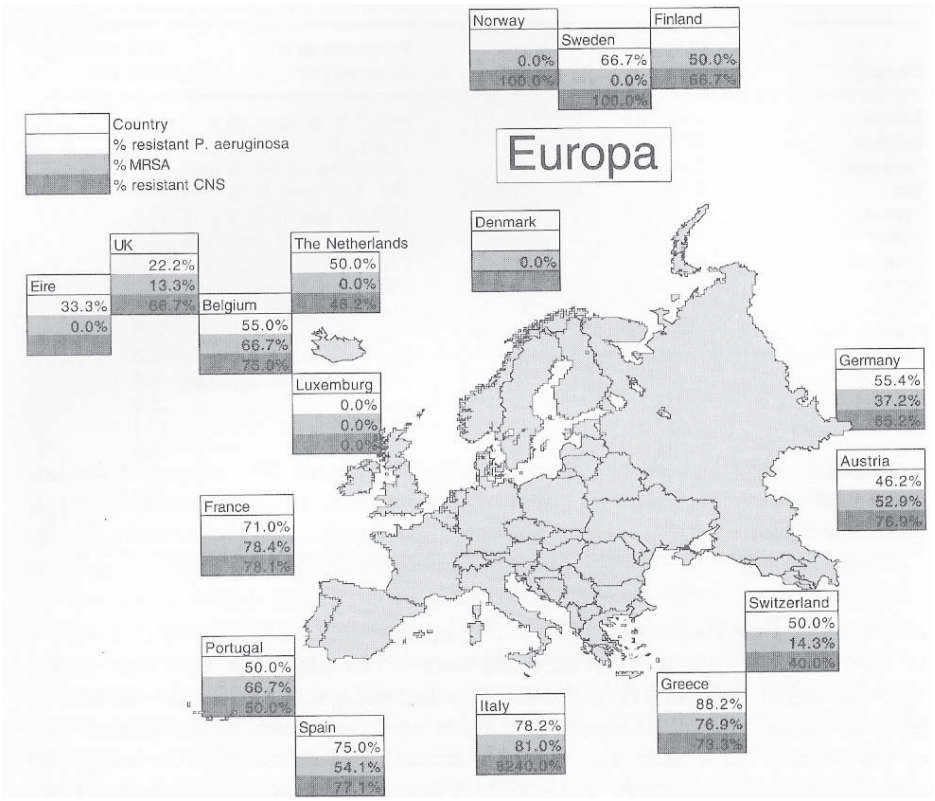

Figure 3. Frequency of resistant *P. aeruginosa*, of MRSA, and of resistant CNS, by country.

lute standards of care. For example, there were substantial differences between the countries in size of the ICU. Most ICUs were of intermediate size, having 6-10 beds. France and Spain had the largest ICUs, with 43% and 42% respectively having ≥ 11 beds. In contrast, in the UK only 5% of ICUs were of this size, while 48% were small ICUs, having up to 5 beds. As mentioned previously, the size of the unit is an infection risk factor it self, with significantly more infections scored in the units of 11 or more beds. There were also wide variations between countries in the ICU resources. Overall, 43% of the ICUs had a microbiologist joining the team, while Denmark, the Netherlands (both 83%) and the UK (73%) had much more often a microbiologist in the team. Discrepancies in patient selection are reflected in differences in the APACHE II scores of the patients on admission to the ICU. The average score overall in Europe was 12.7. There was a more severely ill ICU population in Eire, France, Greece, Italy, Portugal, Spain and the UK, with more than 15% of patients having an APACHE II score >20. In Norway, Sweden, Germany and Switzerland only <10% fell into this category, while >50% had an APACHE II score of 10 or less. Including in the admission criteria also patients just for post-surgical control or surveillance, decreases the average APACHE II score, and most likely decreases the average total length of stay, both with the same impact on the preva-

Table 8. Prevalence of ICU-acquired infection, and mortality rate, by participating country

Country	**No. of ICUs**	**No. of patients**	**Prevalence of ICU infection** (%)	**ICU mortality Rate** (%)
Austria	75	420	20.0	15.3
Belgium	72	669	17.2	14.9
Denmark	12	81	7.4	11.3
Eire	15	91	18.7	11.8
Finland	20	132	15.9	11.9
France	264	2359	24.2	18.7
Germany	268	2010	17.3	14.9
Greece	37	200	30.5	28.5
Italy	110	617	31.6	20.3
Luxembourg	5	29	17.2	13.0
The Netherlands	78	472	15.7	13.8
Norway	23	150	12.7	8.9
Portugal	19	120	23.3	23.9
Spain	137	1233	27.0	19.4
Sweden	39	286	7.7	8.8
Switzerland	49	329	9.7	8.4
United Kingdom	194	840	15.9	19.9
Total	**1417**	**10038**	**20.6**	**16.8**

lence of ICU infections. As part of differences in intensive care practice, there were marked variations between countries with respect to the use of procedural or therapeutic interventions. Overall, the use was often highest in the UK. With respect to antibiotics most countries tended to administer single antibiotic agents for treatment. The exceptions were Eire, France, Greece, Spain and the UK where more than half of the patients with antibiotics were receiving multiple agents. The most considerable difference in the use of antibiotics was noted in the prevalence of SDD. Overall, the majority of ICUs in Europe never use SDD, the scored prevalence for Europe totaly was 6%, while ≥ 40% of units in Austria, the Netherlands and Luxembourg use SDD routinely in a selected patientpopulation.

There turned out to be an enormous intercountry variation in the prevalence of resistant *P. aeruginosa*, of MRSA, and of resistant coagulase-negative staphylococci. Figure 3 shows the frequency of resistance by European countries (taking into account the limitations of a one-day point prevalence survey, and of the sometimes low numbers of patients when analysing this item, making a surprisingly 0% sometimes possible). Apparently several countries have been able to prevent resistance problems in their ICU, by inevitable control measures and screening programs, by using antimicrobial agents only judiciously, and by reinforcing hygienic measures where necessary (47).

SUMMARY

According to the results of the EPIIC study the scope and magnitude of nosocomial ICU infections in Europe is overwhelming. The highlights of the results were the prevalence of pneumonia and other lower respiratory tract infections, the importance of the Enterobacteriaceae (as a class*), S. aureus* and *P. aeruginosa* as the key pathogens, and the high prevalence of microbial resistance of these pathogens to the various antibiotics. Overall, there was a surprisingly growing significance of gram-positive pathogens, and fungi. The key risk factors associated with ICU-acquired infections were in particular a prolonged length of stay on the ICU, and various invasive interventions. Mortality rates were high, with a significant correlation between the prevalence rate of ICU-acquired infection and the mortality rate (in particular pneumonia, laboratory-confirmed bloodstream infection and sepsis were independent risk factors, associated with an increased risk of death).

Europe needs well-implemented infection control policies, to reduce these preventable infections. Data from the EPIIC study are just a starting point and motivating factor to achieve this. Up to this moment there is in Europe no formalised and ongoing surveillance system (such as the NNIS in the USA), needed to establish, stimulate, up date, continuously improve the quality, and evaluate the effectiveness of such control programs. The ultimate aim for the future is more European collaborative efforts in infection control. Recently European boundaries are opened for traffic and tourism, consequently also for micro-organisms, making the task to control resistant pathogens increasingly difficult.

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CHAPTER 3

Scope and magnitude of nosocomial ICU infections; Dutch perspective – a risk analysis

ABSTRACT

Objective: Evaluation of the point prevalence of nosocomial infections, acquired in the intensive care unit (ICU) and determination of risk factors for ICU patients.

Design: Descriptive study.

Setting: 78 Dutch ICUs.

Methods: Collecting data by detailed questionnaires for each patient admitted to one of the participating ICUs, on one specified day (a one-day point prevalence survey: April 29th 1992), and after a follow-up period of 6 weeks.

Results: Included in the study were 472 ICU patients; 176 (37%) suffered from an infection of which 74 (16%) was ICU-acquired. The most important risk factors were: the duration of an ICU stay (relative risk (RR) 4.23 (95% confidence interval: 3.32-5.40), 99.37 (22.26-434.50) and 146.79 (32.83-656.30) for ICU stays of 3-4 days, 1-2 and more than 3 weeks respectively, compared to a stay of 0-2 days), correlated with severity of disease (organ failure) and more medical interventions (mechanical ventilation, urinary catheter). The risk of acquiring a nosocomial ICU infection was lower after elective surgery than after ICU admission without previous surgery; after emergency surgery the ICU infection risk was higher.During follow-up 63 (14%) patients died. Patients suffering from an ICU infection had a higher mortality risk; the strongest prognostic factor to determine the mortality risk was the APACHE II-Score (RR: 13 (3.89-42.69) with a score between 16-26 and RR > 100 (7.67-1377.93) with a score > 31).

Conclusion: ICU-acquired infections are a serious problem. Programmes for infection prevention and strategies in infection control need to be adjusted.

INTRODUCTION

World wide, it has become obvious that the problem of nosocomial infections is increasing. The impact of these nosocomial infections on morbidity, mortality and hospital costs is growing (1-7), despite improvements made within the antisepsis policies, where development of active and passive immune therapy and the further development of antibiotics were important. While we have succeeded to control and treat the infections outside the hospital, nosocomial infections inside the hospital are still increasing. It appears that, contrary to earlier belief that the use of antibiotics was the answer to prevention of these infections, the use of antibiotics will cause colonisation with pathogenic micro-organisms. The "sine qua non" theory (without pathogenic micro-organisms there is no infection), which regarded for long as being the basis of the effort to control micro-organisms and infections, turned out to be fiction. Because of the abuse of antibiotics during the last decades to eliminate pathogenic micro-organisms, more virulent and resistant micro-organisms have emerged.

The growing problem of nosocomial infections is not only due to the growing incidence of resistant micro-organisms. Other factors contributing to this problem include the growing number of patients with (iatrogenic) immune suppression and disturbed endogenous flora, a more frequent use of medical interventions, a longer hospital or intensive care unit (ICU) stay and a higher average age of the patients. Intrinsic risk factors (lower host resistance) together with extrinsic ones (interventions, more virulent and resistant micro-organisms) make the ICU patient most vulnerable to nosocomial infections. Meakins stated: 'Infection is their Achilles heel'(8).

Because there was a lack of knowledge on the prevalence of risk factors for nosocomial infections in European ICUs, a new study was conducted: "the European Prevalence of Infection in Intensive Care" (EPIIC) Study. This article describes the Dutch results of the EPIIC Study.

PATIENTS AND METHODS

The EPIIC Study, which involved 17 West European countries, collected data on the prevalence of ICU infections on one specified day: April 29th 1992 (a one-day point prevalence survey). All ICUs were invited to take part in the study, except for neonatal and paediatric ICUs and coronary care units. All patients (older than 10 years) admitted to one of the participating ICUs, were included in the study.

Prevalence

Infections were defined according to the CDC-criteria (9). ICU-acquired infections were defined as infections clinically manifest or under treatment at the moment of evaluation (April 29th 1992), but not clinically manifest or incubating at the moment of admission of the

patient to the ICU. Hospital-acquired infections were defined as infections clinically manifest or incubating at the moment of admission to the ICU and apparently related to the preceding hospital stay. Externally-acquired infections were defined as infections clinically manifest or incubating at the moment of admission to the hospital or ICU and not related to another preceding hospital stay.

Risk factors

Besides the prevalence of ICU infections, the influence of various infection risk factors was evaluated, in order to identify possible risk groups. For each patient, data were collected by detailed questionnaires, regarding the presence of ICU infections, the bacteriological results and the prescribed antibiotics. In addition, patient data possibly influencing the infection risk were collected, such as age, sex, reason of admission to the ICU and total length of ICU stay. Clinical status at admission was defined by means of the 'Glasgow Coma Score' and the 'Acute Physiology and Chronic Health Evaluation' (APACHE) II-Score. The APACHE II-Score was retrospectively determined, calculated with physiologic data scored during the first 24 hours of the ICU stay (10,11). Additional chronic diseases were scored, such as cancer, diabetes and AIDS. Iatrogenic risk factors, if present, in the week preceding the study day were scored, such as: surgery, invasive interventions, the use of corticosteroids, chemotherapy or other immune modulating therapies, radiotherapy, or the use of sedatives or antacids. In addition, interventions in relation to infection prevention strategies were scored, such as the prophylactic use of antibiotics and selective gut decontamination. Besides, the most important demographic data of each participating ICU, were scored. Finally, data were scored after a follow-up period of six weeks, on the mortality rate and/or discharge from the ICU.

Statistical analysis

The analysed effect of the scored ICU infection risk factors was translated into odds ratios, determined by means of logistic regression models. These odds ratios are like relative risks (RR), in relation to the zero level of this risk factor. In the mean time the influence of possible other infection risk factors is standardised. An RR of one shows no relation between the risk factor and the risk to acquire an infection. Analysing the effect of mortality risk factors, the RRs were standardised for age.

RESULTS

More than half of the ICUs (78/150) in the Netherlands participated in the study, and 472 patients were included (table 1). On the study date, 176 (37%) of the Dutch ICU patients suffered from one or more infections, of which 16% was ICU-acquired, 73% was hospital-acquired and 11% was acquired outside the hospital.

Table 1. Demographics of 472 Dutch ICU-patients (on 29th April 1992)

Characteristic feature	Description	Number of patients (%) *	
Sex	male	300	(64)
	female	172	(36)
Reason for admission	respiratory insufficiency	92	(44)
	cardiovascular insufficiency	64	(30)
	neurologic insufficiency	29	(14)
	postoperative care	267	(57)
≥ 1 previous operation****	in total	306	(65)
	elective **	221	(47)
	emergency **	110	(23)
Type of surgery	abdominal **	117	(25)
	cardiopulmonal	76	(16)
	vascular	50	(11)
Length of ICU stay	< 1 day	118	(25)
	1-5 days	188	(40)
	>5 days	165	(35)
Underlying condition	chronic organ failure	253	(54)
	cancer	75	(19)
	diabetes mellitus	37	(9)
Invasive techniques	peripheral infusion	424	(90)
	central venous catheter	229	(50)
	arterial catheter	286	(62)
	urinary catheter	380	(81)
	pulmonary artery catheter	100	(22)
	wound drain	205	(44)
	thorax drain	81	(18)
	nasotracheal tube	47	(11)
	orotracheal tube	223	(48)
	tracheostomy	40	(9)
Medication	parenteral nutrition	95	(21)
	corticosteroids	84	(18)
	chemotherapy	6	(1)
	other immunosuppresives	11	(2)
	sedatives	216	(47)
	antacids ***	232	(49)
	SDD	68	(15)
	antibiotics in last 48 hours	165	(35)

* Some patients had more than one characteristic.

** Of the patients with multiple operations (n=297), the first operation was in 211 patients (71%) an elective one and in 86 (29%) emergency surgery. The second operation (n=61) was elective in 14 patients (23%) and emergency in 47 (77%). Of the second operations 29 (48%) were abdominal, of the third operations (n=20) 14 (70%) were abdominal.

*** Type of stress-ulcer prophylaxis: 48 patients (10%) used antacids, 131 patients (28%) H2-antagonists, 49 (11%) sucralfate and 29 patients (6%) omeprazole.

**** During last month

There were twice as many male patients as female patients on the Dutch ICUs; 172 females versus 300 males. Most of the patients (87%) were older than 40 years; 35% were aged above 70 years. Only 7% of the patients were admitted primarily to the ICU, without a preceding hospital stay, 57% of the patients were admitted to the ICU for postoperative care. Almost 30% of the patients stayed for 1-2 days in the hospital, before admission to the ICU; 47% of the patients had a preceding hospital stay of more than one week. At admission to the ICU, 8% of the patients were (multi)trauma patients, 54% had one or more chronic organ dysfunctions, 19% were cancer patients and 9% were diabetics. One patient was HIV-seropositive.

Risk factors

Table 2 shows the risk factors with the concomitant RRs and the 95% confidence interval (95% CI). The relative ICU infection risk was significantly lower after elective surgery than after ICU admission without surgery: 0.50. In comparison with an ICU stay of 0-2 days, a stay of 3-4 days had a RR of 4.23. An ICU stay of 1-2 weeks had a RR of 99.37, a stay of more than 3 weeks had a RR of 146.79 (figure 1). The RR for trauma patients was 3.69, the RR for patients with organ dysfunction was 5.03.

The APACHE II score was correlated with the ICU-infection risk; a higher score was correlated with a higher infection risk. In comparison with a score between 0-5, a score between 16-20 had a RR of 9.36 and a score between 26-30 had a RR of 13.90.

Medical interventions with statistically significant RRs were: a central venous catheter, a urinary catheter, mechanical ventilation and a tracheostomy (table 2). The use of antacids had a RR of 3.92.

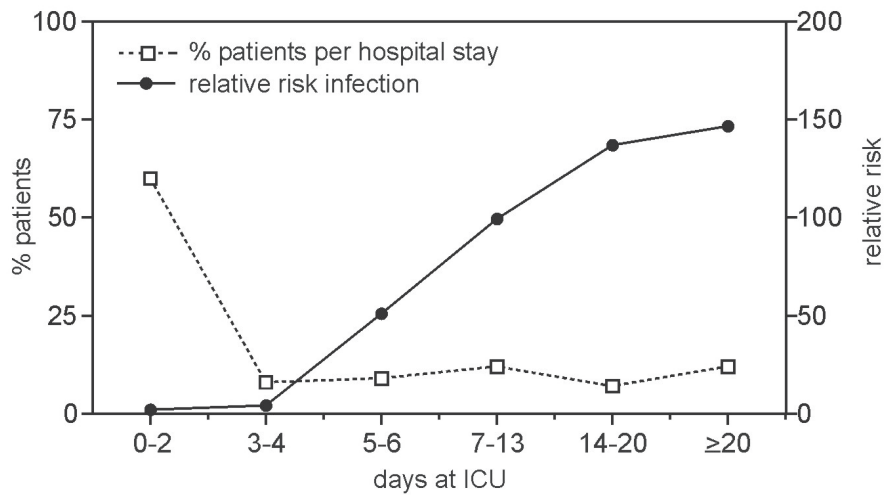

Figure 1. Relative Risk of an ICU-acquired infection, in 472 patients. Left ordinate: percentage of patients by length of stay. Right ordinate: relative risk of infection by length of stay, compared to the risk of infection with an ICU stay of 0-2 days.

Table 2. Relative Risks of potential riskfactors of ICU-infection in 472 patients

Riskfactor	**Relative Risk** *(95% CI)*		**Compared to**
Age			
20-40 years	0.50	(0.10-2.50)	10-20 years
> 60 years	1.25	(0.33-4.62)	10-20 years
Hospital stay before ICU admission			
1-2 days	0.66	(0.32-1.35)	Direct ICU admission
> 3 weeks	1.27	(0.52-3.07)	Direct ICU admission
ICU stay			
3-4 days	4.23	(3.32-5.40)	ICU stay of 0-2 days
1-2 weeks	99.37	(22.2-434.5)	ICU stay of 0-2 days
> 3 weeks	146.79	(32.8-656.3)	ICU stay of 0-2 days
ICU			
Medical ICU	4.17	(1.62-10.72)	Mixed ICU
Surgical ICU	1.69	(0.79-3.62)	Mixed ICU
Surgery			
Elective	0.50	(0.26-0.96)	No surgery
Emergency	1.56	(0.80-3.04)	No surgery
Trauma	3.69	(1.66-8.17)	No trauma
APACHE II score			
16-20	9.36	(2.64-33.14)	APACHE II score 0-5
26-30	13.90	(2.58-75.05)	APACHE II score 0-5
Infusion			
Peripheral	1.34	(0.55-3.27)	No peripheral infusion
Central venous catheter	2.95	(1.73-5.05)	No central venous catheter
Pulmonary artery catheter	1.47	(0.83-2.60)	No pulmonary artery catheter
Ventilation			
Endotracheal tube	5.06	(2.33-10.99)	No endotracheal tube
Tracheostomy	17.59	(6.85-45.20)	No tracheostomy
Any organ insufficiency	5.03	(2.68-9.45)	No organ insufficiency
Respiratory insufficiency	1.48	(0.67-2.89)	No respiratory restriction
Cancer	0.51	(0.22-1.15)	No cancer
Diabetes mellitus	1.28	(0.54-3.04)	No diabetes mellitus
Antacids	3.92	(2.23-6.92)	No antacids
Urinary catheter	10.52	(2.53-43.72)	No urinary catheter

After a follow-up period of 6 weeks, the ICU mortality was 14%. Various mortality risk factors were analysed, all standardised for age. Compared to an ICU stay of 0-2 days, a stay of 5-6 days was correlated with a RR for mortality of 3.37 (95% CI: 1.06-10.73), and a stay of more than 3 weeks had a RR for mortality of 7.12 (3.06-16.54). The most important mortality risk

factor was a higher APACHE II score: a score between 16-26 had a RR of 12.88 (3.89-42.69), a score of more than 31 had a RR > 100 (7.67-1377.93).

Demographics of the ICUs

Finally, data were scored about structure and existing policies of the participating ICUs. Of all the participating ICUs 34% were in University Medical Centers. When subdivided according to type of ICU, 8% were surgical ICUs, 4% were medical ICUs, 78% were combined ICUs and 10% was of other types of specialisation. In comparison to the combined ICU, the medical ICU had a relative infection risk of 4.17 (statistically significant), the surgical ICU had a RR of 1.7 (not statistically significant) (see table 2). ICUs with more than four ventilators had a RR of 2.65 (0.95-7.42) for all patients admitted to this ICU, compared to ICUs with none or a maximum of one ventilator.

DISCUSSION

"The Netherlands belongs to the five cleanest countries of Western Europe, together with Scandinavia and Switzerland". This was the conclusion of a national conference in Amsterdam (March the 12th 1993), dealing with the national and international results of the EPIIC Study (12).

Nevertheless, this conclusion has its limitations, due to the methods and methodology of the survey. Because of these limitations it is better not to overemphasise the results.

The basis of the EPIIC Study is a prevalence survey, during a limited time period of 24 hours (point prevalence survey). Therefore, the data scored in this survey, give only information about the percentages of infection on one specific day of study. One needs to be cautious to extrapolate these data. Obviously, this type of point prevalence survey differs from other types of prevalence surveys, in which prevalence of data in risk groups are scored during a longer period of time. It also differs from an incidence survey, in which only the new patients are scored during a fixed period of time. The choice for a point prevalence survey influences the results. For example, when the incidence of two infections is the same, the point prevalence of the longer lasting infection will be higher than the point prevalence of the infection of a shorter duration.

In the Netherlands 78 of the 150 ICUs participated in the study. Of the 78 ICUs, 34% were in University Medical Centers. This percentage is not representative for all ICUs in the Netherlands, consequently the studied patient group is not representative for all ICUs.

This article only deals with the Dutch results of the EPIIC study, taking into account that the Dutch ICUs are comparable qua structure, policy and patients.

It is not possible to standardise the data for all intrinsic and extrinsic ICU infection risk factors. Consequently, it is not possible to analyse for truly independent risk factors. For example,

the reason for admission to the ICU differs from hospital to hospital; causing a selection bias which influences the prognosis (13). The Dutch ICU differs from the ICUs in foreign countries: the Dutch ICU also has a short postoperative care function, a fact with inevitable a favourable effect to the infection percentages.

The inability to analyse the real independent risk factors was partially solved by calculating the relative risks (odds ratios); in relation to a zero level of the analysed risk factor, fixing other risk factors.

Had the APACHE III Scoring system been part of the methodology of the EPIIC Study, the shortcomings in comparing different hospitals could have been overcome (14,15). However, the APACHE III, recently developed to deal with the shortcomings of the APACHE II, was not ready to be used at the time the EPIIC protocol was formulated.

Despite the fact that "the Netherlands belongs to the five cleanest countries of Western Europe", the results in our own country are disturbing. Whether the infection percentages will increase or decrease will only be known by repeating this kind of prevalence surveys in the future (16).

Which patient is at risk? The most important risk factor to acquire an ICU infection was a longer ICU stay. Compared to a stay of 0-2 days, an ICU stay of 1 week had a relative infection risk of 100. After a stay of 3 weeks, this relative infection risk was 147. A stay in the hospital of more than 3 weeks, preceding the admission to the ICU, had no influence to the infection risk. The reason for this difference is the ICU patient himself, with a reduced immune resistance and multiple exposed entry points, due to invasive devices. In this point of view the ICU stay is like an epiphenomenon, functioning like a positive feed-back mechanism (a so called 'amplifying loop'): the worse the clinical status of the patient, the longer the ICU period and the longer this ICU stay, the more invasive techniques and a more disturbed immune system of the patient. In conclusion: a longer ICU stay gives a higher risk of infection. This amplifying loop influences every analysed risk factor of a patient with a longer ICU stay.

Among the invasive techniques, intubation and mechanical ventilation were associated with the highest risk of acquiring a respiratory tract infection. An even higher infection risk was correlated with a tracheostomy, probably because this device is only used after a longer ICU stay. Patients with a urinary catheter had a relative risk of 10 to acquire an urinary tract infection. Intervenous infusions, central venous catheters, arterial catheters etc., were all associated with a higher ICU infection risk. It is debatable if all these invasive techniques are really necessary, and if these techniques are necessary one needs to wonder if there is not too much routine in this without frequent reassessment. A policy to eliminate, on a daily basis, as many as possible of these potential exposed entry ports, will be the best infection prevention.

Prophylactic medicines, such as sedatives, corticosteroids and antacids, were frequently prescribed. It is better to outweigh the pros and cons in every individual patient of profylactic medicine. Such as the possible increased risk of a pulmonary infection when using prophy-

lactic antacids (17,18). And furthermore, cost and benefits should play a role in the issue of profylactic medicines.

Emergency surgery was associated with a higher ICU infection risk (not statistically significant), while elective surgery was associated with a significant lower infection risk. This difference could be explained both by a difference in the patients preoperative severity of disease and by a difference in the type of surgery; emergency surgery being more frequently of the abdominal type. Of the underlying conditions, organ failure was associated with the highest risk of an ICU acquired infection. In addition, polytrauma patients had an enhanced infection risk.

The APACHE II-Score was strongly correlated with the ICU infection risk, and even stronger with the mortality risk. In this respect, according to this trial the APACHE II-Score was shown to be a good prognostic test.

CONCLUSION

In the Netherlands, ICU-acquired infection is a serious problem with a great impact on and a real threat for every individual ICU patient. In an attempt to reduce this ICU infection problem, a nation wide policy should be implemented dealing with infection prevention and antibiotic prescriptions. The indications for prescribing antibiotics should be tailored and effectiveness should be evaluated. In addition, the indications for and effectiveness of invasive diagnostics and therapeutics should be evaluated.

The EPIIC-Study tries to contribute to the solution of the nosocomial infection problem, by collecting a unique set of data concerning the ICU patients, their conditions and the potential ICU infection riskfactors. A key aim of the EPIIC-Study was to draw attention to the problem of ICU infections and to raise awareness of the possible risks so that further improvements can be made in better infection control in the ICU (19).

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CHAPTER 4

Scope and magnitude of nosocomial ICU infections; Dutch perspective – nature of the infections

ABSTRACT

Objective: Evaluation of the point prevalence of ICU-acquired infections, the type of infection, the bacteriological cultures and the antibiotics used.

Design: Point-prevalence study.

Setting: 78 Dutch ICUs, as part of a study in 17 West-European countries.

Methods: Collecting data by detailed questionnaires for each patient admitted to one of the participating ICUs, on one specified day (a one-day point prevalence survey: April 29th 1992), and during a follow-up period of 6 weeks.

Results: The most frequently seen ICU-acquired infections were: pneumonia and infections of the lower respiratory tract (together 63%), followed by urinary tract infections (16%), sepsis (16%) and wound infections (11%). The most frequently cultured pathogens were Gram-negative bacteria (92%), especially *Enterobacteriaceae* (34%) and *Pseudomonas aeruginosa* (30%), followed by *Staphylococcus* (37%), *Enterococcus* (20%) and surprisingly: 10% fungi. The antibiotics most frequently prescribed were: cephalosporins (30%), followed by broad-spectrum penicillins (17%), metronidazole (17%), and aminoglycosides (13%). No infection with Methicillin-Resistant *Staphylococcus aureus* (MRSA) was found on the day of the point-prevalence study in the Netherlands. Gentamicin-resistant coagulase-negative *Staphylococcus* and ciprofloxacin-resistant *P. aeruginosa* were found however. In many of the hospitals in the Netherlands, microbiologists, infectious disease specialists (84%) and infection control nurses (51%) reside in the ICU team. Nearly half of the hospitals use selective decontamination.

Conclusion: ICU-acquired infections are a serious threat to the ICU patient. Resistance remains a serious problem, despite cautious management of antibiotic therapy.

INTRODUCTION

As described in the previous article, the EPIIC study is an European study of the prevalence of infections acquired in Intensive Care Units (ICUs). In that article the answer to the following question was obtained: "which patient is at risk and which intrinsic or extrinsic factors are related to this risk?" In this article we describe the types of infection found in these ICU patients, the bacterial characteristics of these infections and the course of antibiotics prescribed. Attention was also paid to the prevention of resistant strains of pathogenic micro-organisms in the ICU ward.

PATIENTS AND METHODS

For the chosen method of this point prevalence study we would like to refer to the previous article (1). The data extracted from the questionnaires filled out for each individual ICU-patient were analyzed regarding the type of infection, the localization of the infection, the outcome of the bacterial cultures, and the prescribed antibiotics for either prophylactic or therapeutic intervention.

Infections (if present) could be evaluated in each patient related questionnaire. Each type of infection related to localization was coded according to the "CDC definitions for nosocomical infections" (2) The definitions of ICU-acquired infections, hospital acquired infections and infections acquired outside the hospital are described in previous article (1). The available results of the bacteriological cultures of the diagnosed ICU-acquired infections on the point-prevalence day of the study (April 29th, 1992) were analyzed and divided into the following groups, according to the causal pathogenic micro-organisms: Gram-positive, Gram-negative and anaerobe bacteria, viruses, fungi and protozoa.

The delayed culture results, for up to 1 week following the point-prevalence study day, were analysed too. There was also an analysis of the resistant pathogens, such as methicillin-, or oxacillin-resistent *Staphylococcus aureus* (MRSA) and resistant coagulase-negative staphylococcus and *Pseudomonas aeruginosa*.

RESULTS

78 of the 150 ICUs in the Netherlands participated in this study. A total amount of 472 patients were evaluated.

Infection Policy on the ICUs

In 84% (n=66) of the participating ICUs there was a microbiologist and (or) infectious disease specialist in the team. 51% (40) of the ICUs had an infection control nurse. In 51% (40) of the ICUs is a written antibiotic protocol present and in 81% (63) of the ICUs there is a written protocol regarding infection prevention. Surveillance culturing for bacteriological monitoring occured in 65% (51) of the ICUs. In nearly half of the ICUs (53%; n = 41) selective decontamination of the digestive tract was never used. In 46% (36) of the ICUs selective decontamination was used on indication and 1% (1) of the ICUs used selective decontamination for all admitted ICU patients.

Patient statistics

The discovered ICU-acquired infections and their pathogens are shown in table 1 and 2. The most frequently diagnosed infection was pneumonia, caused by *Enterobacteriaceae* (34%), *P. aeruginosa* (30%) and other Gram-negatives (28%). Table 3 shows the causal micro-organisms per type of infection. Table 4 shows the mostly used antibiotics. 308 Patients (65%) were on an antibiotic treatment on the study day. Of these patients, a total of 173 patients (37%) were on prophylactic antibiotics and 135 (29%) patients were on therapeutic antibiotics. In 58% (178) of the patients antibiotics were given as a mono-therapeutic course, and in 42%

Table 1. The most frequently diagnosed ICU-acquired infections in 472 patients at 78 Dutch ICU's (April 29, 1992)

Type of infection	**Number of infected patients** (%)
Pneumonia	32 (43)
Lower respiratory tract infection	15 (20)
Urinary tract infection	12 (16)
Sepsis	2 (3)
Positive blood culture	10 (13)
Wound infection	8 (11)

Table 2. The most frequently diagnosed pathogens of ICU-acquired infections in 472 patients at 78 Dutch ICU's (April 29, 1992)

Pathogens	**Number of infections** (%)*
Enterobacteriaceae	22 (34)
Pseudomonas aeruginosa	19 (30)
Other Gram-negative micro-organisms	18 (28)
Entrococcus	13 (20)
Coagulase- negative staphylococcus	13 (20)
Staphylococcus aureus	11 (17)
Fungi	7 (10)

*Mixed infections not separately listed which causes the sum to be over 100%

(130) of the patients antibiotic combination therapy was given. A total of 5 patients were part of a clinical trial in experimental medication therapy on the study day.

Although less pneumonias and lower respiratory tract infections were diagnosed in patients subjected to selective decontamination (25 and 8% in patients with selective decontamination, as opposed to 43 and 20% in patients without selective decontamination), more cases of sepsis and (or) positive blood cultures (33% instead of 16%) were diagnosed. The

Table 3. Causal pathogens of the most frequently diagnosed infections in 472 patients at 78 Dutch ICU's (April 29, 1992)*

	Prevalence (%)				
Micro-organism	**Pneumonia**	**LRTI**	**UTI**	**Sepsis**	**Wound**
Pseudomonas aeruginosa	29	29	33	–	63
Staphylococcus aureus	25	–	–	10	25
Enterobacteriaceae	18	–	–	–	38
Escherichia coli	14	–	25	–	–
Haemophilus influenzea	11	14	–	10	–
Fungi	7	–	25	20	–
Serratia	–	21	–	–	–
Other Gram-negative micro-organisms	–	21	–	–	25
Other staphylococcus	–	–	–	60	–
Entercoccus	–	–	–	10	50
Providencia	–	–	–	10	1

LRTI = lower respiratory tract infections; UTI = Urinary tract infections

* Not separately listed which causes the sum to be over 100%

Table 4. Groups of most used antibiotics (therapeutically and prophylactic) in 472 patients at 78 Dutch ICU's (April 29, 1992)*

Antibiotic group	**Treated patients (%)**		
	Therapeutic	**Prophylactic**	**Total (n = 472)**
Cefalosporins	11	19	30
Aminoglycosides	7	6	13
Quinolones	3	2	5
Penicillins	3	5	8
Macrolides	1	1	2
Broad-spectrum penicillins	10	7	17
Imipenem	2	–	2
Glycopetides	2	–	2
Metronidazol	7	9	16
Antimycotix	3	4	7
Antiviral	0.5	0.5	1

*Combined therapy not separately listed

Table 5. Methicilline-resistant *Staphylococcus aureus* (MRSA) at ICUs in a number of European Countries (April 29, 1992)

Country	Number of *Staphylococcus aureus*	MRSA (in %)
Belgium	12	66.7
Germany	78	37.2
Finland	2	50.0
France	153	78.4
Greece	13	77
Ireland	3	0
Italy	63	81
Luxembourg	15	13.3
Netherlands	10	0
Austria	17	52.94
Portugal	50	66.7
Spain	61	54.1
United Kingdom	15	13.3
Sweden	2	0
Switzerland	7	14.3

bacteriological cultures of patients subjected to selective decontamination showed, as already anticipated, less *Enterobacteriaceae* and other aerobe Gram-negative micro-organisms (8 and 8% in patients with selective decontamination as opposed to 34 and 28% in patients without selective decontamination). However, there was a higher occurrence of *Staphylococcus* species in these cultures (58% instead of 37%). No MRSA infections were found in the Netherlands on the study day. In other European countries, MRSA was found (table 5).

In nearly half of the infections caused by coagulase-negative staphylococcus, where a resistance pattern was established, strains were seen with resistance for one or more antibiotic; all were resistant for gentamicin, and some were also resistant for cefotaxim and methicillin. In the infections caused by *P. aeruginosa*, with known resistance pattern, the bacteria was in half of the cases resistant for one or more antibiotic; all strains were resistant for ciprofloxacin and some of them were resistant for gentamicin (table 6).

After 6 weeks, 14% (63) of the patients had died on the ICU. Several risk factors for mortality were present: when standardized for age, patients with a pneumonia had a relative mortality risk (RR) 2.5 times higher (95% confidence interval: 1.01-5.87) than patients without pneumonia; patients with a wound infection had an RR of 3.25 (0.6-17.7) as opposed to patients without wound infection; and patients with sepsis had an RR of 5.0 (0.30-81.07) as opposed to patients without sepsis.

Table 6. Pattern of resistancy of coagulase-negative Staphylococcus and of *Pseudomonas aeruginosa* of 472 patients at 78 Dutch ICU's (April 29, 1992) listed as absolute number of strains of bacteria

Antibiotics	Resistant	sensitive	Missing data
Coagulase-negative Staphylococcus			
Methicillins	4	7	12
Cefotaxim	4	6	13
Gentamicin	6	6	11
Vancomicin	1	9	13
Teicoplanin	0	0	23
Total	6	7	10
P. aeruginosa			
Gentamicin	3	11	6
Imipenem	0	7	13
Ceftazidim	0	14	6
Ciprofloxacin	7	5	8
Ureido-penicillin	0	13	7
Totals	7	7	6

DISCUSSION

The infections most frequently acquired on the ICU were pneumonia and lower respiratory tract infections, although it was not possible to sharply outline the borderline between colonization and actual respiratory tract infection. The explanation for the high number of respiratory infections seemed to be the large number of intubations; intubated patients had a higher risk of infection, and this risk of infection was even higher in patients with a tracheostomy (1). The frequent use of antacids also seemed to contribute to this high percentage of respiratory infections, considering the high percentage of intestinal pathogens as causal micro-organism of the pneumonia (50% *Enterobacteriaceae*, of which the *Enterobacter* and the *Escherichia coli* were mostly cultured) and of the lower respiratory tract infection (53%, mostly *Serratia*). Pneumonia is a serious complication, which increases morbidity and mortality in ICU patients. Patients with pneumonia had a mortality risk which was 2.5 times higher. On the ICU, one needs to be more cautious especially with patients with altered respiratory function. The patient with COPD needs good preoperative care as a preventive measure.

Except respiratory infections, urinary tract infections (UTI) were very common. The risk factor here seemed to be the urinary catheter. It is necessary to mention that two-thirds of these UTIs were nonsymptomatic bacteriuria. It is possible that a great part of these urine cultures were performed as routine.

The percentage of fungi infections was remarkable, this is probably more proof of the immune compromised status of the ICU patient.

It seemed that great care is taken in the Netherlands in the choice and use of antibiotics; broad-spectrum antibiotics like imipenem, glycopeptides (vancomycin), aztreonam and new types of antibiotics were scarcely used (probably to prevent resistance and because of financial cost). This seems to be effective: the Netherlands had only few problems with resistance. On the day of the EPIIC-study, no MRSA infection was found in the Netherlands. When MRSA is found in the Netherlands, the source can be tracked down to patients who imported this infection from foreign hospitals. Most Dutch hospitals have strict policies and protocols regarding MRSA: these patients are in isolated care, which is a costly and time consuming way of treatment and it is (especially for patients and their families)a psychological burden. Nevertheless, this treatment seems to have good results.

A remarkable high resistance of *P. aeruginosa* for the antibiotic ciprofloxacin was registered in the Netherlands (table 6). It is not possible to determine whether this resistance is caused by cross resistance with norfloxacin (an antibiotic which is used in large amounts in the poultry-industry, because of the high occurrence of *Pseudomonas* infections) or by the use of a different method of bacteriologic culturing. The high percentages of ciprofloxacin resistance and coagulase-negative staphylococcus resistance for gentamicin are relatively little relevant, due to the very small numbers obtained.

In contrast to other countries, the Netherlands has a very high percentage of ICUs with a microbiologist, an infectious disease specialist and an infection control nurse on staff in the ICU team. The result of the efforts of these teams is seen in the written procotols regarding use of antibiotics and infection prevention. Frequent (sometimes on a daily basis) culturing for the purpose of surveillance and bacteriological monitoring is part of infection prevention in 65% of the ICUs. One needs to wonder if these standard surveillance cultures are either useful or abundant diagnostics. For example, one has to wonder if therapy is or should be initiated when a urinary tract infection is diagnosed while the patient is not presenting clinical symptoms. In our opinion it is proficient to take cultures at time of admission to the ICU for the purpose of obtaining an overview and start reference, so that specific antiobiotic treatment can be initiated when infection occurs, instead of administering unnecessary broad-spectrum antibiotics.

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CHAPTER 5

The surgical ICU patient: a patient at risk

INTRODUCTION

Infections are common but serious complications of the treatment of critically ill patients. The scope of these ICU infections is overwhelming, with a substantial increase in morbidity, mortality and as a consequence in the overall hospital charges and economic costs (1-4). Moreover, these ICU infections may limit the potential advances to be made in critical care medicine.

ICU patients become more prone to develop nosocomial infections as their severity of illness, the complexity of underlying diseases and exposure to life-saving invasive devices and procedures that breach their host defences, increase(5-8).

It seems to be that the surgical ICU patient is even more prone to nosocomial ICU infections than non-surgical patients. Indeed, surgical departments have a higher rate of nosocomial infections than medical or pediatric departments. The nature of the infections and the spectrum of causative organisms depends on very diverse factors, e.g. type of patient, type of surgical intervention, age of the patient, application of antibiotics (especially peri-operative antibiotic prophylaxis), and training and compliance of the hospital staff.

The focal surgical wound infections are not the only documented infections in surgical ICU patients. In fact, they play a minor part in the frequency of the infection sites in these patients. Ventilator associated pneumonia and respiratory tract infections are the most frequently reported ICU-acquired infections, also in surgical patients (9-11).

Surgical site infection

Outside the ICU, surgical wound infections are the most common nosocomial infections among surgical patients. While usually localised to the incision site, surgical wound infections can also extend into adjacent deeper structures; thus the term surgical wound infection has now been replaced with the more suitable name, surgical site infection (SSI), with a sub-classification of superficial SSI, occuring in the primary incision down to the fascial layer, and deep SSI, located under the fascia. An organ or space SSI may involve any part of the anatomy –other than the incision- that was opened or manipulated during the operative procedure. The Centres for Disease Control and Prevention (CDC) has developed standardised criteria for defining surgical site infections, i.e.: 'infections related to the operative procedure that occur at or near the surgical incision within 30 days of an operative procedure'(12).

In the United States SSI accounts for approximately 40 percent of all nosocomial infections. Same results are documented from surveys in Europe (13-15). Rates of SSI vary widely depending upon the patient population, size of hospital, experience of the surgeon, methods used for surveillance and the type of procedure. For example: several studies noted an increased risk of SSI in patients with cancer who had to undergo surgical procedures (16), and non teaching hospitals have generally lower rates of SSI compared to teaching hospitals (17). The highest rates of SSI occur after abdominal surgery: small bowel surgery (5.3-10.6%),

colon surgery (4.3-10.5%), gastric surgery (2.8-12.3%), liver/pancreas surgery (2.8-10.2%), exploratory laparotomy (1.0-6.9%) and appendectomy (1.3-3.1%) (18).

Most SSI are acquired at the time of surgery; the most common source is believed to be direct inoculation of endogenous- or skin flora (19). There are also exogenous sources of infection with flora from the operating room environment or personnel (20-24).

The species of micro-organisms isolated from SSI have not changed markedly during the last decade (25), but the percentage of antibiotic-resistant pathogens has increased (eg methicillin-resistant *S.aureus* MRSA, methicillin-resistant *S.epidermidis* MRSE and vancomycin-resistant enterococci VRE) (26-29). In addition, fungi -particularly *Candida albicans*- have markedly increased (30,31). This trend toward resistant organisms and *Candida* spp. probably is due to the widespread use of prophylactic and empiric broad spectrum antibiotics, increased severity of illness, and greater number of immuno-compromised patients undergoing surgical procedures. (32).

SSI are associated with substantial morbidity and mortality. Post-operative length of hospital stay increases by 7-10 days, hospital charges increases by 2,000-4,500 US dollars, and death is directly related to 75% of patients with a SSI who die in the postoperative period (33,34). While organ SSI accounts for only one-third of all SSI, they are associated with 93% of death related to SSI. Organ or space SSI are also vastly more costly than incisional SSI (35). SSI caused by multidrug-resistant pathogens are often associated with an even higher morbidity and mortality, due to inadequate or delayed antibiotic treatment (36-38).

Various classification schemes have been developed to predict the overall risk of a SSI, but most of them turned out to be a poor predictor (39). The most used risk score at this moment is from the NNIS. The NNIS surgical patient risk index score was developed in 1990. The risk index score stratified patients undergoing surgery into four risk index groups by assigning each of the following factors a value of one point, if present:

- An American Society of Anesthesiologists (ASA) preoperative assessment score of 3, 4, or 5.
- A surgical wound classified as either contaminated or dirty.
- An operation lasting over T hours, where T depends upon the operative procedure being performed.

The rates of surgical site infections for the different strata were 1.5 for risk index 1 (zero points), 2.9 for index 2 (one point), 6.8 for index 3 (two points) and 13 for index 4 (three points) (40).

Reanalysis conducted by the CDC in the light of the NNIS risk index score, found that the ASA score was more predictive than age or number of underlying diagnoses and that the determined length of the operative procedure (T) was more predictive than an arbitrary two-hour cut-off point (40).The NNIS surgical patient risk index score is a predictive model and also provides a system to make valid comparisons of surgical site infection rates among surgeons, across time, among hospitals, around the world.

Difference between the USA and Europe

There is a remarkable difference in the knowledge of the magnitude of the infection problem in surgical patients between the USA and Europe. In the USA, information about the rates of nosocomial infection, the epidemiology, ethiological organisms and risk factors are relatively easy to retrieve due to the development of various national formalised and ongoing surveillance systems. In the 1960s, the Centres for Disease Control (CDC) began in Georgia, recommending that hospitals conduct surveillance over the occurrence of nosocomial infections to obtain epidemiological evidence on which to base rational control measures (41,42). In January 1974, CDC initiated the SENIC Project (Study on the Efficacy of Nosocomial Infection Control) to determine whether and, if so, to what extent, this control program approach was effective in reducing nosocomial infection risk (43,44). Of more recent date the National Nosocomial Infection Surveillance (NNIS) study was generated by 80 medical centres in the USA from 1980-1992 (45), growing to 300 centres in 2002 (46).

In Europe, no such formalised systems exist, and there had been no large international study to determine the nosocomial infection rates throughout the continent, up to 1992. Before, only a few studies have been undertaken in individual countries (47-49), without the possibility to extrapolate the data from these studies to an overall European ICU setting.

There was room for improvement in the control of nosocomial infections in European ICU's. Small improvements could have a major impact on morbidity and mortality. Easy access to a suitable epidemiological database could be a starting point to provide information concerning the rates of infection. Besides, this could make it possible to determine the patterns of bacterial populations and their susceptibility or resistance to particular antibiotics. Appropriate (empirical) antimicrobial regimens could be devised, patients who are most at risk of developing a nosocomial infection could be identified, the likely outcome of the infections could be gauged and effective infection control policies could be instituted. Ongoing surveillance and collection of data should then be employed to audit the effectiveness of such policies and to identify secular trends to update and tailor the prevention interventions. Indeed, there was room for improvement in the management of nosocomial infections in Europe.

PATIENTS AND METHODS

The aims of the study

It was against this background that in 1992 the European Prevalence of Infection in Intensive Care (EPIIC) Study was undertaken, to deal with the relative lack of information concerning nosocomial ICU infections, providing a new perspective on the scale of the problem in Europe. The EPIIC Study was a one-day study of infections in ICU's across Europe. It was designed to establish the point prevalence of nosocomial and other infections in intensive care units. Besides, it was designed to establish the microbiology, and thus determining those pathogens

considered to be causal of these infections, including their patterns of antimicrobial susceptibility (or resistance) to particular antibiotics. In addition, the relative importance of infection risk factors was established. Specific data were collected on the incidence of problem pathogens such as methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*. To evaluate the impact of risk factors on infection rates and resistance, the following patient parameters were recorded: clinical status on admission; presence of iatrogenic risk factors such as iv lines; the pattern of antimicrobial prescribing; and the use of specific interventions such as selective decontamination of the digestive tract. Basic demographic details were collected on each participating unit. The overall key aim of the EPIIC Study was to raise awareness in Europe of the problem of nosocomial infection in the ICU, and to stimulate discussion, hopefully leading to better prevention, appropriate therapy and improving infection control programs.

The protocol of the study

This point prevalence study was conducted on a 24-hour period, 29 April 1992. In total 1417 ICU's from 17 European countries were eligible to take part in the study. Data of 10038 patients were collected by questionnaire, for later analysis. Nosocomial infections in ICU were classified according to standard definitions of the Centres for disease Control, CDC (50). Assessment of the patient's status on admission was made on the basis of his/her APACHE II Score (Acute Physiology and Chronic Health Evaluation) (51,52). A logistic regression analysis was done to estimate the effects of possible risk factors, measured as odds ratios (OR, comparing relative risks), together with their 95% confidence intervals (CI). In addition multiple logistic regression analysis was done to assess which independent factors affected the overall risks of infection and death, and to investigate the relationship between these different risk factors. The complete methods have been described elsewhere (53). The most important drawback of the study to be mentioned is the difficulty of identifying pathogens, which may have only reflected possible contamination or colonisation instead of representing the cause of the infection.

RESULTS

Over 50% of the 10038 ICU patients had undergone surgery in the month prior to the EPIIC Study. Abdominal surgery was the most frequently performed type of surgery, followed by cardiothoracic surgery and head and neck surgery. Of these surgical patients, 21.3% developed an acquired ICU infection.

THE SURGICAL PATIENT POPULATION AND A RISK ANALYSIS OF POTENTIAL INFECTION RISK FACTORS

Patient sex

Almost two-thirds of the surgical patients were male. The infection risk for males was statistic significantly higher than for females (table 1).

Patient age

More than half of the surgical ICU patients were aged 60 years or more. The infection risk declined when the age increased (table 1 and figure 1).

Underlying conditions; clinical status on admission

Not every underlying condition in this group of surgical ICU patients proved to be an infection risk factor. For example, the surgical patient with cancer had a lower infection risk (OR 0.72), and also diabetes mellitus was of no influence on the infection risk (OR 1.04). Statistically significant risk factors were: trauma (OR 3.31), organ failure (OR 2.74) and respiratory problems (OR 1.42). See figure 2.

Underlying disease severity; APACHE II Score

The statistics of the APACHE II scores on admission showed that together with an increasing APACHE II score the odds ratios for infection risk increased up to a plateau-phase at APACHE scores between 20-30. Higher APACHE scores were associated with a declining odds ratio (figure 3).

Type of surgery

More than half of the ICU patients had undergone elective surgery, one-third needed emergency surgery. The associated infection risk for the emergency surgery was doubled, compared to the elective surgery (OR 2.31). The infection risk was highest for the patient with multiple operations (OR 3.12). Both differences were statistically significant (table 1 and figure 4). The prevalence of elective and emergency surgery by each age group is showed in table 2.

Length of unit stay

60% Of the surgical ICU patients had been admitted to the ICU for more than one week (table 1). The risk of acquiring a nosocomial infection in an ICU increased with the length of ICU stay. The odds ratio for infection increased with the length of unit stay, without reaching a plateau-phase (figure 5). After an ICU stay of one day the risk of acquiring an infection was already 5 times higher, compared to a stay of less than 24 hours. After an ICU stay of one week the infection risk increased 100 times, after 2 weeks it increased 200 times.

Procedural interventions; invasive procedures

The surgical study population in the EPIIC Study experienced a high number of interventions in the week prior to the survey up to the study day (figure 6). Invasive procedures associated with a statistically significant infection risk were a tracheostomy (OR 4.58), stress ulcer prophylaxis (OR 3.21), assisted ventilation (OR 2.53) and a cvp-line (OR 2.15).

THE KEY INFECTION TYPES

The five most frequently reported ICU-acquired infections are shown in table 3. More than half of the ICU-acquired infections of these surgical ICU patients were located in the respiratory tract. The prevalence of the surgical wound infections take only the fourth place.

Table 1. Infection risk factors of surgical ICU patients

Infection Risk Factor		**Prevalence** (%)	**Infection Risk** (%)
Sex	Males	61.7	23.7
	Females	38.3	17.4
Age (years)	10-19	2.6	26.2
	20-39	14.2	28.6
	40-59	26.2	22.6
	60-69	26.9	19.8
	> 69	30.1	17.5
Type of surgery	Elective	54.9	14.6
	Emergency	35.9	28.2
	Both	9.1	34.6
Length of unit stay	0-7	40.8	2.1
(days)	8-14	19.1	14.2
	15-21	12.1	29.5
	>21	28.1	45.7

Table 2. Prevalence of age by type of surgery of surgical ICU patients

	Prevalence (%)		
Age (years)	**Elective surgery**	**Emergency surgery**	**Both types of surgery**
10-19	28.5	59.2	12.3
20-39	37.1	51.8	11.1
40-59	58.0	32.9	9.1
60-69	64.1	26.8	9.1
> 69	54.8	37.2	8.0

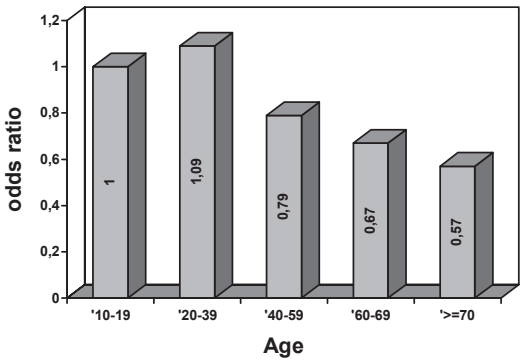

Figure 1. Age and infection risk of the ICU surgical patient.

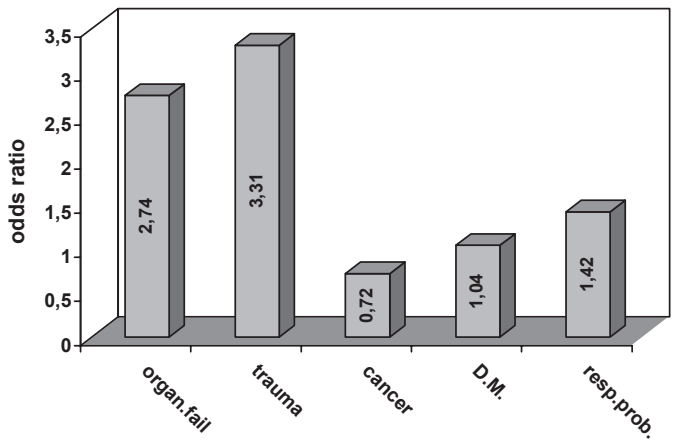

Figure 2. Underlying condition and infection risk of surgical ICU patients.

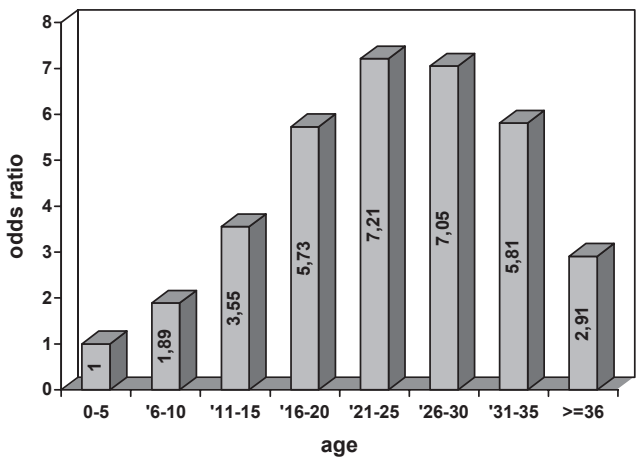

Figure 3. APACHE II Score and infection risk of surgical ICU patients.

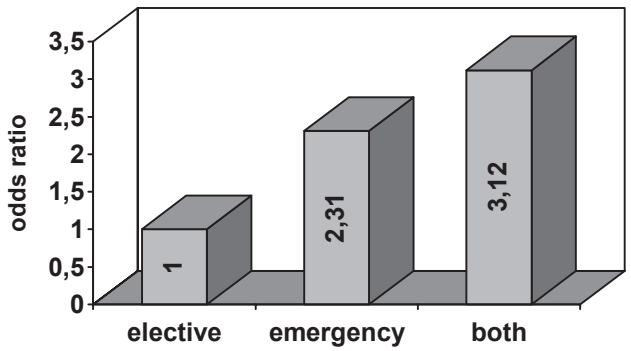

Figure 4. Type of surgery and infection of surgical ICU patients.

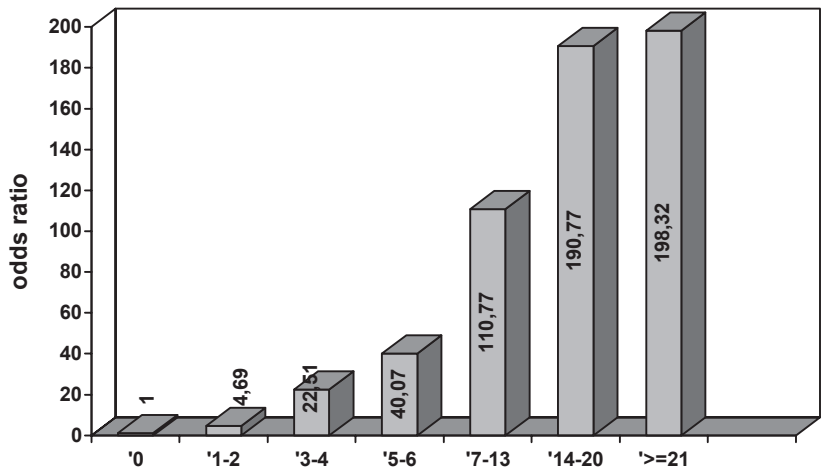

Figure 5. Unit stay (days) and infection risk of surgical ICU patients.

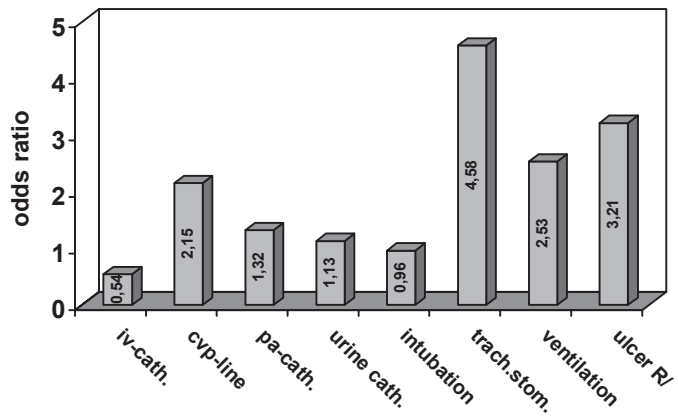

Figure 6. Procedural interventions and infection risk of surgical ICU patients.

THE KEY PATHOGENS

Mentioned in table 3 are only groups of pathogens. The most frequently reported isolates were the gram negative bacteria *(Pseudomonas aeruginosa, E. Coli)*. Secondly, close to the gram negative bacteria, one sees the gram positive bacteria (*Staphylococcus aureus, S. epidermidis*, Enterococci), and thirdly, the fungi are to be noticed.

Table 3. Prevalence of type of infection and type of pathogen in surgical ICU patients

		Prevalence (%)
Type of Infection	Pneumonia	39.5
	Lower respiratory tract	12.2
	Blood stream	11.0
	Wound infection	8.7
	Urinary tract	7.3
Type of Pathogen	Gram-negative bacteria	47.1
	Gram-positive bacteria	40.9
	Fungi	10.8
	Anaerobes	1.1
	Viruses	0.1

MORTALITY IN THE SURGICAL ICU

Information concerning the outcome of patients was collected 6 weeks after the study day. In that period, 85% of surgical ICU patients were discharged alive, thus leaving a mortality rate of 15% in the total group (table 4). The mortality in the group of surgical ICU patients without an acquired infection was 12% and the mortality in the group of patients with an ICU acquired infection was 26%, this is a statistically significant difference. Table 5 shows five pathogens associated with mortality higher than the average rate of 26% in infected surgical ICU patients. The pathogens associated with the highest rate of mortality were the fungi.

DISCUSSION

In search for infection risk factors in the surgical ICU patient population some factors highlighted the special situation of the surgical- versus non-surgical ICU patients.

Surprisingly, the infection risk declined when the age of surgical patients increased. An explanation could be the fact that the associated infection risk for emergency surgery was doubled as compared to elective surgery. This result explains the declining infection odds

Table 4. Mortality in surgical ICU patients

Surgical ICU patient	**Mortality** (%)
Total study group	15
Non-infected surgical ICU patient	12
Infected surgical ICU patient	26

Table 5. Mortality in the surgical ICU patient by type of pathogen

Type of pathogen	**Mortality** (%)
Fungi	31.1
Staphylococcus spp.	29.5
Enterococci	29.3
Pseudomonas aeruginosa	28.4
Escherichia coli	27.0

ratio with increasing age; the prevalence of emergency surgery was highest in younger patients, the prevalence of elective surgery was highest in the older patients (table 2).

The APACHE II score on admission of the surgical patient to the ICU showed an interesting phenomenon: with an increasing APACHE II score the odds ratio for infection risk increased up to a plateau phase. APACHE scores higher than 30 were associated with a declining odds ratio. Apparently these very severely ill patients died, before they could acquire a nosocomial infection.

It is a well-known phenomenon that the risk of acquiring a nosocomial infection in an ICU increases with the length of ICU stay. Analysis of the risk factors in the EPIIC study showed the length of ICU stay to be the most important risk factor, with odds ratios up to 200 when staying longer than 3 weeks. The problem in the analysis of the ICU stay is the complexity of this multifactorial risk factor, also known as the 'epiphenomenon' of the ICU stay: the longer the stay, the more invasive procedures and diagnostic interventions, the greater the risk of an ICU-acquired infection, the longer the ICU stay (a spiral effect).

Notwithstanding that differences in mortality cannot be directly attributed to differences in infection rates, statistical analysis performed on the EPIIC study database confirmed that ICU-acquired infections are associated with increased mortality. The difference between 12% mortality in the group of surgical ICU patients without an infection, and 26% in the group of surgical ICU patients with an ICU-acquired infection is highly significant ($p<0.0001$).

Fungi occupied the third place in the prevalence of key pathogens. The highest associated mortality rate (31.1%) of all pathogens was also due to the fungi. This highlights the growing importance of the fungal pathogens in ICU-acquired infections. Based on the results of other studies (54,55), same as the EPIIC study, fungi are called the 'emerging pathogens'.

CONCLUSION

The most important infection risk factors for surgical ICU patients to be warned for: 1) beware of emergency - and multiple operations. Together with these types of surgery, trauma is a significant risk factor. 2) beware of a longer ICU stay, which increases the odds ratio for infection dramatically. Undoubtedly, this is (also) due to an increasing number of invasive procedures, a prolonged need for assisted ventilation (sometimes in combination with a tracheostomy), more procedural diagnostic interventions and multiple operations. 3) beware of pneumonia and lower respiratory tract infections. Precautions, pre-, per- and post-operative are necessary to attack this type of infection in the surgical patient. 4) Beware of gram-positive bacteria. The gram-negative bacteria are not any longer the most important and most virulent pathogens in nosocomial ICU infections. Gram-positive bacteria, such as the coagulase-negative staphylococci, are not only insignificant contaminants anymore. 5) beware of fungi. Fungi have deranged from colonising a-pathogens, playing a subordinate role, to emerging virulent pathogens.

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CHAPTER 6

Methicillin-Resistant *Staphylococcus Aureus*: acquisition and risk of death

ABSTRACT

Objective: To evaluate the risk of patients in intensive care units (ICU) of becoming infected with methicillin-resistant Staphylococcus aureus (MRSA) and to assess the mortality during a six week follow-up period, compared with patients who developed methicillin-sensitive S aureus (MSSA) infection.

Design: Point prevalence survey.

Setting: 1417 ICU in 17 Western European countries.

Subjects: 10038 patients in ICU who were part in the EPIIC (European Prevalence of Infection in Intensive Care) Study.

Main outcome measures: Prevalence of MRSA and MSSA ICU-acquired infections, risk factors, and mortality.

Results: On the study day 21% of patients had ICU-acquired infections. The most commonly reported pathogen was Staphylococcus aureus (30%). Overall, 60% of strains of S aureus were resistant to methicillin (with a wide intercountry variation). The most commonly reported MRSA infections were pneumonia and lower respiratory tract infections. The most important risk factor for MRSA was the length of stay in the ICU. MRSA infection reduced the chance of survival, particularly when it was found in lower respiratory tract infections: the risk of mortality was three times higher in patients with MRSA than in those with MSSA.

Conclusion: Patients in ICU are at high risk of becoming infected with MRSA. The longer the stay, the higher the risk. Patients with MRSA infections are less likely to survive than those with MSSA.

INTRODUCTION

Pathogens responsible for infections acquired in the intensive care unit (ICU) have changed during the past decades. In the 1960s and 1970s Gram-negative pathogens were predominantly responsible (enterobacteriaceae and *Pseudomonas aeruginosa)* while in the 1990s Gram- positive micro-organisms have become increasingly prominent including *Staphylococcus aureus*, coagulase-negative staphylococci, and enterococci (the last two of which have long been considered to be non-pathogenic).

The susceptibility pattern of these pathogens has also changed. At present, the main infective threat in ICU is the increase in micro-organisms that are resistant to many antibiotics, in particular methicillin-resistant *S aureus* (MRSA), *Staphylococcus epidermidis,* and enterococci, both of which are also becoming increasingly resistant to penicillins. Towards the year 2000 the medical profession will face the challenge of infections against which none of the current antimicrobial agents are effective; many clinicians are not aware of this impending crisis (25). No antibiotic resistance marker has distinguished a species more than methicillin resistance has for *S aureus*. The rapidity with which methicillin resistance developed in Europe after the introduction of methicillin and the subsequent spread of this organism throughout the world has created enormous therapeutic and management problems resulting in heated arguments, confusing and conflicting recommendations, control measures, and many consensus reports (2,24).

The place in which patients are at the greatest risk of acquiring resistant organisms is the ICU, and we evaluated the impact of MRSA on such patients. Do patients infected with MRSA have a different prognosis from those with methicillin-sensitive *S aureus* (MSSA)? What are the risks of patients in ICU becoming colonised and infected with MRSA? What is the mortality in patients with MRSA compared with those with MSSA?

PATIENTS AND METHODS

Data were used from the largest pan-European point prevalence study, the European Prevalence of Infection in Intensive Care (EPIIC) Study, which was conducted on April 29, 1992. On the study day, information was collected for later analyses on 10038 patients in 1417 adult, non-coronary care ICU in 17 Western European countries. Data were collected by questionnaire. This one day study was designed to establish the prevalence and microbiology of nosocomial infections in ICU (classified according to standard definitions of the Centers for Disease Control, CDC) (9), and to establish the relative importance of risk factors for these infections. In addition, data were collected on the clinical state of patients on admission to the ICU and on their outcome during a six week follow-up period. The complete methods and a general survey of the results have been described elsewhere (35).

Statistical analysis: A logistic regression analysis was done to estimate the effects of possible risk factors for ICU-acquired infections, measured as odds ratios (comparing relative risks), together with their 95% confidence intervals (CI). In addition multiple logistic regression analysis was done to assess which independent factors affected the overall risks of infection and death, and to investigate the relationship between these different risk factors.

RESULTS

Overall EPIIC study (35)

On the study day a total of 4501 patients (from the group of 10038) had one or more infections (45%), almost half of which (21%) were ICU-acquired. There were pronounced variations in the rate of ICU-acquired infection, ranging from 7% for patients in Denmark and 8% in Sweden, to 31% for those in Greece and 32% in Italy (Table 1).

S aureus was the 'key pathogen' most frequently isolated (30%).Only the enterobacteriaceae were reported more often (34%), but as a class. The most commonly reported bacterial isolates acquired in the ICU infections are shown in Table 2. Where antibiotic resistance was reported, 60% of strains of *S aureus* were resistant to methicillin (MRSA). There was wide intercountry variation, with the highest proportion of MRSA occuring in Italy and France, while many northern countries had none (Table 1).

The most commonly recorded ICU-acquired infections with MRSA compared with MSSA are shown in Table 3. For both bacteria the most commonly reported infections were in the respiratory tract: pneumonia 52% and 61% respectively, and lower respiratory tract infections 22% and 17% respectively.

The antibiotics given for these infections are shown in Table 4. The most commonly used were the glycopeptides (36%), followed by aminoglycosides (25%) and cephalosporins (23%).

MRSA risk factors

Different risk factors evaluated for MRSA ICU-acquired infections were compared with those for MSSA (Tables 5 and 6), and the odds ratios calculated. An increasing APACHE II score (calculated on admission to the ICU) was significantly related to an increasing incidence of both MRSA and MSSA infections, in contrast with an APACHE II score of more than 21-25 where there was a gradually reduction in the incidence of both infections, decreasing to only 0.4% with an APACHE II score of more than 35 (Table 5).

Another risk factor evaluated was the length of stay in the ICU. The longer the stay, the higher was the risk of an MRSA rather than an MSSA infection (Table 5), with an odds ratio of 4.07 for a stay longer than three weeks on the ICU (95% CI 2.02 to 8.21, $p<0.001$).

Table 1. Number of patients in ICU by country, percentage incidence of ICU-acquired infection, incidence of MRSA as a percentage of total isolates of *S aureus,* and percentage mortality

Country	No. of patients in ICU	% of ICU–acquired infections (n=2064)	MRSA as % of *S. Aureus* (n=528)	% mortality (n=1560)
Austria	420	20	53	15
Belgium	669	17	67	15
Denmark	81	7	0	11
Finland	132	16	50	12
France	2359	24	78	19
Germany	2010	17	37	15
Greece	200	31	77	29
Ireland	91	19	0	12
Italy	617	32	81	20
Luxemburg	29	17	0	13
Netherlands	472	16	0	14
Norway	150	13	0	9
Portugal	120	23	67	24
Spain	1233	27	54	19
Sweden	286	8	0	9
Switzerland	329	10	14	8
UK	840	16	13	20
Total	**10038**	**21**	**60**	**17**

Table 2. Number (%) of reported isolates in ICU-acquired infections

Isolate	No	(%)
S aureus	528	(30)
Ps aeruginosa	504	(29)
Coagulase negative staphylococci	335	(19)
Fungi	300	(17)
Escherichia coli	223	(13)
Enterococci	205	(12)
Acinetobacter spp.	164	(9)
Klebsiella spp.	142	(8)
Streptococci (other than pneumococci)	124	(7)
Enterobacter spp.	115	(7)
Proteus spp.	100	(6)
Other Pseudomonas spp.	77	(4)

Risk factors next evaluated were the type of ICU and the antibiotic policy on the ICU (Table 6). There were no significant differences depending on the type of ICU (medical, surgical, specialist, or mixed unit) or the antibiotic policy.

Table 3. Reported types of ICU-acquired infection by MRSA and MSSA

Type of infection	MRSA		MSSA	
Pneumonia	112	(52)	144	(61)
Lower respiratory tract	48	(22)	40	(17)
Bacteraemia	30	(14)	23	(10)
Wound	17	(8)	19	(8)
Urinary tract	7	(3)	12	(5)
Clinical Sepsis	1	(0.5)	0	

Infections classified according to CDC definitions (9).
Figures are expressed as number (%).

Table 4. Number of strains of MRSA and MSSA (n=528) treated by particular antibiotics and percentage of MRSA and MSSA as a proportion of total isolates in each type of antibiotic

Antibiotic	No. of isolates (%)	
Glycopeptide	189	(36)
Aminoglycoside	132	(25)
Cephalosporin	119	(23)
Quinolone	91	(17)
Broad-spectrum penicillin	83	(16)
Imipenem	68	(13)
Penicillin	43	(8)
Metronidazole	40	(8)
Aztreonam	22	(4)
Macrolide	11	(2)
Other	90	(17)

Mortality

The mortality before discharge from the ICU up to six weeks after the study day for the total study population was 17%. The variation in mortality by country was considerable, ranging from 8% for Switzerland and 9% for Sweden to 29% for Greece (Table 1). The overall mortality for patients infected with MSSA and MRSA were 25% and 32% respectively. The odds ratio for MRSA, compared with MSSA according to survival was 0.70 (p=0.09). The mortality for ICU-acquired MRSA infections compared with that for MSSA infections according to the various infection sites are shown in Table 7, only for those in the lower respiratory tract was there a significant difference in mortality.

Table 5. Percentage prevalence of MRSA and MSSA ICU-acquired infection and odds ratio of risk of developing MRSA infection compared to MSSA, depending on APACHE II score and length of stay in ICU

	MRSA	MSSA	Odds ratio	95% CI	p-value
APACHE II Score					
0-5	9.5	3.3	1.00		
6-10	14.4	20.1	0.26	0.11 to 0.62	<0.001
11-15	24.7	26.4	0.34	0.14 to 0.78	0.01
16-20	29.2	26.7	0.39	0.17 to 0.89	0.03
21-25	14.8	15.4	0.34	0.14 to 0.84	0.02
26-30	4.9	6.2	0.28	0.09 to 0.80	0.02
31-35	2.1	1.5	0.65	0.13 to 3.31	0.61
>35	0.4	0.4	0.39	0.02 to 6.95	0.52
STAY in ICU (days)					
0-14	5.6	18.4	1.00		
15-20	11.1	13.9	2.65	1.12 to 6.26	0.03
> 20	83.3	67.7	4.07	2.02 to 8.21	<0.001

Table 6. Percentage prevalence of MRSA ICU-acquired infection and odds ratio of risk of developing MRSA infection depending on type of ICU and antibiotic policy

	MRSA	Odds ratio	95% CI	p-value
Type of ICU				
Mixed (medical/surgical, surgical/trauma, or medical/surgical/coronary)	55.5	1.00		
Medical	74.1	0.92	0.58 to 1.48	0.73
Surgical	69.8	1.42	0.96 to 2.11	0.08
Specialist (respiratory, trauma, burns, neurosurgical)	59.5	1.45	0.95 to 2.22	0.09
Antibiotic policy				
Other	67.8	1.00		
Formal (written)	52.3	0.73	0.51 to 1.06	0.10
Informal	58.9	0.78	0.57 to 1.08	0.13

DISCUSSION

Virulence of MRSA

Many studies have tried to show that strains of MRSA are more virulent than those of MSSA (10,11,19,32). However, none of them showed that MRSA is clinically more virulent than other strains of *S aureus*. There were no significant differences in the types of infections produced, or in the mortality (1,2,24). On the contrary there were some studies that suggested that many

Table 7. Percentage mortality according to site in MRSA and MSSA ICU-acquired infections and odds ratio of survival from the MRSA infections compared to MSSA (death =OR 1)

Site	Mortality (%)	Odds ratio	95% CI	p-value
EPIIC overall	16.8			
MRSA	32.4	0.7	0.47 to 1.06	0.09
MSSA	25.0			
Wound infection				
MRSA	26.7	0.59	0.11 to 3.20	0.54
MSSA	17.6			
Bloodstream				
MRSA	26.9	0.68	0.17 to 2.74	0.59
MSSA	20.0			
Pneumonia				
MRSA	33.3	0.82	0.46 to 1.45	0.50
MSSA	29.1			
Urinary tract				
MRSA	14.3	3.0	0.24 to 37.58	0.39
MSSA	33.3			
Lower respiratory tract				
MRSA	45.7	0.35	0.13 to 0.94	0.04
MSSA	22.9			

strains of MRSA are neither highly contagious nor have determinants of virulence (5,6,15,16). Most laboratory studies however, found that strains of MRSA have properties of virulence similar to those of MSSA (6,7,8,14, 28,33). There was also no difference in the number of death in animal studies (12,28). So far there is no clinical or laboratory evidence that MRSA is more virulent than other strains of *S aureus.*

However, there is a difference in the virulence of MRSA between patients in acute hospitals and in outpatients. Community-acquired MRSA infections occur sporadically and are of no particular clinical importance. MRSA carriers (colonised persons) will not easily become infected in the outpatient setting. They become at risk at the time of (re)admission to hospital. From an infection control perspective, the home care setting is thus ideal for the patient colonised with MRSA (24). Even in groups of residents colonised with MRSA in American nursing homes and in long term care units associated with Veterans Administration hospitals (where the prevalence of MRSA colonisation is often high), only 5%-15% subsequently developed MRSA infections (2,3,23). However, among patients colonised with MRSA in acute hospitals, 30%-60% will eventually develop an MRSA infection (2,27,36). The risk factors associated with the acquisition of an MRSA infection in hospitals are the same that make a patient at high risk from and more vulnerable to the consequences of this infection. Host factors are probably

the most important determinants of progression of infection. In patients in the need off an ICU admission, therefore MRSA can cause considerable morbidity and mortality.

MRSA risk factors

Patients in ICU have an increased susceptibility to nosocomial ICU-acquired infections (4,31). Special risk factors make them temporarily immunocompromised: the normal host defence mechanisms are often disrupted by multiple invasive devices, impaired by the underlying disease, and reduced by medical interventions and medication. Other risk factors include prolonged stay in hospital and in the ICU, the use of (combination) broad-spectrum antimicrobial drugs, the prevalence of multiply resistant micro-organisms, and sometimes overcrowding. Overall, intrinsic risk factors together with extrinsic ones make the ICU patient extremely vulnerable to nosocomial infections. As stated by Meakins et al "Infection is their Achilles heel"(20).

These are the same risk factors that make a patient more susceptible to *S aureus* infections. *S aureus* is a pathogenic micro-organism, but in normal conditions it is of low virulence (26). Some strains of *S aureus* are more virulent (13,18,34) but this increase in their virulence needs an altered host resistance. A normal functioning immunological (phagocytic) defence mechanism prevents an infection with *S aureus.* For example: selective digestive decontamination alters the normal immunological defence mechanisms, by causing overgrowth of a selection of Gram positive organisms, with the MRSA-strains being of particular importance. Its use should therefore be restricted, particularly in a MRSA-endemic environment.

In search for special risk factors in the ICU that cause patients to become infected with MRSA instead of MSSA, we found that the most important significant difference was the length of stay in the ICU. The odds ratio for ICU-acquired MRSA infection increased dramatically with the length of stay, increasing more than 2.5 times with a stay of longer than two weeks, and increasing more than four times after three weeks, as also reported by Law and Gill (17). This and our study have in common an increasing incidence of nosocomial MRSA infections after starting with only MSSA infections.

This probably is reflected in the APACHE II score, when it is over 30 patients die too soon to become infected with MRSA. These severely ill patients die as a consequence of their underlying disease, whereas the less severely ill patients become exposed to a large number of risk factors that encourage them to develop an ICU-acquired infection.

There is an important correlation between antibiotic consumption and antibiotic resistance. Development of resistance to an antibiotic is usually the consequence of previously high consumption of this antibiotic (21,29). To prevent this kind of antibiotic misuse, an antibiotic policy for prophylaxis and treatment guarded by a microbiologist or infectious disease specialist is needed. We found however that a written as opposed to the "other" antibiotic policy could reduce the odds ratio of MRSA by only one in four (not a significant difference). Did

the antibiotics used for *S aureus* infection in our study have a role in the high prevalence of MRSA? Methicillin resistance is caused not only by the common use of penicillinase-resistant beta-lactams, but also by the use of cephalosporins, as cross-resistance between penicillins and first generation cephalosporins is a common if not ever present feature. Further, methicillin resistance in staphylococci is often linked with resistance to other antibiotics, particularly aminoglycosides, possibly also selecting for methicillin resistance (22). The most commonly used antibiotics for *S aureus* infections (MSSA and MRSA) in our study were the glycopeptides (36%), followed by the aminoglycosides (25%) and cephalosporins (23%, Table 4). Maybe this selection by the clinical use of antibiotics was made because of the high prevalence of MRSA, increasing the chance that the frequent use of glycopeptides in MRSA infections will also induce the development of vancomycin-resistant MRSA (and others, such as methicillin-resistant *S epidermidis* and enterococci).

Another possible risk factor for methicillin resistance is the type of intensive care unit. Mouton et al (22) sought the relationship between methicillin resistance in coagulase- negative staphylococci and the type of clinical department, and found that all types of surgical wards (thoracic surgery, surgical ICU, neurosurgery) scored highest. We could not corroborate these findings, as we found an odds ratio of MRSA infection for the surgical and specialist ICU 1.5 times higher than for the medical and mixed ICU, a difference that was not significant.

Mortality

Mortality in the EPIIC study was higher in those countries with higher ICU-acquired infection rates and these were higher again in those countries with higher MRSA ICU-acquired infection rates. Mortality was higher in those patients infected with MRSA (32%) compared with MSSA (25%), and in those patients infected with MSSA compared with the total number of patients studied in EPIIC (17%). Notwithstanding that differences in mortality cannot be directly attributed to differences in infection rates or differences in microbial resistance, univariate analysis of the EPIIC data confirmed that ICU-acquired infections are among the most important independent risk factors associated with increased mortality. In the six week follow-up period, the greatest risk for all kinds of ICU-acquired infections was associated with clinical sepsis. The greatest mortality risk for the MSSA infections was associated with pneumonia, and for the MRSA infections with lower respiratory tract infections. The chance of survival with a MRSA instead of MSSA lower respiratory tract infection was reduced almost three times. We must conclude that an ICU-acquired infection reduces the chance of survival (4) and MRSA has a greater impact on mortality than MSSA.

MRSA control measures

There turned out to be an enormous intercountry variation in the prevalence of MRSA, with a difference of 0-81%. Apparently several countries have been able to prevent MRSA problems in (and outside) their ICU, by strict control measures.

The emergence of MRSA and other resistant micro-organisms is certainly the result of misuse of antibiotics, not only in but also outside hospital. Training students, residents, and specialists to use antimicrobial agents only judiciously and to reinforce hygienic measures where necessary remains the mainstay in the prevention of MRSA problems. As well as overall restrictions in the use of antibiotics, the special need for the instigation of rigorous MRSA control measures in hospitals persists. In the endemic setting there is a strong need for surveillance of high risk patients to prevent epidemics (2,24, 30,37). All patients at risk of MRSA should be screened before admission to hospital and put in isolation until they are free of MRSA. In case of an outbreak of MRSA (ICU or epidemic) it is absolutely necessary to use hygienic measures such as barrier precautions, strict isolation, cohorting, decolonisation treatment of carriers and antibiotic treatment of patients (2,24). Also MRSA-positive personnel should be given decolonisation treatment and should stay away from the hospital until they are free of MRSA. The costs of a MRSA outbreak (in terms of added morbidity, psychological morbidity, mortality, hospital days and hospital charges) are overwhelming. To prevent such an epidemic is better, easier and cheaper. The scope and intensity of prevention, surveillance, and control programmes designed to limit this nosocomial transmission of MRSA should be tailored to local conditions. The high risk patient in ICU makes the ICU a place in which local control of MRSA is particularly urgent.

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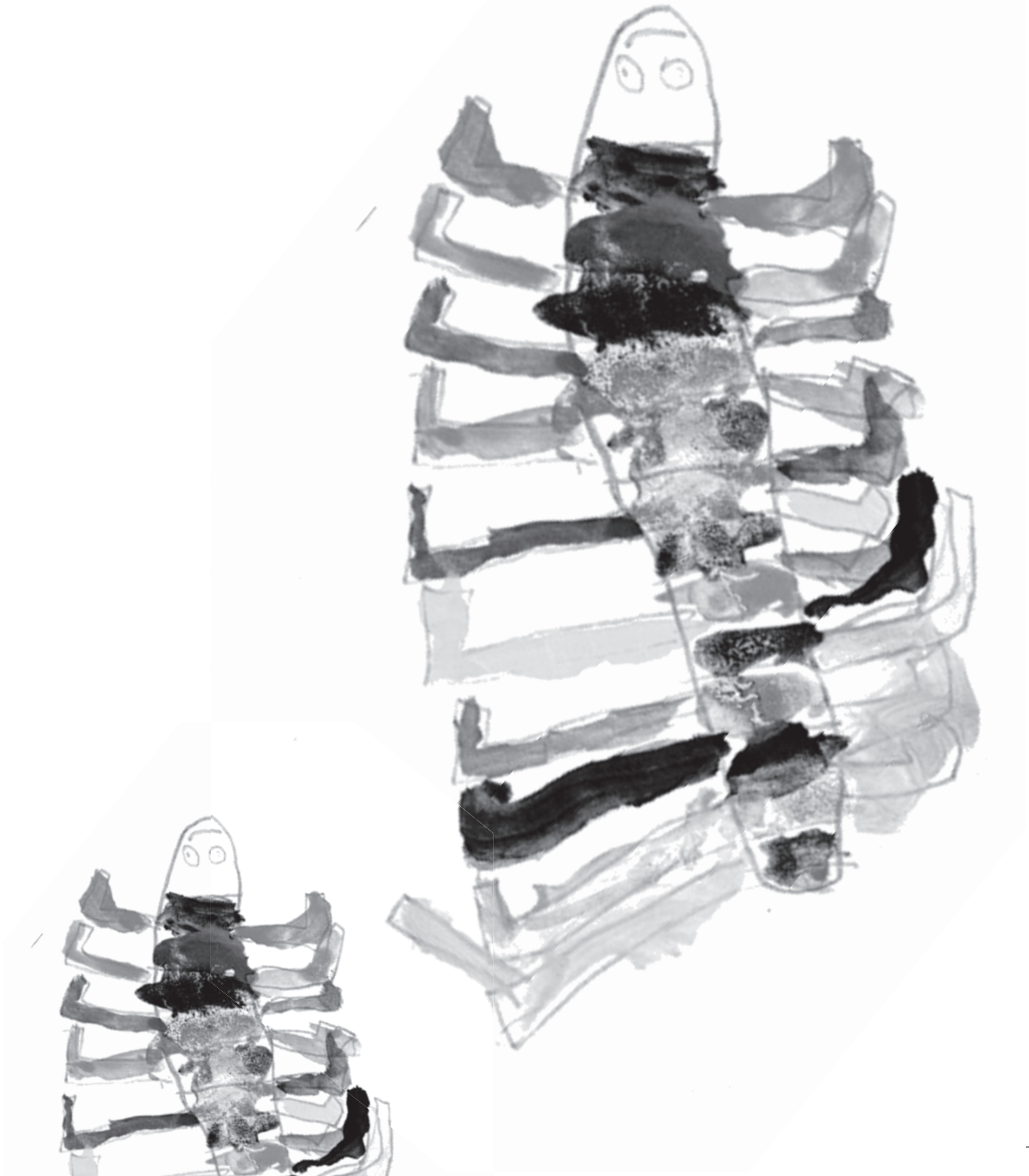
CHAPTER 7

Fungi "the emerging pathogens"; a review



CANDIDA "THE EMERGING PATHOGENS"

Candida species are called "emerging pathogens", because over the past decades their status has changed from colonising a-pathogens, to virulent pathogens causing serious infections. At first, *Candida* was thought to be an insignificant, transient contaminant rather than a significant pathogen (1,2) with the exception for neutropenic patients. This was called the era of the concept of "benign candidaemia", in the 1970's. However, this hypothesis has become outdated and *Candida* nowadays is accepted to be a serious nosocomial pathogen in non-neutropenic critically ill patients in the Intensive Care Unit (ICU) (3-10). The greatest increase in rate of *Candida* infections occurs in surgical services, especially in patients recovering from abdominal surgery (6,11-21).

The increase in nosocomial invasive candidiasis parallels the advance made in the supportive care towards survival of critically ill patients who would previously have died of severe illness. Aggressive invasive diagnostics, multiple therapies and a plethora of invasive devices in combination with a temporarily compromised immunity render the ICU patient population uniquely susceptible to nosocomial (fungal) infections (22-31). Overall, intrinsic risk factors together with extrinsic factors make the ICU patient extremely vulnerable to nosocomial infections. As stated by Meakins et al. "Infection is their Achilles heel" (32).

Probably, one of the most important risk factors for development of invasive fungal infections in these debilitated patients is the enormous increase in (in) appropriate use of broad-spectrum antibiotics (33-38). A carefully considered, restrictive antibiotic policy for infectious diseases in the ICU is a common and proper practice of medicine in patient care (39). However, ill-considered use of antibiotics can lead to a spiralling empiricism of antibiotic therapy, with a major impact on the increase of life-threatening fungal infections (40).

CANDIDIASIS, THE PROBLEMS

Parallel to the growing incidence of fungal infections, the clinical significance of these nosocomial ICU infections is increasing. The increased incidence of fungal infections has resulted in new clinical syndromes with systemic or invasive disease, the expression of which depends largely upon the immune status of the host. At present, clinicians have not succeeded in controlling this growing problem, because the infection itself presents some apparently insurmountable problems.

First, there is no symptom or complex of symptoms specific for invasive candidiasis. The clinical presentation of invasive candidiasis in critically ill ICU patients is very variable and non-specific with pyrexia and/or persistent leukocytosis during antibiotic treatment. The patient may develop a septic shock syndrome or remain hemodynamically stable. A unilateral endophthalmitis may develop. There is a high correlation between the occurrence of

eye-lesions and disseminated infection, with reported endophthalmitis incidences of 15-37% in patients with systemic infection (41,42). In an attempt to define invasive candidiasis in surgical patients, Geldner proposed in 2000 a definition composed of 5 items: 1. clinical signs of infection after surgery 2. absence of bacterial pathogens and/or failure to respond to systemic antibiotics 3. cultivation of *Candida* spp. from normally sterile sites 4. response to antimycotic therapy and 5. diagnostic serum antibody test (43). In clinical practice this is a rather laborious definition.

Secondly, management of serious and life-threatening invasive candidiasis remains severely hampered by the lack of reliable diagnostic methods; there is no (rapid) "gold standard" test available (9,44-47). For example, failure to detect fungemia by bloodculture is a well-known phenomenon. The need for a rapid and accurate multi-species- or even strain-level identification of significant yeast isolates is imperative for prompt institution of appropriate antifungal therapy. Besides the lack of a diagnostic test, the interpretation of the results of mycological cultures is difficult, because most of these facultative pathogenic fungi are part of the physiological flora (48-51).

Thirdly, at present, there is no miraculous antifungal therapy available yet (52-56). No antimycotic drug, effective to all types of *Candida* species exists, without limitations due to toxic side effects. It seems that successful treatment and patient recovery depend on the underlying condition and immune state of the patient. Despite administration of appropriate antifungal agents, these Candida species tend to persist, probably reflecting severe modulations of the immune system of the host with multiple-system organ failure, rather than anti-fungal therapy failure.

MORBIDITY AND MORTALITY

The morbidity and mortality associated with these invasive *Candida* infections is striking, with the median ICU-stay increased by as much as 30 days (57,58) and death rates of 30% to 80% (14,34,59-63). The same extremely high death rates are reported for abdominal candidiasis, and patients often die of complications of the infection in spite of surgical intervention and administration of (appropriate?) antifungal therapy (12,13,15-17, 20,48, 51, 64-65). Needful to mention is that most studies reported the overall crude mortality, and not the excess mortality directly attributable to candidiasis. When estimated the attributable mortality, rates of 40% are reported (34,57,66).

PROPHYLACTIC AND EMPIRIC THERAPY

Because prompt initiation of antifungal therapy is critical for cure but difficult to accomplish, prevention of fungal infections may play an important role in the clinical setting. Several studies assessed the positive effect of early, systemic antifungal therapy on the improved outcome of ICU-patients with invasive *Candida* infections, in terms of a decrease in morbidity and (attributable) mortality (9,13,29,62,67-69). With "early therapy" one should consider both early, prophylactic or pre-emptive antifungal therapy for a selected group of high-risk patients, just in an attempt to prevent *Candida* infections (i.e. in the absence of any evidence of infection, 21,70-77). One should also consider the start of early, empirical therapy upon the first clinical suspicion of a *Candida* infection, even though the exact species are not yet identified (78-80). Both thresholds must be lowered. Targeting patients for antifungal prophylactic therapy entails identifying and quantifying those patients at high risk. Antifungal prophylaxis for all critically ill ICU-patients, irrespective of individual risk factors, on a routine basis is generally not advised (81), because it has never been validated in controlled trials. Furthermore, widespread use of antifungals in the ICU would promote development of the inevitable resistance to azoles and selection of non-*Candida albicans* species. In this regard, fluconazole is no exception to the rule that the prophylactic use of any anti-infective agent might result in increased resistance to this drug.

Because of toxic side effects of amphotericin B (82), the first choice of prophylactic or empiric antifungal therapy is fluconazole (9,68,83-87). Two of the heralded problems in using fluconazole as prophylaxis are the existence of fluconazole resistant *non-albicans Candida* species (88-91), and the possible emergence of *de novo* fluconazole resistance through selective pressure of prolonged azole use. This prolonged use causes a possible selection of less susceptible *non-albicans Candida* species or a shift to fluconazole resistant *Candida albicans* (66, 84, 88, 92-100). This last hypothesis has been supported by reports of fungal infections, which developed in patients with hematologic malignancy (101-104) and in HIV patients (105, 106) with long courses of prophylaxis. The impact on the possible emergence of resistance of short-term courses fluconazole prophylaxis (2-3 weeks) has not been reported so far.

IDENTIFYING HIGH RISK PATIENT GROUPS

Prophylaxis is restricted to a prospectively defined easily identifiable subgroup at high risk of candidiasis. Rigorous selection of high-risk patient groups is crucial to optimise the risk-benefit ratio of preventive prophylactic or empiric antifungal strategies. Various criteria have been proposed to identify patients at risk of candidiasis,but some are not selective enough and others are time consuming and expensive (107). The aim of prophylaxis is to maximize chances of reducing morbidity and mortality while minimizing exposure of low-risk patients

to adverse events, and minimizing the risk of the emergence of *de novo* or *non-albicans Candida* strains.

In chapter 8 an analysis is given concerning the results of a retrospective cohort study during the period of 2000–2003 in the surgical Intensive Care Unit of the Erasmus MC, University Medical Center Rotterdam. This is a study to evaluate the risk of *Candida* species isolation in surgical ICU patients with peritonitis, and to determine independent risk factors or probably to select high-risk patient groups. Defining those groups could guide the selection of patients for prophylactic or empiric therapy. In addition morbidity and mortality were assessed for the groups with and without *Candida* isolation in peritonitis specimen.

RAPID IDENTIFICATION METHODS

Rapid species-(or even strain-) level identification of the significant isolates is thus imperative for prompt initiation of appropriate antifungal therapy, since susceptibility data for the isolated strain may not immediately be available (108) To switch as soon as possible, from the fluconazole prophylaxis to the appropriate antifungal therapy, a rapid identification of the causal *Candida* species is of paramount importance. Also the adequacy of the initial, empirical treatment has proven to attenuate morbidity and mortality. Changes in therapy based on culture results, that are too late initiated, did not affect outcome when the initial regimen was inappropriate (109-111).

Thus, the need for a rapid and accurate multi-species level identification of significant yeast isolates is imperative for prompt institution of appropriate antifungal therapy. Our current techniques are, at best, blunt instruments with limited sensitivity. A convincing tool for the diagnosis of invasive candidiasis has yet to emerge (112).

In chapter 9 an analysis is given concerning the results of a prospective study, comparing the relatively time-consuming conventional microbiological identification of *Candida* species and rapid identification by Raman Spectroscopy. This is a study to evaluate the feasibility and accuracy of the Raman spectroscopic method for rapid identification of clinically relevant *Candida* species in peritoneal specimen of peritonitis patients in the surgical ICU. The Raman Spectroscopy offers probably a rapid identification, with results after one overnight culture, which is at least 3 days earlier than the conventional identification.

A risk analysis of potential *Candida* patients, in combination with a rapid identification of *Candida* species if present, gives the clinician the opportunity to switch as soon as possible from early started prophylactic or empiric antifungal therapy to the appropriate therapeutical antimycotics.

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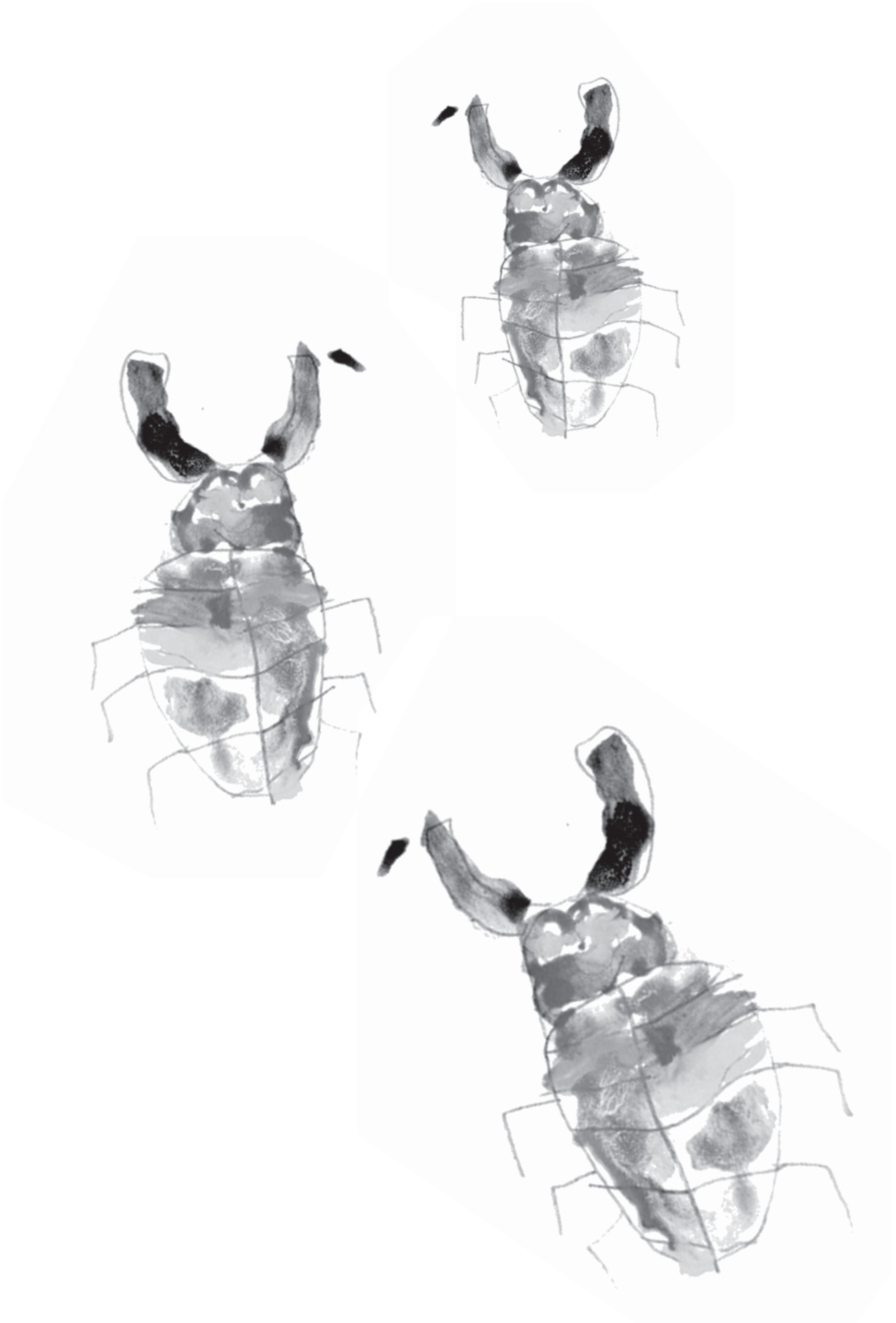
CHAPTER 8

Candida peritonitis in the surgical intensive care unit; a risk analysis



ABSTRACT

Objective: Over the past decades the incidence of nosocomial fungal infections has risen significantly, with the greatest increase occurring in surgical services. We therefore analysed the risk of *Candida* species isolation from peritoneal fluid in surgical Intensive Care Unit (ICU) patients with a peritonitis, and determined independent risk factors

Method: A retrospective cohort study was performed. One hundred and seventeen patients with a peritonitis (bacterial n = 69, *Candida* or mixed *Candida*/bacterial n = 48) hospitalized in a surgical ICU during the period of 2000 up to 2003 were included.

Results: Statistically significant risk factors of *Candida* isolation were pancreatitis (p=0.0073), APACHE II score >30 (p=0.0019), antibiotics used before the day of onset of the peritonitis (p=0.040), and perforation in the lower digestive tract (in a protective fashion, p=0.0342). In contrast to the mortality (p=0.842), the morbidity (defined as length of stay in the ICU) in the *Candida* group was significantly higher than in the bacterial group (27 versus 8 days, p=0.001). In contrast to other nosocomial infections, *Candida* isolation most frequently occurred during the beginning of the ICU stay.

Conclusion: Critically ill peritonitis patients with a high APACHE score are at risk for isolation of *Candida* species from peritoneal fluid, with a special emphasis on patients with pancreatitis. Empirical antimycotics would be recommended in these cases.

INTRODUCTION

After the persisting challenge of the growing incidence of multi-resistant bacterial infections, nowadays a new impending crisis out of the world of microbiology threatens the medical profession: the nosocomial fungal infections. Over the past decades the incidence of nosocomial fungal infections (usually *Candida* species*)* has risen significantly, with the greatest increase occurring in surgical services, especially in patients recovering from (recurrent) abdominal surgery (1,2). In 1981 Guerin stated "Peritonitis due to Candida is both rare and severe" (3). Two decennia later it is not rare anymore, and is certainly severe, with an associated mortality rate of 50-70% (4-7).

The growing incidence of these fungal infections is due to multiple factors, all reflecting the advances made in the critical care of patients who would previously have died of organ failure (2,8,9).

The increased incidence of fungal infections has resulted in new clinical syndromes with systemic or invasive disease, the expression of which depends upon the immune status of the host. It seems that successful treatment and patient recovery depend on the underlying condition and immune state of the patient. Despite administration of appropriate antifungal agents, these *Candida* species tend to persist, probably reflecting severe suppression of the immune system of the host with multiple-system organ failure, rather than anti-fungal therapy failure (10).As yet, clinicians have not been successful in tailoring this growing problem.

Because prompt initiation of antifungal therapy is critical for cure but difficult to accomplish, prevention of fungal infections may play an important role in the clinical setting. Several studies have already provided evidence for a positive effect of prophylaxis or early empiric antifungal therapy on the outcome of ICU-patients with invasive *Candida* infections (11-14).

Rigorous selection of high-risk patient groups is crucial to optimize the risk-benefit ratio of preventive antifungal strategies. The aim of prophylaxis is to maximize chances of reducing morbidity and mortality while minimizing exposure of low-risk patients to adverse events. Various criteria have been proposed to identify patients at risk of candidiasis (15-17). To the best of our knowledge, risk factors for developing fungal peritonitis have not previously been analysed, except for one study, conducted from 1994-1999, which excluded some of the potential risk groups (18).

Our current aim is to determine independent risk factors of *Candida* isolation in peritoneal fluid of all surgical intensive care unit (ICU) patients with a peritonitis, in order to identify high risk subgroups in surgical peritonitis patients, with implications probably relevant for targeting antifungal prophylaxis on the surgical ICU.

PATIENTS AND METHODS

Inclusion and exclusion criteria

A retrospective study was performed, including all patients with a diagnosis of peritonitis on admission to the surgical ICU, or who acquired a peritonitis during their ICU stay, between 2000-2003. All consecutive peritonitis patients were prospectively included in a database. Peritonitis was diagnosed on the basis of both clinical symptoms and a positive bacterial culture taken from peritoneal fluid or from an intra-abdominal abscess, collected during a laparotomy. A peritonitis was considered to be a *Candida* peritonitis when one or more peritoneal cultures were positive for *Candida spp*. Patients referred from other ICU's were excluded, as well as patients with a hospital- or community-acquired peritonitis, culture proven before admission to the ICU.

Data collection

All patient charts were reviewed retrospectively by use of a digital ICU data system and data were collected by detailed questionnaires. Besides the incidence of *Candida spp* isolation in peritonitis patients, the influence of various infection risk factors was evaluated in order to identify possible risk groups. Factors included age, sex, antibiotic use and use of selective digestive decontamination. The time between the admission to the ICU and the onset of peritonitis was calculated, as well the number of days between the onset of peritonitis and isolation of *Candida spp*. The APACHE II score (Acute Physiology and Chronic Health Evaluation II score, 19) was recorded at admission to the ICU. The primary disease and the primary site of infection responsible for peritonitis were recorded, especially livertransplantation, pancreatitis, a laparostomy, and spontaneous perforation or enteral anastomosis breakdown at the different anatomical sites in the upper- and lower gastrointestinal tract. All the possible risk factors were scored for each ICU day separately, except for age and sex (constant factors) and the APACHE II score (which was calculated only during the first 24 hours). Antibiotics were scored for each type separately. Only days of therapeutic dose (DDD) were scored, and counted in a cumulative fashion.

In addition, the type of isolated *Candida* species was recorded, together with the possible use of antimycotics.

Finally, morbidity was scored (for the group without mortality) as the total length of ICU stay. The mortality during the ICU stay was scored, together with the cause of death; was the mortality attributable to the peritonitis?

Statistical Analysis

Patients with a pure bacterial peritonitis (the cohort group) were compared to those who developed a mixed bacterial/ or pure *Candida* peritonitis. Statistical analysis started at the onset of peritonitis as t=0. Statistical analysis finished at the first day of a positive peritoneal

Candida culture (for the *Candida* group) or continued until death or discharge from the ICU (for the peritonitis group without *Candida*).

Univariate analysis of possible risk factors for *Candida* isolation, taking into account the number of days of peritonitis during ICU-stay, was performed with the Kaplan-Meier method and the log-rank test. Factors which might change during the ICU stay (all but age, sex and the APACHE II-score) were analysed using Cox regression with time-dependent variables. The median number of days of antibiotic use at day 0 was analysed between those with and without a *Candida* peritonitis at day 0.

Multivariate analysis of potential independent risk factors for *Candida* isolation was performed using Cox logistic regression.

RESULTS

Included in the study were 117 peritonitis patients admitted to a surgical ICU. Of these 117 patients, in total 1844 ICU days were scored, of which 1319 ICU days were statistically analysed (starting at the first day of peritonitis). This resulted in a database of 136,456 items. Of these 117 patients 48 (41%) acquired a *Candida* peritonitis. In most cases this was a mixed bacterial / *Candida* infection, only 6 patients (13%) presented with a pure *Candida* peritonitis. The main characteristics of the studied patient population are presented in Table 1.

In Table 2 the reason of admission to the ICU is presented, together with the probable mechanism of the peritonitis. The highest frequency in this study population was the group admitted to the ICU because of a liver transplantation.

Table 3 shows the results of the risk analysis of various expected predictive factors of *Candida* isolation in peritoneal fluid of peritonitis patients. Patients with a *Candida* peritonitis presented more frequently with a pancreatitis (p=0.0073), had a higher APACHE score (≥31: p=0.0019) and more frequently received antibiotic therapy before the onset of peritonitis (4.7 versus 3.5 days, p=0.040). There was no significant difference between the two groups in the antibiotic use during the ICU stay overall (p=0.131). The relationship between the total cumulative days of antibiotic use and the days of peritonitis for the groups with and without *Candida* are illustrated in Figure 1. This figure also shows the result that the highest frequency of *Candida* isolation occurred during the beginning of the ICU stay. There was a tendency towards significance in favour of the *Candida* group and upper digestive tract origin of peritonitis (p=0.061), whereas a lower digestive tract origin of peritonitis was statistically significant in a protective fashion (p=0.0342). Kaplan-Meier curves of three of these risk factors for *Candida* isolation are shown in Figure 2. In the multivariate Cox-regression analysis this 'protection' of lower digestive tract origin was not statistically significant anymore, whereas pancreatitis (p=0.012) and an APACHE score ≥ 31 (p=0.002) remained as independent significant risk factors for *Candida* isolation.

The type of *Candida* species isolated in peritoneal specimen of the 48 patients with *a Candida* peritonitis is shown in Table 4. Most frequently isolated was *Candida albicans* (83%). In 5 patients (10%) there was a mixed infection, with a combination of *Candida albicans* and a non-*albicans Candida* species.

The difference in morbidity between both groups was defined as difference in total length of ICU stay, from the day of onset of the peritonitis up to the day of discharge from the ICU. Only patients without mortality were included. The median length of ICU stay for the peritonitis group without *Candida* was 8 days, whereas the ICU stay for patients with a *Candida* peritonitis was 27 days (p=0.001).

Mortality, attributable to the peritonitis, was only scored during ICU stay. Mortality in the total group was 35%, whereas mortality in the *Candida* group was 44%. A *Candida* peritonitis was associated with a 7% higher mortality than the mortality in the group without *Candida* (p=0.842).

Table 1. Characteristics of the patient population with peritonitis

	Peritonitis Group without *Candida*: n = 69 (%)		**Peritonitis Group with *Candida*: n = 48 (%)**	
Age (years*)	56.3 ± 15		55.8 ± 15	
Sex				
Male	48	(70%)	28	(58%)
Female	21	(30%)	20	(42%)
Perforation				
upper digestive tract	28	(41%)	26	(54%)
lower digestive tract	22	(32%)	5	(10%)
Pancreatitis	1	(1%)	6	(13%)
Liver transplantation	15	(22%)	10	(21%)
Laparostomy	18	(26%)	9	(19%)
APACHE II Score				
≤ 20	24	(35%)	15	(31%)
21-30	42	(61%)	24	(50%)
≥ 31	3	(4%)	8	(17%)
SDD	3	(4%)	3	(6%)
ICU stay before onset of peritionitis (days)				
1	18	(26%)	13	(27%)
2-6	33	(48%)	20	(42%)
> 6	18	(26%)	15	(31%)

* = mean ± SD; SD = standard deviation; APACHE II Score = Acute Physiology and Chronic Health Evaluation; SDD = Selective Digestive Decontamination; T 0 = onset of peritonitis

Table 2. Indication of admission to the ICU and cause of peritonitis

Indication of ICU admission	n =	Cause of peritonitis*	n =
Upper digestive tract			
Oesophagus operation	9	Complications of oesophagus resection	6
Pancreatic operation (Whipple)	10	Complications of Pancreatic operation	9
Pancreatitis	5	Pancreatitis	9
Liver transplantation	25	Complications of liver transplantation	23
Hepatobiliary operation	6	Biliary tract	13
Lower digestive tract			
Intestinal resection	13	Leakage of anastomosis	6
Perforation digestive tract	9	Perforation of digestive tract	27
Gunshot intra-abdominal	6		
Ileus	4	Ischaemia digestive tract	14
Crohn	2	Intra-abdominal abcesses	6
Urological operation	4	Urological tract	6
Gynaecological operation	3		
Vascular operation			
Ruptured aneurysm	5		
Multi trauma	9		
Other	7	Other	9

* ≥1 cause of peritonitis in each patient is possible.

DISCUSSION

To improve the outcome of invasive *Candida* infections, preventive antifungal strategies are crucial. Early prophylactic antifungal therapy for a selected group of easily identifiable high-risk patients is considered to be necessary, in an attempt to prevent *Candida* infections (i.e. in the absence of any evidence of infection, 14, 20, 21). One should also consider the start of early empirical therapy upon the first clinical suspicion of a *Candida* peritonitis, even though the exact species have not yet been identified (22). Both thresholds must be lowered. Antifungal prophylaxis for all critical ill ICU patients on a routine basis, irrespective of individual risk factors, is generally not advised (23). Targeting patients for antifungal prophylaxis entails identifying and quantifying those patients at high risk.

First choice of prophylactic or empiric antifungal is fluconazole (24-26). This preference is not because of the antimycotic spectrum of fluconazole itself, but because of the toxic side effects of amphotericin B. Two of the heralded problems in using fluconazole as prophylaxis are the existence of fluconazole resistant *non-albicans Candida* species and the possible emergence of *de novo* fluconazole resistant *Candida albicans,* or a possible selection of less susceptible *non-albicans Candida* species through selective pressure of a liberal and prolonged azole use (27-30). This is why a rigorous selection of defined high-risk patient groups is even more crucial to optimize the risk-benefit ratio of antifungal prophylactic strategies.

Table 3. Risk analysis of predictive factors of *Candida* isolation in peritonitis

Risk factor	Univariate Analysis
Upper dig. tract origin	p = 0.061
Lower dig. tract origin	p = 0.0342 *
Pancreatitis	p = 0.0073
Livertransplantation	p = 0.2735
Laparostomy	p = 0.848
Antibiotics used at onset of peritonitis (t = 0)	p = 0.040
Antibiotics used after onset of peritonitis (t = 0)	p = 0.793
APACHE ≥ 31	p = 0.0019
ICU stay (days) before onset of peritonitis (t = 0)	p = 0.5719

***** a negative statistic significance

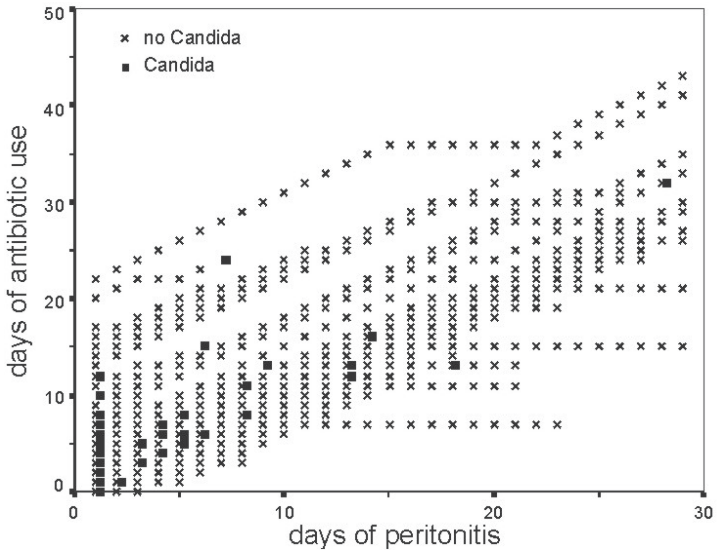


Figure 1. Graphic of days of peritonitis by days of antibiotic use for both groups with and without *Candida*

Some limitations of this study need to be addressed. First, retrospective assessment of risk factors to define high-risk patient groups is subject to criticism and may limit the conclusions and recommendations to be made. However, all consecutive peritonitis patients were prospectively included in a specific database. Because digital data of every ICU patient were available, there were almost no missing data as a potential bias in this retrospective analysis. After the univariate analysis we performed a multi-variate analysis in search for independent risk factors. Secondly, only 6 patients (13%) had a pure *Candida* peritonitis, whereas the remainder of the 87% of *Candida* patients had a polymicrobial mixed *Candida*/bacterial peritonitis. However, this corresponds to the low rate of pure *Candida* peritonitis reported in literature.

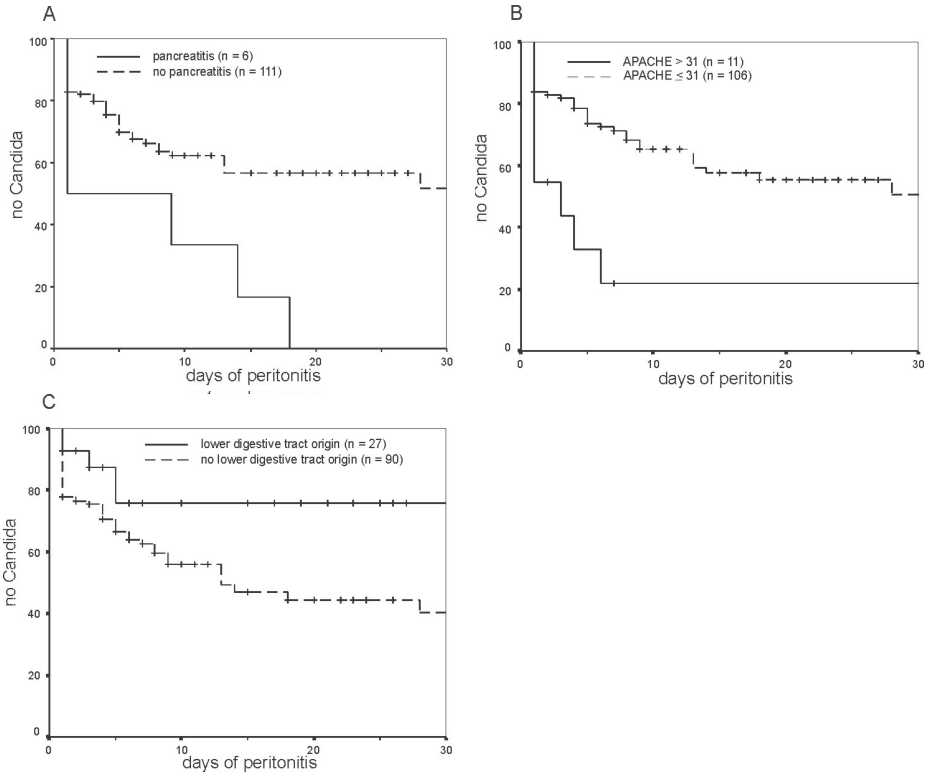


Figure 2. Kaplan-Meier curves of the risk factors A: pancreatitis (p = 0.0073), B: APACHE II-Score ≥ 31 (p = 0.0019) and C: lower digestive tract origin (p = 0.0342*), predicting/protecting for *Candida* isolation in peritonitis patients.

Table 4. Type of *Candida* species isolated in *Candida* peritonitis

Type of candida species	**n =**
Candida albicans	40
Candida glabrata	2
Candida tropicalis	1
Candida albicans + *Candida glabrata*	3
Candida albicans + *Candida tropicalis*	1
Candida albicans + *Candida parapsilosis*	1

We identified, with multivariate Cox-regression analysis, two factors independently associated with *Candida* isolation from peritoneal fluid. First, pancreatitis turned out to be an independent risk factor (p=0.012). Several studies concerning acute necrotizing pancreatitis provide evidence for the increasing clinical significance of *Candida* infection (31-33). This may be due to increased recognition through improved laboratory techniques or to more aggressive diagnosis by percutaneous aspiration. Maybe the most crucial fact is the application of broad-spectrum antibiotics for prophylaxis of pancreatic infection, in an attempt to prevent

a septic course. This can favour opportunistic infection of *Candida* species by modulation of the endogenous flora. Because of the lack of randomized, prospective trials, standardized recommendations for use of antifungal prophylaxis in acute pancreatitis would be premature. The answer to the problem of opportunistic infections due to antibiotic prophylaxis could be selective decontamination of the digestive tract (SDD). In 1995 Luiten published the data of a controlled, prospective clinical trial of SDD for the treatment of severe acute pancreatitis, and found a significantly reduced morbidity and mortality by SDD, without an increase in opportunistic infections (34). Some other experimental (35,36) and clinical (37,38) trials with SDD did follow this trial, but a widespread use in clinical setting failed to occur. Whether antifungal agents should be added to the prophylactic antibiotic regimens for patients with necrotizing pancreatitis remains questionable.

An APACHE II Score ≥ 31 was the second independent predictive factor of Candida isolation (p=0.002). As expected this score was associated with severity in peritonitis patients, and with mortality (p=0.0010). We divided the range of calculated APACHE scores in three groups for statistical risk analysis. Initially, the plan was to remove the highest APACHE scores, because in several trials (39) these very severely ill patients died, before they could acquire a nosocomial infection. However, the results showed for *Candida* infections that this group is the highest risk group.

In contrast to the described risk of broad spectrum antibiotics used for prophylaxis in pancreatitis patients, antimicrobial therapy overall in the peritonitis group of this study was not a significant risk factor for *Candida* isolation (p=0.793). One explanation could be the fact that statistical analysis started at the onset of peritonitis (t=0), whereas from that day on, all 117 studied peritonitis patients received antibiotics. Another fact to be considered is the time to *Candida* isolation in peritoneal fluid, which is for nearly half of the patients immediate from the onset of peritonitis (46% at t=0) or during the first days of peritonitis (77% within the first week). This is in contrast to other nosocomial ICU infections and is not consistent with the 'epiphenomenon of ICU stay'. Because of this finding we also analysed the previous antibiotic use from the admission to the ICU to the onset of peritonitis. At the first day of peritonitis there is a statistically significant difference in received antibiotics between the 22 patients with already a *Candida* in the peritonitis (a mean of 4.73 days of previous antibiotics) and the 95 patients without a *Candida* (3.54 days of previous antibiotics, p=0.040).

There was a tendency towards significance in favour of the *Candida* group and upper digestive tract origin of peritonitis (p=0.061), whereas the lower digestive tract origin of peritonitis was statistically significant in a protective fashion (p=0.0342). In the multivariate analysis this was no longer significant (p=0.084). Some studies suggested that perforated gastro duodenal ulcers are the most frequent cause of upper digestive tract origin of *Candida* isolation (18,40,41). Interestingly, in this study a pancreatic-biliary origin of peritonitis (both bilio-digestive anastomosis breakdown and pancreatitis) was frequently more responsible for

Candida isolation than perforated ulcers. The mechanism of the protection by lower digestive tract origin to *Candida* isolation is probably an overload of bacteria.

Although the liver transplant recipients formed the greatest group of peritonitis patients admitted to the ICU, liver transplantation was not a significant risk factor for *Candida* peritonitis (p=0.2735). This was the only group with immunosuppresive therapy. Nosocomial infections overall are a constant threat for liver transplant recipients. Therefore, in some centers it is common to use antibiotic prophylaxis, which proved to be a significant risk factor for invasive candidiasis in these patients (42). A recent study to evaluate risk factors for invasive candidiasis in liver transplant recipients mentioned antibiotic prophylaxis, retransplantation and posttransplant dialysis to be independent risk factors (43). In our hospital up to 2000 we used SDD as prophylaxis in every liver transplant recipient. Because of serious side effects with gram-positive bacterial infections the protocol was changed in use of SDD only in case of retransplantation or repeat surgery. Five out of 6 patients mentioned in Table 1 with SDD were liver transplant recipients. Surprisingly, SDD was seen both in the group with and without *Candida*.

A laparostomy was not a significant riskfactor for *Candida* isolation (p=0.848). Reflecting that a *Candida* infection is an endogenous infection and not a exogenous infection, like most nosocomial infections. This is probably one of the explanations why *Candida* infections are acquired in the beginning of ICU stay, in contrast with other nosocomial infections.

The morbidity (in terms of ICU stay) was significantly longer for the *Candida* group (27 versus 8 days, p=0.001), whereas – in contrast with several other studies (4-7,32,33.44) – the mortality in this study was not significantly higher (7%, p=0.842). Probably, the pathogenicity of *Candida* peritonitis is not solely related to the infection itself, and may be more a reflection than a cause of adverse outcome.

CONCLUSION

According to the results of this trial, critically ill surgical peritonitis patients with a high APACHE score are at risk for isolation of *Candida* species, with a special emphasis on patients with a pancreatitis and patients with antibiotic use before the onset of the peritonitis. These results tend to the recommendation to combine the therapeutic antibiotics with antimycotic prophylaxis in these cases, immediate from the onset of ICU stay. However, the results of this retrospective trial have to be controlled in a prospective trial, in order to define the real high risk groups who will benefit from antimycotic prophylaxis or pre-emptive therapy.

Probably the most remarkable result of this study is the fact that a *Candida* peritonitis doesn't comply with 'the epiphenomenon of ICU stay', i.e. the longer the stay in the ICU the higher the risk of acquiring a nosocomial infection. According to this trial the risk of *Candida* species isolation is not increasing during the ICU stay, almost half of the *Candida* infections

occurred at the day of onset of the peritonitis (46%), or during the first week of ICU stay (in total 77%). This is another argument to start antifungal prophylaxis early in the course of ICU stay, or empirical therapy early in the course of the disease.

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CHAPTER 9

Rapid identification of *Candida* species in peritonitis patients by Raman spectroscopy

ABSTRACT

Objective: This prospective study evaluated Raman spectroscopy for the identification of clinically relevant *Candida* species in peritonitis patients.

Methods: A Raman database was developed by measuring spectra from a set of 93 reference strains comprising 10 different *Candida* species. Clinical samples were obtained from the surgical department and intensive care unit of a tertiary university hospital. In total, 88 peritoneal specimens of 45 patients with a primary, secondary or tertiary peritonitis were included, of which 31 cultures were positive for *Candida*. Specimens were cultured initially on a selective Sabouraud medium that contained gentamicin to suppress bacterial growth. For conventional identification, a chromogenic medium was used for presumptive identification, followed by use of the Vitek 2 system for definitive identification (requiring a total turn-around time of 48-96 hr). Raman measurements were taken on overnight cultures from Sabouraud-gentamicin medium. We compared the feasibility, accuracy and turn-around time of this Raman technique, with the conventional identification as reference method.

Results: Using multivariate statistical analyses, a prediction accuracy of 90% was obtained for Raman spectroscopy, which appears to offer an accurate and rapid (12 to 24hr) alternative for the identification of *Candida* species in peritonitis patients.

Conclusion: The reduced turn-around time is of great clinical importance for the treatment of critically ill patients with invasive candidiasis in intensive care units.

INTRODUCTION

Candida species are often referred to as "emerging pathogens". First *Candida* was thought to be an insignificant, transient contaminant. However this hypothesis has been abandoned and *Candida* is nowadays a serious nosocomial pathogen in non-neutropenic critically ill patients on the Intensive Care Unit (ICU) (1-3). Over the past decades the incidence of *Candida* infections has risen significantly. The greatest increase in rate of *Candida* infections occurs in surgical services, especially in patients recovering from abdominal surgery (1,4-7).

The morbidity and mortality associated with these invasive *Candida* infections is striking; the median ICU-stay increased by as much as 30 days (8,9) and death rates of 30% to 80% are reported (10-13).

Several studies assessed the positive effect of early, systemic antifungal therapy on the improved outcome of ICU-patients with invasive *Candida* infections, in terms of a decrease in morbidity and (attributable) mortality (3,4,11,14-17).

Because of toxic side effects of amphotericin B, fluconazole is often first choice of prophylactic or empiric antifungal (3,18,19). Two of the heralded problems in using fluconazole as prophylaxis are the existence of fluconazole-resistant *non-albicans Candida* species (20), and the possible emergence of *de novo* fluconazole resistance through selective pressure of prolonged azole use. This prolonged use causes a possible selection of less susceptible *non-albicans Candida* spp. or a shift to fluconazole-resistant *Candida albicans* (21).

Rapid species-or even strain- level identification of the significant isolates is thus imperative for prompt institution of appropriate antifungal therapy, since susceptibility data for the isolated strain may not immediately be available. To switch as soon as possible to the appropriate antifungal therapy, a rapid identification of the causal *Candida* species is of paramount importance. Also the adequacy of the initial, empirical treatment has proven to attenuate morbidity and mortality. (Too) late changes in therapy based on culture results did not improve outcome when the initial regimen was inappropriate (22).

In conclusion, the need for a rapid and accurate multi-species level identification of significant yeast isolates is imperative for prompt institution of appropriate antifungal therapy. Our current techniques are, at best, blunt instruments with limited sensitivity. A convincing tool for the rapid diagnosis of invasive candidiasis has yet to emerge (23).

Vibrational spectroscopic techniques (Raman and infrared spectroscopy) yield spectra that are molecule specific. When applied to complex biological samples such as cells or tissues the spectra are a summation of the signal contributions of all molecular species in the organism, and therefore reflect the overall molecular composition of a sample. Such spectra have been shown to be highly suitable for rapid identification of both bacteria (24,25) and yeasts (26,27), because they are reproducible and distinct for different bacterial and fungal species. Previous publications indicate that the technique might provide sufficient resolving power, to enable the discrimination of microorganisms even at the strain level and contain information about

the susceptibility for antibiotics or antimycotics (26,28). Vibrational spectroscopy appears to offer many advantages: requiring minimal biomass, a minimum sample handling, and enabling direct analysis of samples, rapidity, automation and accuracy. This appears to render spectroscopic techniques clearly superior to current routine methods for the identification of *Candida* species.

Recently, we reported from our own Center for Optical Diagnostics and Therapy, a new and rapid method for the identification of clinically relevant microorganisms directly on solid culture medium based on confocal Raman micro-spectroscopy. Reproducible Raman spectra were obtained from microcolonies of 10-100 μm, after an incubation time of only 6 hours (29,30).

Our current aim is to evaluate the Raman identification in a prospective, clinical study for the identification of *Candida* species in peritoneal specimens of peritonitis patients, by testing feasibility, accuracy and turn-around time of this technique.

MATERIALS AND METHODS

Database strains

A collection of 93 reference *Candida* strains, comprising 10 different *Candida* species was used. Strains were either obtained from culture collections or from collections of clinical isolates identified to the species level by the conventional identification methods. Strains were stored at –80°C in a brain-heart infusion broth (Becton Dickinson, Franklin Lakes, New Jersey, USA) containing 10% glycerol until use. Before measurements, strains were cultured on Sabouraud–gentamicin medium (Merck, Darmstadt, Germany) for 12 to 24 hours, at 30°C. For each database strain 2 independent cultures were used to collect Raman spectra from.

Technical Procedures of confocal Raman microspectroscopy

Raman spectra were acquired as described previously (29,30). Briefly, with the CaF_2 substrate placed under a microscope (fitted with an 80x near-infrared objective, MIR Plan 80x/0.75, Olympus), Raman spectra were obtained using a System 1000 Raman microspectrometer (Renishaw plc, Wotton-under-Edge, UK). From each smear 10 spectra –obtained at randomly chosen positions within the smear- were measured, using approx. 100 mW laser light (830 nm), and a signal collection time of 30 seconds per spectrum.

Statistical Analysis

All spectral analysis were performed as described previously (30). Briefly, the first derivatives of the spectral range from 400 to 1800 cm^{-1} were used to minimize the influence of background signal due to slight sample fluorescence. Per sample, the 10 spectra collected from each smear were averaged. Then, the amount of data was reduced using principal compo-

nent analysis (PCA), performed using the PLS toolbox (Eigenvector Research Inc., Manson, WA) for the Matlab software (the Mathworks Inc., Natick, MA). These PCA scores were used in a hierarchical cluster analysis (SPSS,Chicago, IL) to generate a dendrogram. Based on the major clusters found in the dendrogram, 6 linear discriminant models (LDA) were calculated, to construct an identification scheme. For LDA only PC scores accounting for more than 1% of the variance in the data set were retained. A two-sided t-test was used to individually select those PC scores that showed the highest significance in discriminating the different microbial groups presented. The number of PC scores that was used as input for an LDA model was kept at least two times smaller than the number of spectra in the smallest model group to prevent overfitting in the LDA model. The prediction accuracy of this model was tested using a 'leave-one-strain-out' method: the spectra of all but one strain were used to generate the LDA model (30). By repeating this procedure, and leaving the spectrum of each strain out in turn, information is obtained on the accuracy and reproducibility of the identification scheme, i.e. if there was enough discriminating information in the Raman spectra to identify spectra of unknown samples correctly.

Patient sample collection

During 11 trial weeks in 2001 all patients from the surgical ICU or from the general surgical ward, with a primary, secondary or tertiary peritonitis were included prospectively. Specimens from peritoneal fluid or from an intra-abdominal absces were obtained during a laparotomy, specimens from CAPD-fluid were obtained directly out of the CAPD-catheter. Upon arrival in the microbiology laboratory, each specimen was devided in two: one for the conventional microbiological identification (the reference method) and one for the identification by Raman microspectroscopy.

Conventional microbiological identification of patient samples

For the conventional isolation and identification of yeasts, samples were cultured on CHROMagar *Candida* medium (Becton Dickinson, USA). After 2 days of incubation at 30°C a presumptive identification was made, based on distinctive coloured colonies. A definitive identification was obtained using the Vitek 2 system (bioMerieux, Lyon, France), requiring a total turn-around time of 48-96 hr.

Raman measurements and identification of patient samples

Patient samples were cultured under identical conditions as the database strains. From the overnight culture, if positive for yeasts, a biomass from several well-isolated colonies was smeared onto a CaF_2 substrate. The smears were dried in a desiccator over drying beads for at least 25 minutes, prior to Raman measurements. The performed identification scheme was applied to these spectra of unknown samples, in order to arrive at a species identification.

RESULTS

Representative Raman spectra acquired from database *Candida* strains are shown in Figure 1. Closer inspection of the spectra reveals that there are, indeed, spectral differences characteristic of the various species. These spectra were treated by multivariate analysis as described in the section on Material and Methods under "Statistical Data Analysis", to calculate 6 linear discriminant models. Figure 2 shows the schematic representation of this sequential identification model. The strength of this model based on the training set was evaluated using the 'leave-one-strain-out' method. The prediction accuracy of this model was 87%. Spectra of patient specimens to be identified were predicted by using this species identification scheme.

During the study period 88 peritoneal specimens were obtained. 55 Specimens were obtained from 20 ICU patients, 22 specimens were obtained from 17 patients hospitalised on general surgical wards and 11 specimens were from 8 patients with a CAPDitis. 31 (35%) of these specimens were positive for *Candida*. 30 (55%) of the specimens from ICU patients were positive for *Candida*, 1 (5%) of the specimens from patients of the general surgical ward was positive for *Candida,* none of the 11 specimens out of a CAPD-catheter was *Candida* positive.

29 of the 31 *Candida* isolates were available for evaluation; two *Candida* strains failed to grow on further subculture, one in the Raman arm and one in the conventional arm of the study.

Results of the conventional microbiological identification of the 29 *Candida* strains are reported in Table 1: 20 specimens were pure *Candida* cultures, 9 specimens were mixed *Candida* cultures.

The Raman species identification of these 29 isolates was predicted by presenting their spectra to models 1 to 6 of the database sequential identification scheme (Figure 2). Results are shown in Table 1. In 3 *Candida* strains there was a difference between the microbiological and the Raman identification. One *Candida albicans* was predicted by the Raman technique as a *Candida tropicalis,* and another as a *Candida dubliniensis* (Figure 2: model 2). One *Candida albicans/glabrata* mixed culture was misidentified as a *Candida tropicalis*. From the other 8 mixed *Candida albicans/glabrata* cultures we only identified *Candida albicans (*6) or *Candida glabrata* (2) by means of Raman spectroscopy. Taking the conventional microbiological identification as reference method, the prediction accuracy of the Raman identification was 90%.

DISCUSSION

During the last decades the incidence of nosocomial invasive candidiasis has risen. Since the mid-1990s there is a perceived shift in the etiology of *Candida* infections resulting in a selec-

tion of less susceptible *Candida* species. In the USA SCOPE Survey, looking at nosocomial *Candida* bloodstream infections, it appeared that 50% of *Candida* isolates were non-albicans species (31). Awareness, especially in intensive care practice, of the growing impact of invasive candidiasis is the first step in a rapid identification and diagnosis.

Because of the increasing incidence of less susceptible non-albicans species the need for a rapid and accurate identification of clinical significant yeast isolates is even more imperative for the prompt institution of appropriate antifungal therapy. The adequacy of the initial, empirical treatment has proven to be of paramount significance on morbidity and mortality in critically ill patients with an invasive *Candida* infection (32).

Clinical microbiologists face an important challenge to select a system for yeast identification that is rapid and accurate (high specificity and sensitivity). No current available method fully meets these criteria. Conventional identification is based on an extensive series of biochemical assays, following an obligatory culture time to obtain enough biomass of 10^6-10^8 cells (33). This "gold standard" identification is time-consuming, with an unavoidable turnaround time of 48-96 hr. A large variety of methods have been developed with the aim of facilitating rapid same-day yeast identification, but most of these systems are designed to discriminate between two common species or to confirm only a presumptive identification (28,34). A second identification system, like the commercial yeast identification panels, is often needed for a definitive identification (35,36). Consequently, up to four days may go by before a definitive report reaches the clinician. Besides, the reported accuracies of these

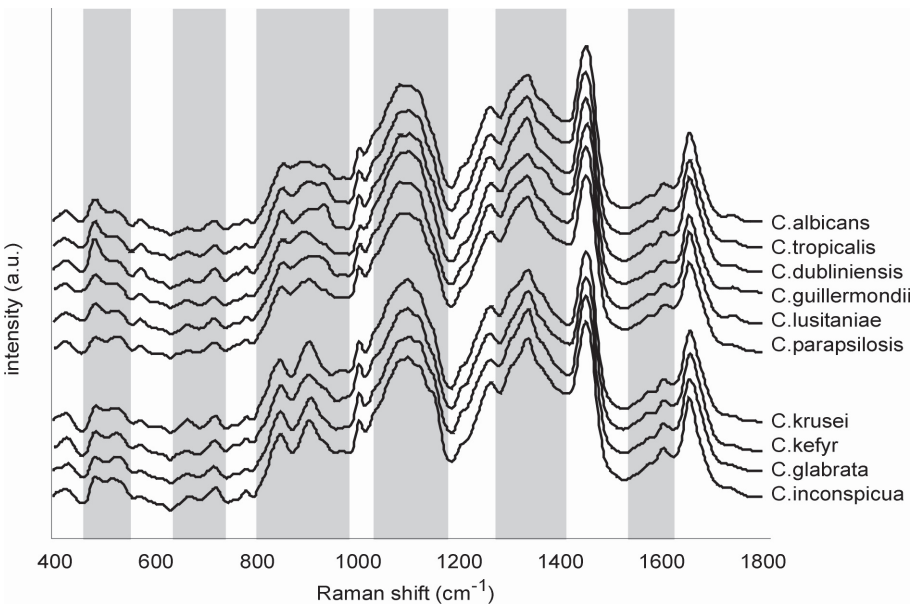

Figure 1. Representative Raman spectra of 10 *Candida* species, used for the *Candida* database in this study. The shaded areas highlight some characteristic differences between the species. (a.u. = arbitrary units).

commercial yeast identification systems varies from 60-99% (28,37). So, the need for a rapid and accurate multi-species level identification of significant yeast isolates is imperative for prompt institution of appropriate antifungal therapy.

Confocal Raman microspectroscopy is highly suitable for the rapid identification of *Candida* species since Raman spectra can be directly obtained from microcolonies on a solid culture medium after only 6 hours of culturing. Following the development in our Center for Optical Diagnostics and Therapy of a new, rapid method for the identification of clinically relevant microorganisms (29), we evaluated this method to test the feasibility of this technique for the identification of *Candida* species (30). In that study we used a set of 42 reference *Candida* strains comprising 5 clinically relevant species and obtained Raman spectra directly from microcolonies on a solid culture medium after only 6 hours of culturing. We concluded that Raman microspectroscopy also offers a potentially powerful technique for the rapid identification of *Candida* species, with an obtained high prediction accuracy of 97-100%.

In the present clinical study the prediction accuracy of the Raman identification was 90%. One *Candida albicans* was predicted by the Raman technique as a *Candida dubliniensis*. Sul-

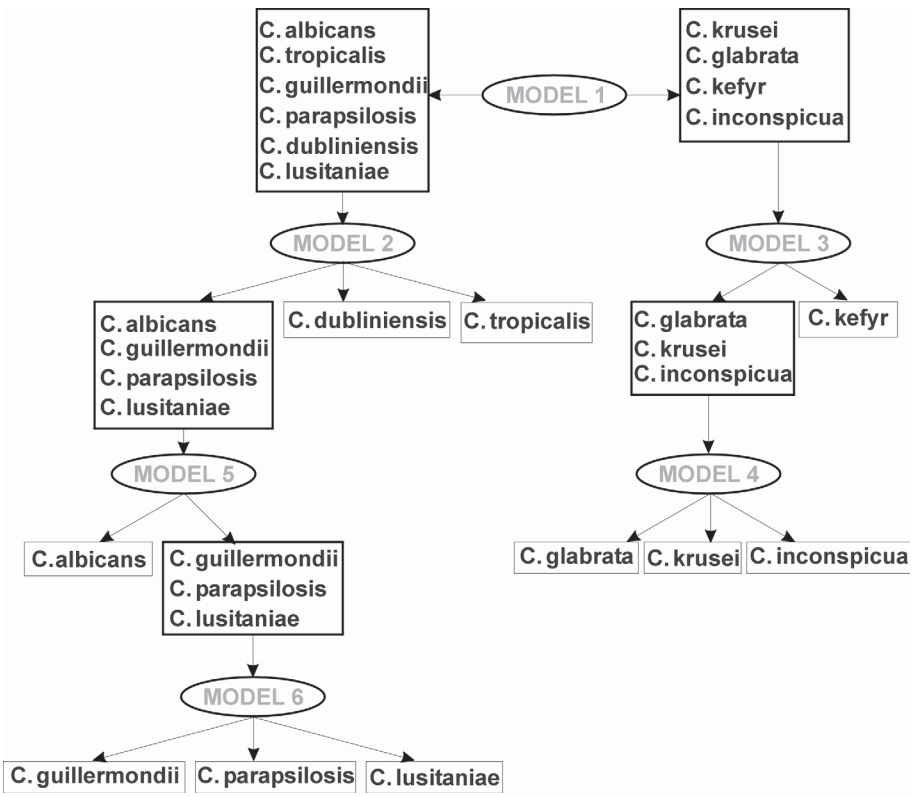

Figure 2 Schematic representation of the sequential species identification procedure, based on the *Candida* database LDA model 1 to 6. Spectra of trial specimens to be identified are predicted by using model1, followed by subsequent the next projections.

Table 1. Results of the conventional microbiological identification and Raman identification of the *Candida* strains from 29 trial specimens

Conventional identification	**Raman identification**					
Species	***C.albicans***	***C.glabrata***	***C.inconspicua***	***C.tropicalis***	***C.dubliniensis***	**Total**
C.albicans	13			1	1	15
C.albicans/glabrata	6	2		1		9
C.glabrata		2				2
C.inconspicua			2			2
C.tropicalis				1		1
Total	19	4	2	3	1	29

livan and coworkers characterized a novel species associated with oral candidiasis in human immunodeficiency virus infected individuals (38). This species *Candida dubliniensis* shares many phenotypic properties with *Candida albicans*. As a result, this uncommon species is often identified as *Candida albicans* in the microbiology laboratory (28). Because of possible resistance of *Candida dubliniensis* to azole antifungal agents, it is of great importance to differentiate the two species. Easy-to-perform selective isolation procedures for these closely related species do not exist. Marot-Leblond et al (39) described an anti-*Candida albicans* cell wall surface-specific monoclonal antibody which might be a candidate for the differentiation of *Candida albicans* from *Candida dubliniensis*. Tintelnot et al (27) from the Robert Koch Institute, evaluated discriminatory phenotypic markers for *Candida dubliniensis* and concluded that only Fourier transform infrared spectroscopy combined with hierarchical clustering proved to be as reliable as genotyping for discriminating the two species. Future Raman studies with *Candida albicans* and *Candida dubliniensis* strains may reveal the accuracy in discriminating these two related species.

From 8 mixed *Candida albicans/glabrata* cultures we only identified *Candida albicans* or *Candida glabrata* on the Sabouraud medium, presumably because we did not detect the existence of a mixed culture and measured only spectra of one *Candida* species. The identification of only one instead of both *Candida* species of a mixed culture was not counted as a misidentification. Although this influences the prediction accuracy, we believe that the underlying problem is not due to the intrinsic identification capabilities of Raman spectroscopy. However, we assign this to the sample preparation protocol, prior to Raman measurements. Optimising of this preparation protocol, in order to detect the existence of mixed cultures could provide a solution. Because of the absence of any differential indicator in the Sabouraud medium used, chromogenic isolation media are often used for the recognition and presumptive identification of mixed yeast cultures. We have successfully measured Raman spectra directly on CHROMagar medium, after only one overnight passage (unpublished data). Future studies will be directed to measure Raman spectra directly on CHROMagar medium, followed by an incubation of the *Candida* isolates for another 2 days on the same medium,

to facilitate the recognition of an eventually mixed culture. If so, the first identification of one species precedes the second identification of another *Candida* species by another Raman measurement. A review of recent literature shows mixed *Candida* cultures to be uncommon, but defenitely not rare. If mentioned in trials, we found mixed *Candida* culture percentages of 9-38% (12,15,40). At this moment chromogenic isolation media are the only tests demonstrating a better detection rate of yeasts in mixed cultures than traditional media, but still with the restriction of only a presumptive identification. A rapid and accurate test for the definitive identification of these mixed *Candida* cultures is still lacking.

The last item to be evaluated in this study was the rapidity, compared to the conventional identification. Raman spectra were measured from colonies after overnight culturing, smeared onto CaF_2 glass slides. This method differs from the sample preparation in our preclinical *Candida* trial, where we obtained spectra of microcolonies after only 6 hours of culturing. In the present study we have chosen for the most practical way in a clinical setting. Raman measurements from smears are easier and more rapid to perform, but are not as homogenous as microcolonies. In all 29 *Candida* strains it was feasible to measure representative Raman spectra from overnight cultures, resulting in a turn-around time of maximal one day, instead of 3-4 days required for the conventional identification.

CONCLUSION

Raman spectroscopy offers an accurate and rapid alternative for the identification of *Candida* species in ICU-peritonitis patients. Further investigations should be directed to optimise the technique for a better detection of mixed *Candida* cultures and to evaluate the impact of this novel identification on clinical practice and patient outcome in a prospective, clinical trial.

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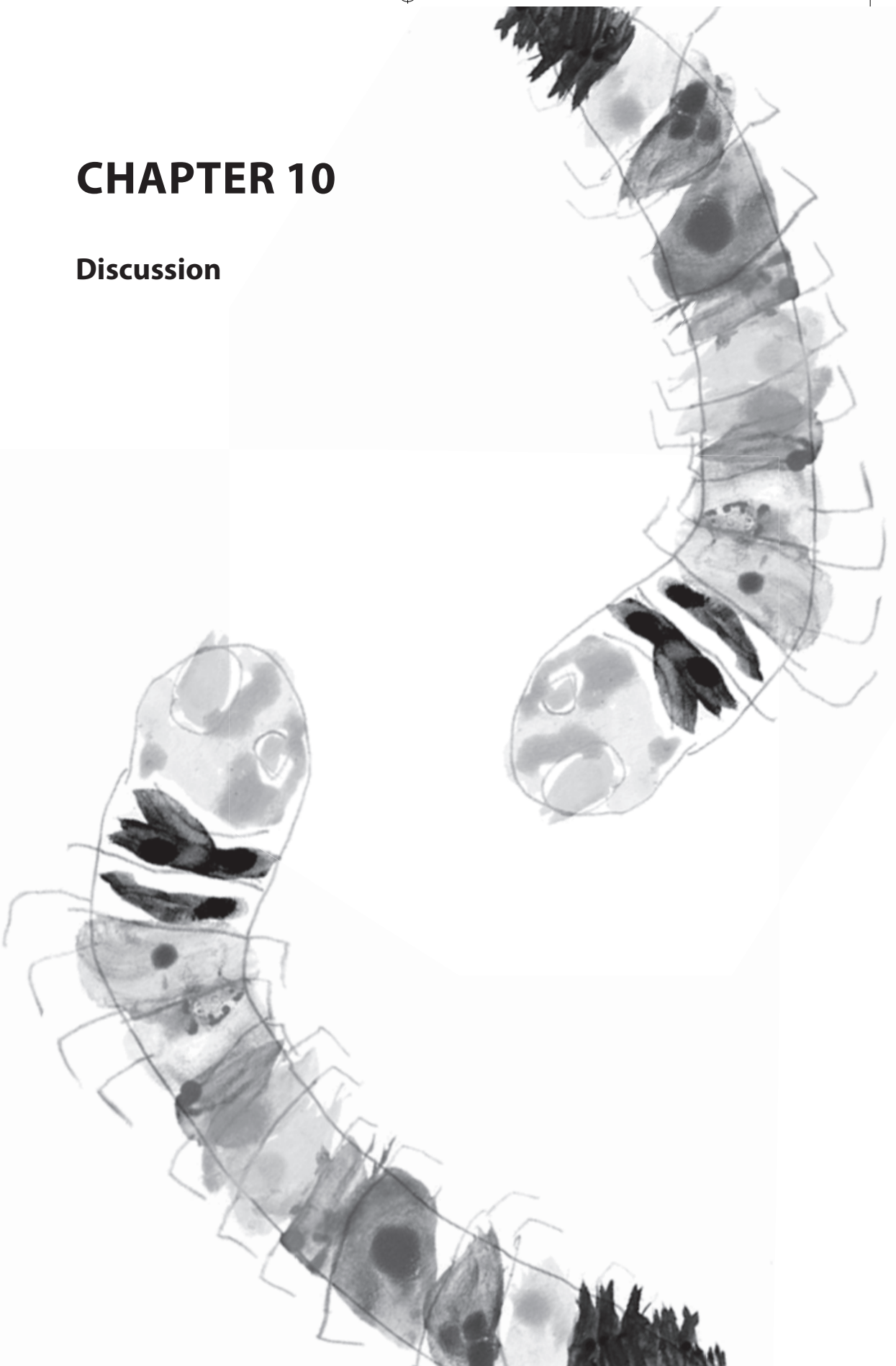
CHAPTER 10

Discussion



THE POST EPIIC PERIOD IN EUROPE

Was the EPIIC study the start to a new European era in which ongoing European wide surveillance over the occurrence of nosocomial infection determines the appropriate antimicrobial regimens? Was 1992 the start of an ongoing European collaboration on data collection to audit the effectiveness of European infection control programs? The answer is unfortunately no. No European SENIC Project, no European NNIS Study followed the major undertaking of the EPIIC Study. Ongoing surveillance programs were not implemented throughout Europe. No European infection control policies were instituted. No European counterpart to the Centers for Disease Control and Prevention (CDC), which was started in the 1960's in Georgia, and which recommended that hospitals in the USA conduct surveillance on the occurrence of nosocomial infections, was instituted. The goal of the CDC was to obtain epidemiological evidence on which to base rational control measures. Four decades later, Europe still has not followed this American model.

Again individual studies undertaken in individual countries dominate the European perspectives on critical care infectious diseases (1-6), individual studies with a wide variety in study design. It is inappropriate to extrapolate the data from these trials for use in a European wide setting. However, the results of all these individual studies emphasise again the difference in prevalences of nosocomial infections in ICU's between Southern and Northern European countries. The same is stresssed in the difference in reduced antibiotic susceptibility among ICU bacterial pathogens. The reason for these existing differences is the great difference in control strategies and formulary programs between countries.

Recently European boundaries have been opened for traffic, economics and tourism, consequently also for micro-organisms. This makes the task to control pathogens, especially resistant pathogens in Europe increasingly difficult.

THE FUTURE CHALLENGES OF INFECTION CONTROL; LOOKING FORWARD

The goal of eradicating nosocomial infection from ICU's is one that is unlikely to be attainable in the future. However, where eradication is impossible, the goal to reduce and control this ever growing problem is feasible.

What are the challenges to address in future?

A EUROPEAN SURVEILLANCE NETWORK

The ultimate aim for the near future is a European Surveillance network with more European collaborative efforts in infection control. A European wide network is the only way to mea-

sure and constantly re-measure the scope and magnitude of the incidence of ICU infections. A European-wide network is the only way to measure the organisms causing these nosocomial infections and the antibiotic resistancy patterns of these pathogens. A European- wide network is the only way to guide in antibiotic policy and formulary decision making.

A European-wide network is also the only way to generate a database that would make a real contribution to the understanding of the nature and frequency of nosocomial infection in the ICU. It is important to have as accurate a picture as possible of the scale of the problem and the factors that affect it. Easy access to a suitable epidemiological database is a good starting point. With these data, patients most at risk of developing nosocomial ICU infections can be identified, to target those patients at risk who will benefit from antimicrobial or antifungal prophylactic strategies.

The outcome of nosocomial ICU infections can be gauged and effective infection control policies can be instituted. Ongoing collection of data can then be employed to audit the effectiveness of such policies. For example, the act of systematically collecting, tabulating and analysing data on the occurrence of nosocomial infections is known as 'surveillance'. Another method to easily measure the efficacy of infection control policies is by repeated prevalence surveys.

Evaluation of cost-benefit of new infection control measures will be crucial because of the high economic burden of ICU infections. Financial incentives may ultimately be the most proactive catalyst for every European country to ensure the implementation of infection control policies to save substantial money for the hospital budget.

It is important that collected data are translated into positive action, to improve infection control and management. Therefore, it is of paramount concern to all European countries to take an active role in reducing this problem of nosocomial ICU infections. An increased collaborative effort in infection control will provide the roots for a European perspective on nosocomial infections in ICUs, and will begin to establish some solutions to this growing problem.

NEW TYPES OF DEVICES

The farmaceutical companies are constantly in search for new devices with antibacterial effects. Some examples under investigation are urinary catheters impregnated with antimicrobial or antiseptic agents which is expected to reduce catheter-associated urinary tract infection. Silver-hydrogel urinary catheters prevent adherence of bacterial and yeast pathogens to the catheter surface. Some trials with these kinds of urinary catheters have shown promise, but definitive studies have not yet been published.

Innovation in sutures has developed a new antibacterial suture with a zone of inhibition that is effective against the pathogens that most frequently cause surgical site infections.

For prevention of ventilator associated pneumonia, endotracheal tubes with continuous subglottic suctioning decrease the risk of aspiration of secretions that pool around the endotracheal cuff, which has been shown to prevent ventilator associated pneumonia. Noninvasive ventilation is an alternative to intubation and mechanical ventilation, to reduce the risk of nosocomial pneumonia.

Undoubtedly, the most effective method to prevent a nosocomial infection caused by an indwelling device is to avoid unnecessary placement of this device, or to limit the duration of use once a device is in place. A policy to withdraw devices as soon as possible will be more preventive than the use of high-tech, newly developed, costly devices.

NEW TYPES OF SURGERY

Minimally invasive surgery

Minimally invasive surgical procedures have been increasingly performed by surgeons in the last decades. In addition to faster functional recovery and improved cosmetics, a patient undergoing laparoscopic surgery may benefit from lower rates of surgical site infections. Surgical stress derails the functions of both cellular and humoral immunity, resulting in immunosuppression and consequently an increased risk of postoperative infection. Laparoscopic surgery may result in less induced surgical trauma than conventional open surgery which is translated in a reduced inflammatory response and minimal immuno-suppression. Several comparative studies of cellular immunity after laparoscopic and conventional surgery demonstrated immunologic advantage conferred by laparoscopy (7,8).

A recently described lucky coincidence of laparoscopic surgery is the bacteriostatic effect of 100% CO_2 (9). CO_2 has been combined with cold storage since the 1930's for the preservation of food. Animal studies showed the attenuated inflammatory response to the abdominal insufflation with CO_2 (10). No human studies had been reported, but in this particular case, the laparoscopists are in the unusual position in that the trials have been partially conducted before the hypothesis has been advanced. At present, it is probably ethically incorrect to go back to prospective, randomized trials with other types of insufflation gases, to measure the bacteriostatic effect in comparison with CO_2.

With regard to minor surgical procedures such as laparoscopic cholecystectomy(11,12) and laparoscopic appendectomy (13-15) this immunologic benefit is most obvious, and several randomized studies assessed significant lower rates of surgical site infection after these procedures. Also mesh-related infections after hernia repair surgery seems to be considerably lower after endoscopic or laparoscopic procedures (16-17). However, for more complex procedures such as laparoscopic surgery for cancer of the esophagus, colorectal cancer surgery (18-19) and for hepato-biliary or pancreatic surgery, these laparoscopic benefits are not immediately obvious or studied yet.

It will be necessary to wait for the results of more randomised, clinical trials of a greater variety of laparoscopic procedures to provide further data and clarification of these immunologic and nosocomial infection benefits of laparoscopic surgery.

Fast-track surgery

Fast-track surgery, also called fast-track rehabilitation, is an interdisciplinary, multimodal concept to accelerate postoperative reconvalescence and reduce general morbidity. Fast-track rehabilitation focuses on preoperative patient education, atraumatic and minimal-invasive access to the operative field, optimized anesthesia under normovolemia and prevention of intraoperative hypoxia and hypothermia, effective analgetic therapy without high systemic doses of opioids, enforced postoperative patient mobilisation, early postoperative oral feeding, and avoidance of tubes and drains. This set of rules is recorded in a multimodal rehabilitation programme. The overall aim is to hasten recovery, to reduce hospital stay, and to reduce morbidity and mortality.

One aspect is the restart of oral intake as soon as possible, possibly the evening of the operation day, which is expected to have a favourable effect on the intestinal flora and thus on the possible endogenous postoperative infections (20,21). Fast-track rehabilitation for major surgery should be evaluated in randomized, controlled trials, both for open and laparoscopic surgery.

Ambulatory same-day or outpatient surgery

In these days of high-pressure health-care systems, hospital financial budgets, and rapid surgical throughput there is an increase in ambulatory same-day or outpatient surgery. A very rapid throughput of patients often leads to overcrowding and high bed occupancy rates, a situation in which infection control principles are likely to be undermined. Also in ambulatory and outpatient care we have to adhere to the principles of infection control.

NEW TYPES OF MEDICINES OR REGIMENS

The farmaceutical companies are constantly in search for new types of antibiotics,new types of antimycotics, and a new 'miracle' drug. For example, a human genetically recombinant antibody against the immunodominant hsp90 antigen of *Candida albicans* has been developed, which has demonstrated protective potential in murine models of invasive candidiasis. A phase II double-blind, prospective study with this antibody in patients with disseminated candidosis is going on.

New types of regimens have been used to decrease the overall utilization of antimicrobial agents. These measures should, in turn, decrease selective pressure that can foster the emergence of resistant strains. Antibiotic cycling by regularly cycling different antimicrobial

classes, is one of the newer methods for antibiotic control (22). The goal is to prevent prolonged overutilization of a single antimicrobial class in an attempt to prevent widespread class resistance throughout an ICU and to improve the appropriateness of antimicrobial therapy, by limiting the emergence of resistant bacteria. In theory, by rotating different classes of antibiotics, overall resistance is kept at a low level, and when a particular class is reintroduced (ie, when the cycle is repeated), most pathogens are susceptible. Despite the theoretical promise, studies of antibiotic cycling have been difficult to interpret. The independent effects of antibiotic cycling need to be more thoroughly studied, particularly after agents have been reintroduced in an ICU several times (after several cycles), before definitive conclusions can be drawn regarding the efficacy of this strategy.

Selective digestive decontamination (SDD) is an infection-prophylaxis regimen that was introduced into intensive care medicine in 1984 (23). SDD is based on the concept of colonisation resistance, according to which the indigenous intestinal flora has a protective effect against secondary colonisation with gram-negative aerobic bacteria. The approach aims to eradicate colonisation of aerobic potentially pathogenic micro-organisms from the oropharynx, stomach, and the gut, while leaving the indigenous anaerobic flora largely undisturbed. Controversy exists about the effect of SDD on mortality, on the emergence of infections caused by gram-positive bacteria, and on antibiotic resistance. Several prospective, randomised, clinical trials showed a decrease in ICU mortality and infection with gram-negative aerobic bacteria (24,25). However, the effects of these methods on resistant flora and infection rates in ICUs and hospitals as a whole have not been rigorously studied and cannot currently be accepted as standard of care.

Immunonutrition has met with various successes in the prevention of nosocomial ICU infections. Perioperative immune modulation using specialized enteral (or parenteral) diets containing specific immunonutrients (formula supplemented with combinations of arginine, omega-3 fatty acids, ribonucleic acid, antioxidants, and glutamine) may improve postoperative outcomes in critically ill patients. Several trials showed that immunonutrition reduced the number of infectious complications, and improved the function of the immune system (26,27). However, there are still many questions regarding the place of immunonutrition in clinical practice. There may be patients who will not benefit or even suffer detrimental effects from immunonutrition. L-arginine is an important immunonutrient having both beneficial and adverse effects. The former effect occurs in necrotizing enterocolitis; the latter influence is seen in septic patients. Immunonutrition merits further study before used in clinical practice.

Probiotics are living microorganisms that, ingested in adequate amounts, exert beneficial effects. Due to the lack of proven efficacy and an unidentified mode of action, probiotics were dismissed by the traditional medical sector for many years. Today, some probiotics represent prophylactic or therapeutic standards in certain indications (28). However, the administration

of oral probiotic supplementation (such as Saccharomyces boulardii and Lactobacillus sp.) remains controversial, and merits further study.

Aside from the impact of the emergence of various new types of antibiotic and antimycotic medicine, the results of several studies reinforced the conviction that an effective, restrictive antibiotic policy may be one of the most important patient care standards for preventing life-threatening infections. A more tailored antibiotic regimen should be implemented, with no broad-spectrum antibiotic regimen for everyone anymore, but with an antibiotic regimen with the smallest spectrum possible, only for specific risk groups.

AWARENESS OF THE PROBLEM

Last, but certainly not least, raising awareness of the problem of nosocomial ICU infections is of utmost importance. A key 'milestone' of the future challenges to control infection should be to raise awareness of the problems of nosocomial infection in the ICU among all ICU personnel, and to stimulate discussion, research, and consideration of ways to improve infection control and management. All these different aspects together will jump-start the progress towards better infection control in ICUs.

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CHAPTER 11

Summary and conclusions

SUMMARY AND CONCLUSIONS

Chapter 1

The scope and magnitude of nosocomial Intensive Care Unit (ICU) infections is overwhelming, with a negative impact on both the added morbidity, mortality, and as a consequence on the overall hospital charges and economic costs. Aggressive invasive diagnostics, multiple therapies and a plethora of invasive devices in combination with a temporarily compromised immunity -intrinsic risk together with extrinsic factors- renders the ICU patient population uniquely susceptible to nosocomial infections.

The growing incidence of the nosocomial ICU infections will continue to limit the potential advances to be made in modern critical care medicine, which has to deal with more complex critically ill patients. In chapter 1 the problem of this growing incidence and impact of the nosocomial ICU infections is further elucidated, followed by an outline of the thesis.

Chapter 2

There is a remarkable difference in the knowledge of the magnitude of the infection problem between the USA and Europe. In the United States systematized information concerning the rates of nosocomial infections is available due to the development of various national formalized systems for ongoing surveillance. In Europe, no such formalized system exists, and there has been no large international study to determine the nosocomial infection rates throughout the continent, up to 1992. It was against this background that in 1992 the European Prevalence of Infection in Intensive Care (EPIIC) Study was undertaken, - the largest ever one-day point prevalence survey, conducted throughout Europe- to deal with the relative lack of information concerning nosocomial ICU infections.

Chapter 2 describes the results of the overall study, taking part in 1417 ICU's in 17 Western European countries, with data from 10,038 ICU patients. According to the results of the EPIIC study 45% of the total ICU patient population had one or more infections, almost half were ICU- acquired infections (21% of the total). The highlights of the results were the high prevalence of pneumonia and other lower respiratory tract infections (a prevalence together of 63% of the total infection types), the importance of *S. aureus* (with a prevalence of 30.1% the most frequently isolated pathogen), *P. aeruginosa* (28.7%), and the Enterobacteriaceae (as a class) as the key pathogens, and the high prevalence of microbial resistance of these pathogens to the various antibiotics. Most obvious was the resistance to methicillin in 60% of strains of *S. aureus*, with a remarkable difference between the various countries in Europe. Overall, there was a surprisingly growing significance of gram-positive pathogens, and fungi. The key risk factors associated with ICU-acquired infections were in particular a prolonged length of stay on the ICU (with a relative risk (RR) of infection of 15.01 after an ICU stay of 1 week, RR of 30.75 after 2 weeks and RR of 76.06 after 3 weeks), and various invasive interventions. Mortality rates were high (16.8%), with a significant correlation between the prevalence

rate of ICU-acquired infection and the mortality rate. In particular pneumonia, laboratory-confirmed bloodstream infection and sepsis were independent risk factors, associated with an increased risk of death.

Chapter 3

Chapter 3 describes the scope and magnitude of nosocomial ICU infections in the Netherlands. Data from 472 patients in 78 ICU's in the Netherlands are separated from the data of the EPIIC Study.

37% Of the ICU patients suffered from an infection, of which 16% of the total was ICU-acquired. The most important risk factors were: the duration of an ICU stay (relative risk (RR) of 4.23, 99.37 and 146.79 for ICU stays of 3-4 days, 1-2 and more than 3 weeks respectively), correlated with severity of disease (organ failure) and more medical interventions (mechanical ventilation, urinary catheter). The risk of acquiring a nosocomial ICU infection was lower after elective surgery than after ICU admission without previous surgery; after emergency surgery the ICU infection risk was higher. During follow-up 14% of patients died. Patients suffering from an ICU infection had a higher mortality risk; the strongest prognostic factor to determine the mortality risk was the APACHE II-Score (RR of 13 with a score between 16-26 and RR > 100 with a score > 31).

Chapter 4

The risk analysis of infections in Dutch ICU patients is completed with an analysis of the nature of these ICU-acquired infections, as described in chapter 4. Pneumonia and infections of the lower respiratory tract had the highest prevalence (together 63%), followed by urinary tract infections (16%), sepsis (16%) and wound infections (11%).

The most frequently cultured pathogens were Gram-negative bacteria (92% in total), especially *Enterobacteriaceae* (34% as a class) and *Pseudomonas aeruginosa* (30%), followed by *Staphylococcus* (37%), *Enterococcus* (20%) and surprisingly: 10% fungi.

The antibiotics most frequently prescribed were: cephalosporins (30%), followed by broad-spectrum penicillins (17%), metronidazole (17%), and aminoglycosides (13%). No infection with Methicillin-Resistant *Staphylococcus aureus* (MRSA) was found on the day of this study in the Netherlands, in contrast to many other European countries. Gentamicin-resistant coagulase-negative *Staphylococcus* and ciprofloxacin-resistant *P. aeruginosa* were found however. In many of the hospitals in the Netherlands, microbiologists, infectious disease specialists (84%) and infection control nurses (51%) reside in the ICU team.

Chapter 5

Chapter 5 starts with a review of the current literature about the surgical ICU patients and surgical site infections (SSI). The most used risk score for SSI's at this moment (the NNIS surgical patient risk index score) is described.

This review is followed by the results of the surgical ICU patients, separated from the data of the EPIIC Study. Over 50% of the 10,038 ICU patients had undergone surgery in the month prior to the EPIIC Study. Abdominal surgery was the most frequently performed type of surgery, followed by cardiothoracic surgery and head and neck surgery. Of these 5066 surgical ICU patients, 21.3% developed an ICU-acquired infection. A risk analysis of the most important infection risk factors for surgical ICU patients focused on: emergency - and multiple operations (RR of 2.31 and 3.12 respectively). Together with these types of surgery, trauma was a significant risk factor (RR of 3.31) The infection risk was highest for the younger patient population (age between 20-40 years), and declined when the age increased. A longer ICU stay increased the odds ratio for infection dramatically, also due to an increasing number of invasive procedures, a prolonged need for assisted ventilation (sometimes in combination with a tracheostomy), more procedural diagnostic interventions and multiple operations. More than half of the ICU-acquired infections of these surgical ICU patients were located in the respiratory tract (prevalence of 51.7%), whereas the prevalence of wound infections was 8.7%. Gram-negative bacteria had the highest prevalence (47.1%), followed by the gram-positive bacteria (40.9%), and fungi (10.8%).

The mortality in the group of surgical patients with an ICU-acquired infection was significant higher (26 versus 12%), the pathogens associated with the highest rate of mortality were the fungi (31.1%).

Chapter 6

To evaluate the risk of patients in ICU's of becoming infected with methicillin-resistant *Staphylococcus aureus* (MRSA) and to assess the mortality, compared to patients with a methicillin-sensitive *S. aureus* (MSSA) infection, data were separated from the EPIIC Study about prevalence of MRSA and MSSA infections, risk factors and mortality. Overall in Europe, 60% of strains of *S aureus* were resistant to methicillin, with a wide intercountry variation; the highest proportion of MRSA occured in Italy (81%) and France (78%), while many northern countries had none.

For both bacteria the most commonly reported infections were in the respiratory tract: pneumonia 52% and 61% for MRSA and MSSA respectively, and lower respiratory tract infections 22% and 17% respectively. The most important risk factor for MRSA was the length of stay in the ICU (with a RR of 4.07 for a stay longer than three weeks), and an increasing APACHE II score. MRSA infection reduced the chance of survival, particularly when it was found in lower respiratory tract infections: the risk of mortality was three times higher in patients with MRSA than in those with MSSA.

Chapter 7

Fungi are called the 'emerging pathogens', because over the past decades they deranged from colonising a-pathogens, playing a subordinate role, to emerging virulent pathogens.

The EPIIC results highlighted the growing prevalence of fungi, with a surprisingly high frequency of 17% in the total study group, 10% in the Dutch subgroup and 11% in the surgical group.

Chapter 7 reviews the current literature about fungal infections and the epidemiology. There are some major problems of candidiasis to be mentioned: first, there is no complex of symptoms specific for the diagnosis invasive candidiasis. Secondly, there is a lack of reliable diagnostic methods; there is no rapid "gold standard" test available. Thirdly, at present, there is no 'wonder weapon' antifungal therapy available yet. The morbidity and mortality associated with these invasive *Candida* infections is striking, with reported mortality rates of 40-80%. The positive effect is described of early, systemic antifungal prophylaxis or empirical therapy on the outcome of ICU patients with candidiasis.

Chapter 8 focuses on the identification of high risk patient groups, to target antifungal prophylaxis. Chapter 9 focuses on a new rapid identification method of *Candida* species.

Chapter 8

Chapter 8 describes a retrospective cohort study to analyse the risk of *Candida* species isolation from peritoneal fluid in surgical Intensive Care Unit (ICU) patients with a peritonitis, and to determine independent risk factors. During the period of 2000 up to 2003, one hundred and seventeen patients with a peritonitis (bacterial n = 69, *Candida* or mixed *Candida*/bacterial n = 48) hospitalized in a surgical ICU of a tertiary university hospital were included. Statistically significant risk factors of *Candida* isolation were pancreatitis (p=0.0073), APACHE II score >30 (p=0.0019), antibiotics used before the day of onset of the peritonitis (p=0.040), and perforation in the lower digestive tract (in a protective fashion, p=0.0342). In contrast to the mortality (p=0.842), the morbidity (defined as length of stay in the ICU) in the *Candida* group was significantly higher than in the bacterial group (27 versus 8 days, p=0.001). In contrast to other nosocomial infections, *Candida* isolation most frequently occurred during the beginning of the ICU stay.

According to these results, we concluded that: Critically ill peritonitis patients with a high APACHE score are at risk for isolation of *Candida* species from peritoneal fluid, with a special emphasis on patients with pancreatitis. Empirical antimycotics would be recommended in these cases

Chapter 9

Chapter 9 describes a prospective study which evaluated Raman spectroscopy for the identification of clinically relevant *Candida* species in peritonitis patients. A Raman database was developed by measuring spectra from 93 reference strains belonging to ten different *Candida* species. Clinical samples were obtained from the surgical department and intensive care unit of a tertiary university hospital. In total, 88 peritoneal specimens of 45 patients with a primary, secondary or tertiary peritonitis were included, of which 31 cultures were

positive for *Candida*. Specimens were cultured initially on a selective Sabouraud medium that contained gentamicin to suppress bacterial growth. For conventional identification, a chromogenic medium was used for presumptive identification, followed by use of the Vitek 2 system for definitive identification (requiring a total turn-around time of 48-96 hr). Raman measurements were taken on overnight cultures from Sabouraud-gentamicin medium. We compared the feasibility, accuracy and turn-around time of this Raman technique, with the conventional identification as reference method. Using multivariate statistical analyses, a prediction accuracy of 90% was obtained for Raman spectroscopy, which appears to offer an accurate and rapid (12 to 24hr) alternative for the identification of *Candida* species in peritonitis patients. The reduced turn-around time could be of great clinical importance for the treatment of critically ill patients with invasive candidiasis in intensive care units.

Chapter 10

In chapter 10 the question is addressed whether there is an ongoing European collaboration on infection data collection and whether there are European infection control programs.

Challenges of infection control to address in future are discussed, such as: a European surveillance network, new types of devices, new types of surgery (minimally invasive surgery, fast-track surgery and ambulatory same-day or outpatient surgery), new types of medicines or regimens, and last but not least: raising awareness of the problem

IN CONCLUSION THE MOST IMPORTANT RISK FACTORS FOR NOSOCOMIAL INFECTIONS IN ICU PATIENTS TO BE WARNED FOR:

- Beware of prolonged length of stay on the ICU, which increases the odds ratio for infection dramatically. Also the risk for infection with a resistant pathogen, like MRSA, increases with the length of ICU stay.
- Beware of pneumonia and lower respiratory tract infections. Precautions, pre-, per- and post-operative are necessary to attack this type of infection in the surgical patient.
- Beware of gram-positive bacteria. The gram-negative bacteria are not any longer the most important and most virulent pathogens in nosocomial ICU infections. Gram-positive bacteria, such as the coagulase-negative staphylococci, are not only insignificant contaminants anymore.
- Beware of fungi. Fungi have deranged from colonising a-pathogens, playing a subordinate role, to emerging virulent pathogens, with high associated morbidity and mortality rates.
- Beware of emergency - and multiple operations. As a consequence, trauma is a significant risk factor for surgical ICU patients.
- Beware of a high APACHE score on admission to the ICU.

- Beware of the growing resistance of these pathogens to the various antibiotics. There is a correlation between antibiotic consumption and antibiotic resistance; stressing the need for programs with restricted antibiotic policies.
- Beware of indwelling devices, invasive procedures and diagnostic interventions, which all have proven to be independent risk factors for ICU-acquired infections. A policy to withdraw devices as soon as possible is recommended.

SAMENVATTING EN CONCLUSIES

Hoofdstuk 1

De ziekenhuis verworven infecties op de intensive care (IC) vormen een overweldigend groot en complex probleem, met een negatieve invloed op zowel de geassocieerde morbiditeit en mortaliteit, als dientengevolge op het ziekenhuis budget en de economische kosten van de zorgsector als geheel. Invasieve diagnostiek, agressieve behandelings methoden en een veelvuldig gebruik van invasieve catheters, in combinatie met een tijdelijk gecompromiteerde immuniteit –intrinsieke en extrinsieke risico factoren- maken dat de IC patient populatie bij uitstek gevoelig is voor ziekenhuis verworven infecties.

De groeiende incidentie van IC verworven infecties vormt een potentiele bedreiging voor de nog te boeken vooruitgang in de behandeling van de steeds complexere ziektebeelden, waar de huidige intensive care geneeskunde mee te maken heeft. Hoofdstuk 1 beschrijft dit probleem van de groeiende incidentie en impact van IC verworven infecties, gevolgd door een korte uiteenzetting van de doelstellingen van dit proefschrift.

Hoofdstuk 2

Er is een schrijnend verschil tussen Europa en de USA, in de kennis over de reikwijdte van het infectie probleem. In de Verenigde Staten worden kwantitatieve en kwalitatieve gegevens over de ziekenhuis verworven infecties systematisch gedocumenteerd, door middel van diverse nationaal geformaliseerde programma's voor continue monitoring. In Europa bestaan dergelijke programma's niet, en tot 1992 is er geen grote internationale studie uitgevoerd waarmee het probleem van de ziekenhuis verworven infecties voor heel Europa in kaart kon worden gebracht. Dit was de reden dat in 1992 de European Prevalence of Infection in Intensive Care (EPIIC) Study werd opgezet, de grootste prevalentie studie ooit verricht in heel Europa; teneinde deze leemte aan kennis over de ziekenhuis verworven IC infecties te corrigeren.

Hoofdstuk 2 beschrijft de resultaten van deze studie, uitgevoerd op 1417 Intensive Care's in 17 West-Europese landen, met 10.038 geïncludeerde IC-patienten. Van de totale IC populatie had op de studiedag 45% een of meerdere infecties, waarvan bijna de helft IC- verworven was (21% van het totaal). De meest opvallende resultaten waren de hoge prevalentie pneumonieen en lagere luchtweg infecties (tezamen een prevalentie van 63% van het totaal aantal infectie typen), *S. aureus* (met een prevalentie van 30.1% de meest frequent geisoleerde pathogeen), *P. aeruginosa* (28.7%), en de Enterobacteriaceae (als groep) als de belangrijkste pathogenen, en de hoge prevalentie pathogenen met een resistentie tegen een of meerdere antimicrobiele middelen. Meest opmerkelijk was de resistentie voor methicilline in 60% van de *S. aureus* stammen, met een opzienbarend grote variatie in prevalentie tussen de diverse Europese landen. In zijn geheel was er een opvallende groei in de prevalentie van gram-positieve pathogenen en fungi. De belangrijkste risico factoren voor een IC-verworven infectie

waren, met name een langduriger IC verblijf (relatief risico (RR) voor infectie was 15.01 na een IC verblijf van 1 week, RR: 30.75 na 2 weken, en 76.06 na 3 weken), verder diverse invasieve interventies. De mortaliteit was hoog (16.8%), met een significante correlatie tussen de prevalentie van IC-verworven infecties en de mortaliteit. Met name pneumonie, bacteriaemie en sepsis waren onafhankelijke risico factoren, geassocieerd met een verhoogde kans op mortaliteit.

Hoofdstuk 3

Hoofdstuk 3 beschrijft het probleem van de ziekenhuis verworven infecties op de intensive care in Nederland. Gegevens hiertoe, van 472 patienten, gelegen op 78 Nederlandse intensive care's, werden verkregen uit het totaal bestand van de EPIIC studie.

Van de patienten op de Nederlandse IC's had 37% een infectie, waarvan 16% IC-verworven was. De belangrijkste infectie risico factoren waren: de duur van het IC verblijf (RR: 4.23, 99.37 en 146.79 na een IC verblijf van respectievelijk 3-4 dagen, 1-2 weken en langer dan 3 weken), gecorreleerd aan de ernst van het ziektebeeld (orgaan falen) en een groter aantal medische interventies (zoals beademing en een blaascatheter). Voor een electief geopereerde patient was het risico op een IC-verworven infectie kleiner dan voor een patient zonder voorafgaande operatie; na een spoedoperatie was dit infectie risico juist groter. Gedurende de follow-up overleed 14% van de patienten. Patienten met een IC-verworven infectie hadden een hogere mortaliteit; de best prognostische waarde teneinde mortaliteit te voorspellen, had de APACHE II-Score (RR voor mortaliteit: 13 voor een APACHE score tussen 16-26, en RR>100 voor een score>31).

Hoofdstuk 4

De risico analyse naar de IC verworven infecties op de Nederlandse intensive care's wordt in hoofdstuk 4 vervolgd door een analyse betreffende het type IC-verworven infecties. Pneumonie en lagere luchtweg infecties hadden tezamen de grootste prevalentie (63%), gevolgd door urineweg infecties (16%), sepsis (16%) en wondinfecties (11%). De meest frequent gekweekte pathogenen waren de gram-negatieve bacterien (92% in totaal), met name de *Enterobacteriaceae* (34% als groep) en *Pseudomonas aeruginosa* (30%), gevolgd door *Staphylococcus* (37%), Enterococcus (20%) en verrassend: fungi (10%).

De meest voorgeschreven antibiotica waren: de cephalosporinen (30%), breed-spectrum penicillinen (17%), metronidazol (17%) en aminoglycosiden (13%). Geen infectie met Methicillin-Resistant *Staphylococcus aureus* (MRSA) werd op deze studiedag in Nederland waargenomen; dit in schril contrast tot vele andere Europese landen. Gentamicine-resistente coagulase-negatieve *Staphylococcus* en ciprofloxacine-resistente P. *aeruginosa* werden echter wel waargenomen. In de meeste Nederlandse ziekenhuizen maakten microbiologen, ziekenhuis hygienisten (84%) en infectie controle verpleegkundigen (51%) deel uit van het intensive care team.

Hoofdstuk 5

Hoofdstuk 5 begint met een review van de huidige literatuur over chirurgische IC patienten en chirurgische infecties (surgical site infections SSI). De thans meest gebruikte risico score voor chirurgische infecties wordt beschreven: de NNIS surgical patient risk index score.

Vervolgens worden de resultaten van uitsluitend de chirurgische IC patienten uit de EPIIC studie behandeld. Meer dan 50% van de in totaal 10.038 IC patienten hadden chirurgie ondergaan in de maand voorafgaande aan de EPIIC studie. Abdominale chirurgie werd het meest frequent uitgevoerd, gevolgd door thorax- en hoofd/hals chirurgie. Van de 5066 chirugische IC patienten ontwikkelde 21.3% een IC-verworven infectie. De belangrijkste infectie risico factoren voor deze chirurgie patienten waren spoed- en multipele operaties (RR respectievelijk: 2.31 en 3.12); dientengevolge was trauma een significante risico factor (RR: 3.31). Het infectie risico was het hoogste voor de jongere IC patienten (leeftijd 20-40 jaar), en nam af met het stijgen van de leeftijd. Een langer IC verblijf verhoogde het relatieve risico voor infectie dramatisch, mede ten gevolge van een stijgend aantal invasieve procedures, een langere beademings periode (al dan niet in combinatie met een tracheostoma), meer diagnostische interventies en meerdere operaties. Meer dan de helft van de IC-verworven infecties bij de chirurgische patienten was gelocaliseerd in de tractus respiratorius (prevalentie 51.7%), terwijl het percentage wond infecties 8.7% betrof. Gram-negatieve bacterien hadden de hoogste prevalentie (47.1%), gevolgd door de gram-positieven (40.9%) en fungi (10.8%). De mortaliteit voor chirurgische patienten met een IC-verworven infectie was significant hoger (26 versus 12%), de pathogenen welke geassocieerd waren met de hoogste mortaliteit waren de fungi (31.1%).

Hoofdstuk 6

Teneinde het risico voor IC patienten te evalueren op een infectie met methicilline-resistente *Staphylococcus aureus* (MRSA), in plaats van een infectie met methicilline-sensitieve *S. aureus* (MSSA), werden data betreffende MRSA en MSSA prevalentie, risico factoren en mortaliteit verkregen uit het totale EPIIC bestand. In Europa als geheel was 60% van de *S. aureus* stammen resistent voor methicilline, met een grote variatie tussen de diverse Europese landen; de hoogste prevalentie MRSA werd gezien in Italie (81%) en Frankrijk (78%), terwijl in vele noorderlijke landen geen MRSA werd gezien.

De meest gerapporteerde infecties voor beide bacterien waren pneumonie (prevalentie van 52% voor MRSA en 61% voor MSSA) en lagere luchtweg infecties (respectievelijk 22% en 17%). De belangrijkste risico factoren voor MRSA waren een langer IC-verblijf (RR: 4.07 bij een IC duur langer dan 3 weken), en een hogere APACHE-II score. Een MRSA infectie verlaagde de kans op overleving, met name indien gelocaliseerd in de lagere luchtwegen: het risico op mortaliteit was drie keer hoger voor patienten met een MRSA infectie dan voor diegenen met een MSSA infectie.

Hoofdstuk 7

Fungi worden wel 'the emerging pathogens' genoemd, daar ze in de laatste decennia zijn veranderd van koloniserende, klinisch onbelangrijke a-pathogenen, in opkomende virulente pathogenen. Ook de EPIIC resultaten lieten deze groei van fungi zien, met een verrassend hoge infectie prevalentie van 17% fungi in de totale EPIIC groep, 10% in de Nederlandse subgroep en 11% in de chirurgische subgroep.

Hoofdstuk 7 geeft een overzicht van de huidige literatuur betreffende schimmel infecties en de epidemiologie. De belangrijkste problemen van candidiasis worden toegelicht: ten eerste, is er geen symptoom complex specifiek voor de diagnose invasieve candidiasis. Ten tweede, ontbreekt het aan bruikbare,snelle diagnostische methoden; er is geen gouden standaard test beschikbaar. Ten derde, is er tot op heden geen 'wonder' antimycoticum beschikbaar, geschikt voor alle typen schimmel infecties. De morbiditeit en mortaliteit geassocieerd met invasieve *Candida* infecties is hoog, met gerapporteerde mortaliteits cijfers van 40-80%. Het positieve effect van vroege, systemische prophylaxe of antimycotische therapie op empirische gronden op de uitkomst van IC patienten met candidiasis, wordt beschreven.

Hoofdstuk 8 richt zich op de identificatie van hoog risico patienten, teneinde subgroepen voor prophylaxe te definieren. Hoofdstuk 9 richt zich op een nieuwe, snellere identificatie methode van *Candida* spp.

Hoofdstuk 8

Hoofdstuk 8 beschrijft een retrospectieve, cohort studie naar het risico op isolatie van *Candida* spp. in peritoneaal vloeistof van chirurgische IC patienten met een peritonitis. Tevens werd gezocht naar onafhankelijke risico factoren. Van 2000-2003, honderdzeventien patienten met een peritonitis (bacterieel: n=69, *Candida* of mix *Candida*/bacterieel: n=48) werden geincludeerd, op de intensive care van een tertiair, universiteits ziekenhuis. Statistisch significante risico factoren voor *Candida* isolatie waren: pancreatitis ((p=0.0073), een APACHE II score >30 (p=0.0019), antibiotica gebruik voor het begin van de peritonitis (p=0.040) en een perforatie in de onderste tractus digestivus (in beschermende zin, p=0.0342). In tegenstelling tot de mortaliteit (p=0.842), was de morbiditeit (gedefinieerd als de duur van het IC verblijf) in de *Candida* groep significant hoger dan in de bacteriele groep (27 versus 8 dagen, p=0.001). In tegenstelling tot andere IC-verworven infecties, treedt *Candida* isolatie voornamelijk in het begin van het IC verblijf op.

Naar aanleiding van deze resultaten concludeerden wij dat: ernstig zieke peritonitis patienten met een hoge APACHE score at risk zijn voor isolatie van *Candida* species in peritoneaal vloeistof, met speciale aandacht voor pancreatitis patienten. In deze patienten zouden antimycotica op empirische gronden in een vroeg stadium geadviseerd worden.

Hoofdstuk 9

In hoofdstuk 9, een prospectieve studie wordt beschreven, welke Raman spectroscopie evalueert voor de identificatie van klinisch relevante *Candida* species in peritonitis patienten. Een Raman database werd ontwikkeld met behulp van gemeten spectra van 93 referentie stammen van tien verschillende *Candida* spp. Vervolgens werden klinische kweken verzameld via de afdeling heelkunde en de intensive care unit, van een tertiair universiteits ziekenhuis. In totaal werden 88 peritonitis kweken geincludeerd, van 45 patienten met een primaire, secundaire of tertiaire peritontis, waarvan er 31 positief bleken voor *Candida*. Kweken werden ingezet op een selectief Sabouraud medium, dat gentamicine bevat teneinde bacteriele groei te onderdrukken. Conventionele identificatie startte met een chromogeen medium voor de zogeheten presumptive identificatie, gevolgd door het gebruik van het Vitek 2 systeem voor de definitieve identificatie (een uiteindelijke vereiste turn-around time van 48-96 uur). Raman metingen werden verricht op overnacht kweken, eveneens op Sabouraud-gentamicine medium. De uitvoerbaarheid, de sensitiviteit en turn-around time van deze Raman techniek werd geanalyseerd, vergeleken met de conventionele identificatie methode als referentie. Met behulp van multivariaat statistische analyse bleek Raman spectroscopie een voorspellende waarde van 90% te hebben, waarmee Raman spectroscopie een accuraat en snel (12-24 uur) alternatief vormt voor de identificatie van *Candida* species in peritonitis patienten. De verkorte turn-around time zou van groot klinisch belang kunnen zijn voor de behandeling van kritisch zieke IC patienten met een invasieve candidiasis.

Chapter 10

Hoofdstuk 10 probeert de vraag te beantwoorden, of er een vervolg bestaat op de EPIIC studie, met in Europees samenwerkings verband het documenteren van infectie gegevens, en het formeren van infectie controle programma's.

Nieuwe uitdagingen in de infectie controle in het heden dan wel de (nabije) toekomst worden bediscussieerd, zoals: een Europees infectie controle netwerk, nieuwe typen catheters of interventies, nieuwe typen chirurgie (minimaal invasieve chirurgie, fast-track chirurgie, en poliklinische dagbehandeling), nieuwe typen medicijnen, en een verdere stimulering van de brede bewustwording van het infectie probleem.

Concluderend, de belangrijkste risico factoren voor ziekenhuis verworven infecties op de intensive care unit zijn:

- Wees gewaarschuwd voor een langere verblijfsduur op de intensive care, hetgeen het relatieve risico voor infecties dramatisch verhoogt. Evenzo stijgt het risico op infecties met resistente pathogenen, zoals MRSA, met een langer IC verblijf.
- Wees gewaarschuwd voor pneumonieen en lagere luchtweg infecties. Voorzorgsmaatregelen, zowel pre-, per- als post-operatief zijn noodzakelijk teneinde de kans op dit type infectie voor de chirurgie patient te verlagen.

- Wees gewaarschuwd voor gram-positieve bacterien. De gram-negatieve bacterien zijn niet langer de meest voorkomende en meest virulente pathogenen van ziekenhuis infecties. Gram-positieve bacterien, zoals de coagulase-negatieve *Staphylococcus* zijn meer dan slechts niet significante contaminanten.
- Wees gewaarschuwd voor fungi. Fungi zijn veranderd van koloniserende, klinisch onbelangrijke a-pathogenen, in opkomende virulente pathogenen met een hoge geassocieerde morbiditeit en mortaliteit.
- Wees gewaarschuwd voor spoed- en multipele operaties. Zo ook is trauma een significante risicofactor voor infecties in chirurgische IC patienten.
- Wees gewaarschuwd voor hoge APACHE scores bij opname op de intensive care.
- Wees gewaarschuwd voor het groeiende resistentie probleem van de IC pathogenen voor de diverse antibiotica. Er bestaat een correlatie tussen antibiotica gebruik en resistentie vorming tegen ditzelfde antibioticum, hetgeen een strikt antibioticum protocol alleen nog maar noodzakelijker maakt.
- Wees gewaarschuwd voor catheters, invasieve procedures en diagnostische interventies, welke ieder afzonderlijk, onafhankelijke risico factoren vormen voor IC-verworven infecties. Een beleid waarin iedere catheter zo spoedig mogelijk wordt verwijderd wordt gepropageerd.

APPENDICES

PATIENT INFORMATION

1 Date of birth

2 Sex

3 Date of current admission to hospital (any)

4 Date of admission to your Unit

5 Has the patient undergone major surgery (ie requiring general anaesthesia) on one or more occasions since 29.3.92?

6 If you answered **Yes** to Question 5, please indicate the date of surgery, the site of surgery (see Codes below) and the type of procedure-elective or emergency.

CODES: SITE OF SURGERY

01 abdominal
02 cardiothoracic
03 major head and/or neck surgery
04 vascular
05 gynaecological
06 genito-urinary
07 neurological
08 orthopaedic
09 transplant
10 other

PATIENT STATUS ON ADMISSION TO THE ICU

7 Was the patient admitted for postsurgical control/surveillance?
If **Yes**, please go to Question 9.
If **No**, please complete Question 8.

8 If the patient was admitted for any reason other than postsurgical surveillance, please indicate up to three organ systems (in most-, next most- and third most important), which were the main reason for admission to the ICU, according to the items below:

- Central nervous system
- Cardiovascular
- Respiratory
- Gastrointestinal
- Hepatic
- Renal
- Genito-urinary
- Musculoskeletal
- Haematological
- Metabolic / endocrine
- Skin / burns
- Other

9 Which of the following conditions were present on admission?
(Please refer to Definitions below.)

- Cardiovasculair failure
- Respiratory
- Renal failure
- Haematological failure
- Neurological failure
- Abnormality in liver function
- Multiple trauma
  with head injury
  without head injury
- Cancer
- Diabetes
- Chronic respiratory insufficiency
- Impaired respiratory reflex
- AIDS/HIV-positive

DEFINITIONS: ORGAN FAILURE

- **Cardiovascular failure**

  Presence of one or more of the following:

  a. heart rate < 55/min
  b. mean arterial blood pressure < 50 mmHg
  c. occurrence of venticular tachycardia and/or ventricular fibrillation
  d. serum pH < 7.25 with a $PaCO_2$ of <50 mmHg

- **Respiratory failure**

  Presence of one or more of the following:

  a. respiratory rate<6/min or >49/min
  b. $PaCO_2$>50 mmHg
  c. (A-a)DO_2>350 mmHg

     (A-a)DO_2 = 713 FiO_2 -$PaCO_2$ -PaO_2
  d. dependent on ventilator on **fourth** day of organ system failure

- **Renal failure**

  Presence of one or more of the following:

  a. urine output < 480 ml/24h or < 160 ml/8h
  b. serum BUN >100 mg/100 ml
  c. serum creatinine > 3.5 mg/100 ml (>375µmol/l)

- **Haematological failure**

  a. WBC<1001/mm^3
  b. platelets < 20001/mm^3
  c. haematocrit < 21%

- **Neurological failure**

  When Glasgow Coma Score is <9 (For details of score, see question 11)

- **Abnormality in liver function**

  Defined by:

  a. a raised bilirubin >200µmol/l (>12mg/100ml)

  and/or

  b. alkaline phosphatase/aspartate transaminase > 3 times normal

- **Chronic respiratory insufficiency**

  Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction, ie unable to climb stairs or to perform household duties; documented chronic hypoxia, hypercapnia, secondary polycythaemia, severe pulmonary hypertension (>40mmHg); ventilator dependency.

- **Impaired respiratory reflex**
  Airways reflexes may be considered impaired when spontaneous breathing, glottic closure and cough reflexes were impaired or absent on admission and/or there was no defence reaction to endotracheal intubation or pharyngeal suctioning.

CLINICAL STATUS OF THIS PATIENT ON ADMISSION TO THE ICU

10 Was neurological injury present on admission.

11 If you answered **Yes** to Question 10, please record the best values for the Glasgow Coma Score in each case, in the boxes provided in the following table.

Eyes Open Score		Best Verbal Response Score		Best Motor Response Score	
Spontaneously	4	Orientated and adequate	5	Obeys spoken command	6
On spoken command	3	Disorientated	4	To painful stimulus:	
To pain	2	Inadequate words	3	Localised pain	5
No response	1	Incomprehensive sounds	2	Flexion withdrawel	4
		No response	1	Flexion abnormal	3
		If patient is intubated, use clinical judgement for verbal response:		Extension	2
				No response	1
		Patient appears able to converse	5	Movement without any control	4
		Patient's ability to converse in question	3		
		Patient generally unresponsive	1		

12 The following data will be used to calculate an admission APACHE II Score for this patient. **This information is important. Please record all variables.** For each variable take the worst value over the **first 24 hours** on the ICU, eg the highest tempreature. (NB: If any item of information is not available please indicate by writing N/A.)

Acute Physiology Variable

- Temperature-rectal (°C)
- Mean arterial pressure (mmHg)

$$= \frac{2 \times \text{diastolic BP} + \text{systolic BP}}{3}$$

- Heart rate (beats/minute)
- Respiratory rate (breaths/minute)
  Spontaneous
  Ventilated or CPAP rate

- Oxygenation: (A-a)DO_2 or PaO_2
  i) If FiO_2 >49% record (A-a)DO_2
  kPa
  mmHg
- ii) If FiO_2 < 50% record PaO_2
  kPa
  mmHg
- Arterial pH
- Serum HCO^-_3 (venous mmol/l or mEq/l). (Not preferred, use if no arterial blood gases)
- Serum sodium (mmol/l or mEq/l)
- Serum potassium (mmol/l or mEq/l)
- Serum creatinine (mmol/l) and (mg/l)
- Haematocrit (%)
- White cell count (total/mm^3) (in 1000s)

Chronic Health Points

i) Does the patient have a history of severe organ system insufficiency prior to this hospital admission?
(Please refer to Definitions below)

ii) Was the patient immunocompromised? (Please refer to Definitions below).

If **Yes**, please indicate cause:
- immunosuppressive therapy
- chemotherapy
- radiotherapy
- long-term or recent high-dose steroids
- diseaese-related

iii) Please indicate if the patient is:
- non-operative or emergency post-operative
- elective post-operative

DEFINITIONS: ORGAN SYSTEM INSUFFICIENCY

Organ insufficiency or immunocompromised state must have been evident prior to this hospital admission and conform to the following criteria:

- **Liver**
  Biopsy-proven cirrhosis and documented portal hypertension, episodes of past upper gastrointestinal bleeding attributed to portal hypertension, or prior episodes of hepatic failure, encephalopathy, coma.
- **Cardiovascular**
  New York Heart Association Class IV
- **Respiratory**
  Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction, ie unable to climb stairs or perform household duties; documented chronic hypoxia, hypercapnia, secondary polycythaemia, severe pulmonary hypertension (>40mmHg); ventilator dependency.
- **Renal**
  Receiving chronic dialysis

Immunocompromised

The patient has received therapy that supresses resistance to infection, eg immunosuppression, chemotherapy, radiation, long-term or recent high-dose steroids; or has a disease that is sufficiently advanced to suppress resistance to infection, eg leukaemia, lymphoma, AIDS

PATIENT STATUS DURING THE WEEK 23.4.92 TO 29.4.92

13 Has the patient had any of the following therapeutic interventions in the last week?

- iv catheter
- CVP line
- Arterial catheter
- PA catheter (Swan Ganz)
- Urinary catheter
- Chest tube
- Wound drain
- Intracranial pressure monitoring
- Peritoneal dialysis
- Haemodialysis
- Atrial and/or ventricular pacing

- Nasotracheal intubation
- Orotracheal intubation
- Tracheostomy
- Assisted ventilation
- Central iv hyperalimentation
- Peripheral iv hyperalimentation

14 In the last week, has the patient received any of the following:
- long-term or high-dose steroids?
- cancer chemotherapy?
- other immunosuppressive drugs?
- radiotherapy?
- sedation?

15 In the last week, has the patient received any of the following anti-ulcer agents?

- antacids
- H_2-antagonists
- sucralfate
- omeprazole
- other

16 In the last week, has the patient received:
- selective digestive decontamination?
- prophylactic antibiotics given for no longer than 48 hours to cover the risk of infection related to a clinical procedure?

17 Is the patient receiving selective digestive decontamination **today** 29.4.92?

18 Is the patient receiving antibiotics for prophylaxis **today** 29.4.92?

19 If **Yes**, please specify the indication for prophylaxis:
- presurgical
- immediate post-operative
- cover for invasive procedure, eg CVP catheterisation
- other

PATIENT STATUS TODAY

20 For each variable please record the **worst value** from **midnight** to **midnight**.

- Temperature – rectal (°C)
- Mean arterial pressure (mmHg)

  $$= \frac{2 \times \text{diastolic BP} + \text{systolic BP}}{3}$$
- Heart rate (beats/minute)
- Arterial pH
- Urine output (ml/24h)

21 Is the patient currently receiving antibiotics for treatment or prophylaxis of infection today?

22 If **Yes**, which antibiotics are the patient taking? Please also indicate the date on which the antibiotic was started and whether it was prescribed for treatment or prophylaxis.

- **Cephalosporin**
  cefazolin
  cefuroxime
  ceftriaxone
  ceftazidime
  cefotaxime
  other cephalosporin
- **Aminoglycoside**
  gentamicin
  tobramycin
  amikacin
  netilmicin
  other aminoglycoside
- **Quinolone**
  ciprofloxacin
  ofloxacin
  perfloxacin
  other quinolone
- **Penicillin**
  benzylpenicillin
  flucloxacillin
  cloxacillin
  other penicillin

- **Macrolide**
  erythromycin
  other macrolide
- **Broad-spectrum penicillin**
  ampicillin or amoxycillin
  amoxycillin/clavulanate
  mezlocillin
  piperacillin
  ticarcillin/clavulanate
  carbenicillin
  other broad-spectrum penicillin
- **Imipenem**
- **Glycopeptide**
  vancomycin
  teicoplanin
- **Metronidazole**
- **Aztreonam**
- **Other**

23 Please indicate if any of the following are being prescribed for treatment or prophylaxis today:

- **Antifungal**
  amphotericin
  flucytosine
  other
- **Antiviral**
  acyclovir
  ganciclovir
  other

24 During this admission, has the patient received:

- monoclonal antibody against endotoxin?
- any other drug under clinical trial?

25 Is this patient infected? (Please indicate 'Yes' if there is active infection, suspected infection or the patient is receiving antibiotics for the *TREATMENT OF INFECTION*.)

26 Please indicate infection diagnosis (enter **up to four** infections in order of severity). (*Please refer to Codes and Definitions below*)

CODES: INFECTION DIAGNOSIS

The following Codes are based on CDC Definitions for nosocomial infections. (see below).

A1 Incisional surgical wound infection
A2 Deep surgical wound infection

B1 Laboratory-confirmed primary bloodstream infection
B2 Clinical sepsis

C1 Pneumonia
D1 Symptomatic urinary tract infection
D2 Asymptomatic bacteriuria
D3 Other infection of the urinary tract

E1 Osteomyelitis
E2 Joint or bursa infection
E3 Vertebral disc space infection

F1 Arterial or venous infection
F2 Endocarditis
F3 Myocarditis or pericarditis
F4 Mediastinitis

G1 Intracranial infection
G2 Meningitis or ventriculitis
G3 Spinal abscess without meningitis

H1 Conjunctivitis
H2 Other eye infections
H3 Otitis externa
H4 Otitis media
H5 Otitis interna
H6 Mastoiditis
H7 Oral cavity infection
H8 Sinusitis
H9 Upper respiratory tract infection

I1 Gastroenteritis

I2 Hepatitis
I3 Gastrointestinal (GI) tract infection
I4 Intra-abdominal infection

J1 Bronchitis, tracheobronchitis, bronchiolitis, tracheitis without evidence of pneumonia
J2 Other infections of the lower respiratory tract

K1 Endometritis
K2 Episotomy site infection
K3 Vaginal cuff infection
K4 Other infections of the male or female reproductive tract

L1 Skin infection
L2 Soft-tissue infection
L3 Decubitus ulcer infection
L4 Burn infection
L5 Breast abscess or mastitis

M1 Systemic infection

CDC DEFINITIONS

Surgical Wound Infection

A1 Incisional surgical wound infection. Infection at incision site within 30 days of surgery, and involves skin, subcutaneous tissue or muscle above the fascial layer, and any of the following:

- purulent darinage from incision, or drain located above fascial layer
- organism isolated from fluid culture from wound closed primarily
- surgeon deliberately opens wound, unless wound site culture-negative
- surgeon's or physican's diagnosis

A2 Deep surgical wound infection. Infection at the site of the incision within 30 days of surgery (within 1 year if implant is left in situ), and infection appears related to surgery, and involves tissues or spaces at or beneath fascial layer, and any of the following:

- purulent darinage from drain beneath fascial layer
- wound spontaneously dehisces or is deliberately opened by surgeon when patient has fever (>38°C) and/or localized pain or tenderness unless culture-negative

- an abscess or other sign of infection seen on direct examination, during surgery, or on histopathological examination
- surgeon's diagnosis

Primary Bloodstream Infection

B1 Laboratory-confirmed primary bloodstream infection must meet one of the following criteria:

1. Recognised pathogen isolated from blood culture and pathogen is not related to infection at another site
2. One of the following: fever (>38°C), chills or hypotension and any of the following
   - common skin contaminant isolated from two blood cultures drawn on separate occasions and not related to infection at another site
   - common skin contaminant isolated from blood culture from patient with intravascular access device and physician institutes appropriate antimicrobial therapy
   - positive antigen blood test and pathogen is not related to infection at another site.

B2 Clinical sepsis must meet one of the following criteria:
fever (>38° C), hypotension (systolic pressure <91 mmHg) or oliguria (.20 ml/h) with no other recognised cause and all of the following:
- blood culture not performed or no organisms or antigen detected in blood
- no apparent infection at another site
- physician institites appropriate antimicrobial therapy for sepsis.

Pneumonia

C1 Pneumonia must meet one of the following criteria:

1. Rales or dullness to percussion on physical examination of the chest and any of the following:
   - new onset of purulent sputum or change in character of sputum
   - organism isolated from blood culture
   - pathogen isolated from transtracheal aspirate, bronchial brushing or biopsy specimen.
2. Chest radiographic examination shows new or progressive infiltrate, consolidation, cavitation or pleural effusion and any of the following:
   - new onset of purulent sputum or change in character of sputum
   - organism isolated from blood culture
   - isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing or biopsy
   - isolation of virus or detection of viral antigen in respiratory secretions

- diagnostic single antibody titre (IgM) or four-fold increase in paired serum samples (IgG) for pathogen
- histopathological evidence of pneumonia.

Urinary Tract Infection

D1 Symptomatic urinary tract infection must meet one of the following criteria:

1. One of the following: fever (>38° C), urgency, frequency, dysuria or suprapubic tenderness and a urine culture of 10^5 or more colonies/ml urine with no more than two species of organism.
2. Two of the following: fever (>38°C), urgency, frequency, dysuria or suprapubic tenderness and any of the following:
   - dipstick test positive for leucocyte esterase and/or nitrate
   - pyuria (10 or more white blood cells (WBC)/ml^3 or 3 or more WBC/high power field of unspun urine)
   - organisms seen on Gram stain of unspun urine
   - two urine cultures with repeated isolation of the same uropathogen with 10^2 or more colonies/ml urine in non-voided specimens
   - urine culture with 10^5 or less colonies/ml urine of single uropathogen in patient being treated with appropriate antimicrobal therapy
   - physician's diagnosis
   - physician institutes appropriate antimicrobial therapy.

D2 Asymptomatic bacteriuria must meet either of the following criteria:

1. An indwelling urinary catheter is present within 7 days before urine culture, and patient has no longer fever (<38°C) or urinary symptoms, and has urine culture of 10^5 or more organisms/ml with no more than two species of organisms.
2. No indwelling urinary catheter present within 7 days before the first of two urine cultures with 10^5 or more organisms/ml urine of the same organism and no more than two species and patient has no fever or urinary symptoms.

D3 Other infections of the urinary tract (kidney, ureter bladder, urethra, etc) must meet one of the following criteria:

1. Organisms isolated from culture of fluid (not urine) or tissue from affected site.
2. An abscess or other evidence of infection seen on direct examination, during surgery, or by histopathological examination.
3. Two of the following: fever (>38°C), localised pain, or tenderness at site and any of the following:
   - purulent drainage from affected site

- organism isolated from blood culture
- radiographic evidence of infection
- physician's diagnosis
- physician institutes appropriate antimicrobial therapy.

27 Is the infection
- active (ie clinical symptoms are present)?
- no longer clinically active but under treatment with antibiotics?
- suspected?

28 Is the infection
- localised?
- generalised (signs of sepsis)?

29 On what date was this infection diagnosed (day/month/year)?

30 In your judgement, is this infection (Please refer to Definitions below)
- ICU-acquired?
- hospital-acquired?
- community-acquired?

DEFINITIONS OF INFECTION

ICU-acquired
An infection active or under active treatment on 29.4.92 but not clinically manifest or incubating at the time of admission to the ICU

Hospital-acquired
An infection manifest or incubating on admission to the ICU and deemed to be related to the preceding hospital admission (same or other hospital)

Community-acquired
An infection manifest or incubating on admission to the hospital or ICU

31 Are bacteriological culture results available for this infection?

32 If **Yes**, please enter the organisms considered to be causal. Enter up to three. (See Codes below)

CODES; ORGANISMS

Gram-positive

ENT Enterococci
PNE Pneumococci
OST Other *Streptococcus* spp.
SAN *Staphylococcus aureus*
SCN Other *Staphylococcus* spp.
OGP Other Gram-positive

Gram-negative

ENS *Enterobacter* spp.
CIS *Citrobacter* spp.
ECO *Escherichia coli*
PRM *Proteus mirabilis*
PRI Other *Proteus* spp.
MOS *Morganella* spp.
PRS *Providencia* spp.
SES *Serratia* spp.
ACS *Acinetobacter* spp.
PSA *Pseudomonas aeruginosa*
PSS Other *Pseunomonas* spp.
HEI *Haemophilus influenzae*
LES *Legionella* spp.
BRC *Branhamella catarrhalis*
KLS *Klebsiella* spp.
OGN Other Gram-negative

Anaerobes

BAF *Bacteroides fragilis*
CLS *Clostridium* spp.
OTB Other anaerobes

Viruses

CMV Cytomegalovirus
HSV Herpesvirus
HIV Human immunodeficiency virus
HEP Viral hepatitis
OTV Other virus

FUN Fungi

PRO Protozoa

33 If *Staphylococcus aureus* was isolated, was it methicillin-resistant or oxaccillin-resistant?
If coagulase-negative staphylococci were isolated, were they resistant to any of the following?

- Methcillin/oxacillin
- Cefotaxime
- Gentamicin
- Vancomycin
- Teicoplanin

If *Pseudomonas aeruginosa* was isolated was it resistant to any of the following?

- Gentamicin
- Imepenem
- Ceftazidime
- Ciprofloxacin
- A ureidopenicillin, eg azlocillin/piperacillin

34 If no organism has been isolated, what pathogen is considered responsible for the infection?

- Gram-positive bacteria
- Gram-negative bacteria
- Mixed bacterial infection
- An anaerobe
- Fungus
- Virus
- Protozoa
- Impossible to say

35 If no pathogens have been identified, are culture results awaited?

36 Have any specimens for culture been taken today **29.4.92**?
If the answer to either question 35 or 36 is YES go to *Bacteriological results* below.

PATIENT OUTCOME

Section 1

1 Date of birth (day/month/year)

2 Sex

Section 2

3 Was the patient discharged

- dead? Date of death (day/month/year)
- alive? Date of discharge (day/month/year)

For those patients discharged from the unit

4 Please indicate, in your judgement, the prognosis:

- likely to survive 1 week
- likely to survive 1 month
- likely to survive 1-6 months
- likely to survive more than 6 months

Bacteriological results

Bacteriological results from specimens collected on 29.04.92 or before 29.04.92 but not available on The EPIIC Study day

Please complete this section by 06.05.92

Please enter the bacteriological results for specimens collected for the infections recorded in Question 26 to 36. Codes for the specimens are supplied below.
Include date of collection and pathogen (enter up to 3 pathogens see codes question 32).

Codes

X 0 Blood
X 1 iv catheter
X 2 Sputum aspirate
X 3 Tracheal aspirate
X 4 BAL or protected distal specimen
X 5 Urine – voided sample
X 6 Urine – catheter sample
X 7 Skin or wound swab
X 8 Drain fluid (not nasogastric tube)
X 9 Stool culture

"Sentiment" (wijs *Margherita*, Marco Borsato)

In de verte spreekt een stem
Die ik herken van vroeger tijden
Nooit veel woorden, laat staan zinnen
Over al jouw rijl en zeilen
En dan voel ik weer die afstand
Van klein meisje tot opleider
Die mij altijd bij zal blijven
Ook al groeit het meisje verder.

In een waas hoor ik die stem weer
Als je eindelijk kreeg te horen
'het gaat goed zo, ga zo verder,
je gedrag is naar behoren'
En al luisterend naar die woorden
Ging het weerwoord op in wolken
Murw geslagen, niets te vragen
Een verpletterende man.

Kille woorden, oppervlakkig
Maar inmiddels weet ik beter
Een strak masker als fasçade
Wat de afstand safe verzekerd
Maar nu vele jaren verder
Komt de ware aard naar boven
Weinig woorden, laat staan zinnen
Maar een hart dat doet geloven;

Het klein mens hoog op die sokkel
Is meer mens dan Fries gebleken
Met een hart te groot voor woorden
Werd ook jij als mens bekeken
Nog bezorgder dan een vader
Nam hij jou onder zijn hoede
Sust jou kinders in zijn armen
Wie had dat kunnen vermoeden?

Het is net of iemand anders
Achter weinig woorden schuilgaat
Waarmee het beeld uit jonger jaren
Langzaam in luchtledig opgaat
Dat is onze Kieje Bruining
Onze man, voor altijd-eeuwig
Niemand kan daar nog aan tippen
Want hij is gewoon van goud.

DANKWOORD

Prof.dr. H.A. Bruining, beste Kieje, ik ben jou en Evelien ongelooflijk veel dank verschuldigd. Dank voor mijn opleiding uberhaupt, maar ook voor dit boekje, voor de vele gastvrije, culinaire onthalen in Nederland dan wel Frankrijk, en vooral voor jou oneindige engelen geduld met mij (weer een dikke buik, dus boekje weer een jaartje verder); een eigenschap die weinig mensen jou zullen toedichten. Ik weet beter. Eens heb ik mijn dank en waardering verwoord in de tekst van een lied, hetgeen ik in ons 'Brownies Girls' cabaret -ter ere van je emeritaat- heb gezongen. De tekst heb ik geschreven in de auto, staand op de parkeerplaats van het Leyenburg ziekenhuis, alwaar ik te vroeg was gearriveerd voor een sollicitatie- gesprek. Zoals altijd: onder stress presteert men het beste. Beter kan ik het niet zeggen, vandaar een herhaling van deze tekst "Sentiment".

De andere leden van mijn promotiecommissie: Prof.dr. H.W. Tilanus, Prof.drs. J.H.P. Wilson, Prof.dr. H.A. Verbrugh, Prof.dr. H.J. Bonjer, Dr. H.Ph. Endtz, en Dr.Ir. G.J. Puppels dank ik allen voor het beoordelen van het manuscript, voor de interesse in de infectieuze problematiek en voor de bereidheid zitting te willen nemen achter de tafel in mijn Commissie.

Prof.dr. H.W. Tilanus, beste Huug, het was een waar genoegen om jou als CHIVO-opleider te hebben. Ik ben er trots op dat ik uit jouw 'symphonie der handen' de buismaag onderwezen heb gekregen. Jouw nimmer stuitende energie, optimisme en humor maken het werk tot een feest. Ook 's nachts om 4 uur kom je nog met een grap op de OK binnen, kijkt naar de toch wel essentieel doorgenomen structuur, mompelt hooguit 'niet zo mooi', zet alles met grote steken weer aan elkaar, en verdwijnt weer met een zwaai. Waren we allemaal maar zo.

Prof.dr. H.J. Bonjer, beste Jaap, dank voor je eeuwige enthousiasme waarmee je iedereen voor je weet te winnen, en je nimmer aflatende optimisme; voor alles bestaat een oplossing, zo niet, dan toch. Canada is een onbegrensd gedreven mens, chirurg, laparoscopist maar vooral ook group-builder rijker. Zij wel.

Dr. H.Ph. Endtz, beste Hubert, dank voor je microbiologische sturing aan van die snijdende microbiele leken. Als de chaos daar is weet jij zonder probleem orde in de wereld der microben te scheppen door vlijmscherpe correcties in protocollen, dan wel geschriften te plaatsen.

Dr.Ir. G.J. Puppels, beste Gerwin, dank voor je begeleiding aan zo'n a-technische, witte jassen, aanvankelijk Raman-barbaar. Je hebt een ongekend nuchtere en snelle kijk op alles, waardoor ieder probleem inclusief het antwoord binnen 3 seconden in slechts 3 woorden wordt samengevat. Heb je soms Bruining als opleider gehad?

Dr. N.D. Bouvy, beste Nicole, veel hebben we gemeen: onze goede, oude RVSV tijd, de Ikaziaanse bakermat, de liefde voor het chirurgenvak die gedeeld moet worden met de liefde voor de kleine guppies thuis, het gezamenlijke gepuf op de dikke buiken gym, en de voorliefde voor de wat genuanceerdere trocar-chirurgie. Samen zijn we uitgevlogen (wanted, but gone) uit Rotterdam: jij naar je miami-vice bunker in de Limburgsche heuvels, ik naar mijn hutje in de duinen. Dank voor deze mooie tijden, ik ben er trots op dat jij je tussen de groten der aarde in de wereld der laparoscopie begeeft, en ik ben er trots op dat je mijn paranimf wilt zijn.

Drs. G.P. Gerritsen, beste Pieter, mijn Tilburgse room-mate en steun en toeverlaat. Beiden hebben we onze roots in Rotterdam liggen, hetgeen toch een soort gelijkgestemde sociale radiofrequentie geeft. Je bent een ongekend breed (sorry; figuurlijk, of zeg je dan juist letterlijk?) chirurg van de oude stempel, met een honger naar moderne, chirurgische ontwikkelingen als van een jonge hond. Het is goed om de Tilburgse horizon steeds verder te verleggen, en onze praktijk nog mooier te maken. Dank dat je mij, ook als paranimf, terzijde wilt staan.

Beste Oene van Meer en Pleunie Rood, dank voor al jullie monnikenwerk. Dat het een database met 136.456 gegevens zou worden hebben we gelukkig van te voren niet geweten. Vele operatieverslagen, APACHE Score berekeningen en onuitspreekbare Candida namen zijn in weekenden en nachten de revue gepasseerd. Maar uiteindelijk mag het resultaat daar zijn.

Dr. W.C.J. Hop, beste Wim, je bent een magistraal goochelaar met cijfers, hetgeen in nettere bewoordingen ook 'statisticus' heet te wezen. Achteraf als je thuis op je gemak de stapels computer uitdraaien met de aanvankelijk volledig onbegrijpelijke tabellen, berekeningen en curves gaat bekijken, blijkt het wel mee te vallen met het gegoochel, en blijken er nog logische en causale verbanden te bestaan ook. Sorry, maar die causale gedachtengang gaat bij jou miraculeus veel sneller. Dank voor al dat gereken.

De Raman groep: Kees, Tom, Peter, Rolf, Senada, Annieke, Bas, Sweder en natuurlijk de grote baas Gerwin. Jullie zijn als een soort trein, nee een TGV, waarbij ik een stuk hard heb mogen meerijden, om vervolgens duizelend bij het volgende station uit te stappen. Dank voor dit en voor de enorme lol; die lachsalvo's van Rolf hoor ik nu nog over de gang. Kees verdient een extra, heeeeel groot bedankje; dat onbegrensde geduld waarmee jij telkenmale de filosofieën achter optiek, spectroscopie en moleculen probeerde uit te leggen aan deze witte jas ('dit is een appel en dit is een ei'). Tenslotte begreep ik het (op appel en ei niveau) nog ook. We zouden veel meer als witte jassen en techneuten moeten samen werken, daar zouden nog mooie en bruikbare diagnostische ontwikkelingen uit kunnen voortvloeien.

Dr. H.F. Veen, beste Herman, dank voor jou chirurgische hoeksteen. Wat was het ook al weer die allereerste steen? Ik geloof een schouder botbiopt. Ik, volledig ongeremd door welke chirurgische ervaring dan ook, eager op een operatie. Jij, de kersverse opleider die de jongste oogappel wel door de ingreep zou sturen, volledig stupefait door zoveel niet te staven voortvarendheid. We hebben in de jaren erna nog mooie dingen samen gedaan, ik heb veel van je geleerd. Je bent een geboren opleider; onder jou toeziend oog lijkt het of iedere ingreep zo simpel is als een lipoompje.

Chirurgen en assistenten heelkunde uit Rotterdam, dank voor de geweldige Rotterdam tijd die ik met jullie heb mogen beleven. "We" (sorry Tilburg) zijn sociaal en chirurgisch een heel bijzondere stad, beter in Nederland heb je niet. Ik zal altijd trots blijven dat ik een zogeheten chirurgische Rotterdammer ben. Proost op Rotterdam!

Mijn Tilburgse maten: Stefan Brenninkmeijer, Ron van Doorn, Marnix de Fijter, Pieter Gerritsen, Fred Jacobs, Steef Kranendonk, Eddy Leerkotte, Diederick Wouters en Stefan van Zutphen. Dank dat jullie mij het voordeel van de twijfel hebben durven geven. Het alles innemende chirurgen bestaan combineren met een thuisfront klinkt ongeloofwaardig, doch is dit niet. Tilburg is vooruitstrevender gebleken dan de rest van conservatief, angstig, chirurgisch Nederland. We hebben veel plannen met z'n allen voor de toekomst; chirurgisch Tilburg wordt steeds fraaier.

Dr. I.G. Schoots, beste Ivo, dank voor je spontaan en genereuze aanbod om de afronding van mijn boekje computertechnisch te ondersteunen. Als een door de AMC-wol geverfde figuren&tabellen producerende pdf-engel kwam je uit de Tilburgse hemel vallen.

Beste Angelique Gilles, als Ivo de Tilburgse-computer-engel is, ben jij de Tilburgse-engelse-spelling-controller-engel uit diezelfde hemel. Mijn hemel wat een hoeveelheid taal- en spelfouten weet jij nog te corrigeren. Dank daarvoor.

Beste Irene van Nuland, dank voor je fabuleuze kaftontwerp, en de sturing van mijn kinders daarbij. Het moet een Wolkers achtig tafereel zijn geweest: een tafel vol met rondkruipend, in de tuin gevangen ongedierte, hetgeen als 'infectieus' tekenmodel voor mijn kinders moest dienen. Het is een heus kunstwerk geworden.

Mijn ouders, pa en ma, zonder jullie was ik niet zo ver gekomen. Dat evenwicht tussen opvoeding, vrijheid en stimulans tot een opleiding moet ik zelf in de opvoeding van mijn kinders nog maar zien te vinden. Mama, dit boekje is voor jou. Voor al jouw liefde, geduld en vertrouwen wat je ons hebt meegegeven. Kon je er nog maar bij zijn, en kon je het nog maar bewust meemaken. Je zou trots zijn op wat ik geworden ben dankzij jou.

Lieve, lieve Meike, Wobbe en Dieuwe, jullie zijn m'n alles, het leven is prachtig met jullie. Een ding: lees dit boek nooit! Gooi het weg (op de kaft na dan), sorry dat het bestaat, het is vreselijk. Het heeft ons een heleboel zeer kostbare speeltijd gekost. Wat lezen we vanavond weer op het grote bed: Pluk, Sjakie of Assepoesje?

Last but not least, lieve Harrie. Als men mij vraagt wat het geheim achter mijn (voort)bestaan is, zeg ik steevast: Harrie. Ik wil vanuit deze positie dan ook toekomstige chirurgen sollicitatie commissies van een ongevraagd advies dienen, indien zij een vrouwelijke kandidate voor zich hebben. Behoudens dat de kandidate zelf het chirurgenvak in haar hart moet hebben, is minstens zo belangrijk wie zij als wederhelft in die andere ventrikel heeft geborgen. Is hij ook een chirurg?: niet aannemen. Twee niet flexibele mensen in een ouderpaar lopen m.i. vast. Is hij een brave burgerman?: niet aannemen. Hij moet op z'n minst zoveel van zijn liefde houden, dat hij tot absurde daden in staat is. Zoals alle vergaderingen en afspraken aan z'n laars lappen, op het moment dat er thuis een kleine ziek is en moeder moet werken. Zoals hele weekenden, wanneer moederlief in het ziekenhuis de productie cijfers nog wat bijschaaft, voor alle kindermondjes, billen en bedjes thuis zorgen. Zoals een hulpmoeder op schoolreisje willen zijn. IK heb zo'n vent. Daarom ben ik zo trots op jou, daarom ben ik zo trots op onze 3 miljoentjes, die een vader hebben die evenveel vader is als ik moeder ben, en daarom hou ik zoveel van jou.

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CURRICULUM VITAE

Maaike Ibelings werd op 16 december 1964 te 's Gravenhage geboren, doch is getogen onder de rook van Rotterdam. Aldaar doorliep zij de middelbare school op het Emmaus College, en studeerde vervolgens van 1984 tot 1991 geneeskunde aan de Erasmus Universiteit te Rotterdam. In 1988-1989 deed zij een veldonderzoek naar 'Prevalence of anaemia in children' in Tamil Nadu, South India.

Via haar studentlidmaatschap van de Medisch Ethische Commissie van het AZR-Dijkzigt, en via een onderzoek naar 'Congenitale duodenumobstructie en Morbus Down' bij prof.dr. J.C. Molenaar, verkreeg zij in 1991 haar eerste artsenbaan als AGNIO kinderchirurgie in het Sophia Kinderziekenhuis te Rotterdam. Een jaar later werd zij aangenomen voor de opleiding heelkunde in Rotterdam. Zij ving in 1993 de opleiding aan in het Ikazia ziekenhuis (opleider dr. H.F. Veen), om deze in 1996 te vervolgen in het toenmalige Academisch Ziekenhuis Rotterdam-Dijkzigt (opleiders prof.dr. H.A. Bruining en prof.dr. H.J. Bonjer). Zij completeerde de algemene heelkunde opleiding met een chirurg in vervolg opleiding in de gastro-intestinale chirurgie, in het inmiddels tot Erasmus Medisch Centrum omgedoopte AZR (opleiders prof. dr. H.W. Tilanus, dr. W.R. Schouten, dr. C.H.J. van Eijck). Gedurende deze AZR/EMC periode werkte zij aan onderhavig promotie onderzoek naar 'Infecties op de Intensive Care'.

Sedert 2003 is zij uit het Rotterdamsche vertrokken, om als lid van de maatschap chirurgie toe te treden in het TweeSteden ziekenhuis te Tilburg. Zij is daar – vanaf het verkrijgen van de opleiding heelkunde per 2004 – vice-opleider, om te zijner tijd het opleidersstokje van dr. S.E. Kranendonk over te nemen.

Zij is getrouwd met Harrie van de Pas, zij hebben drie kinderen: Meike, Wobbe en Dieuwe, en zij wonen in de Drunense duinen.