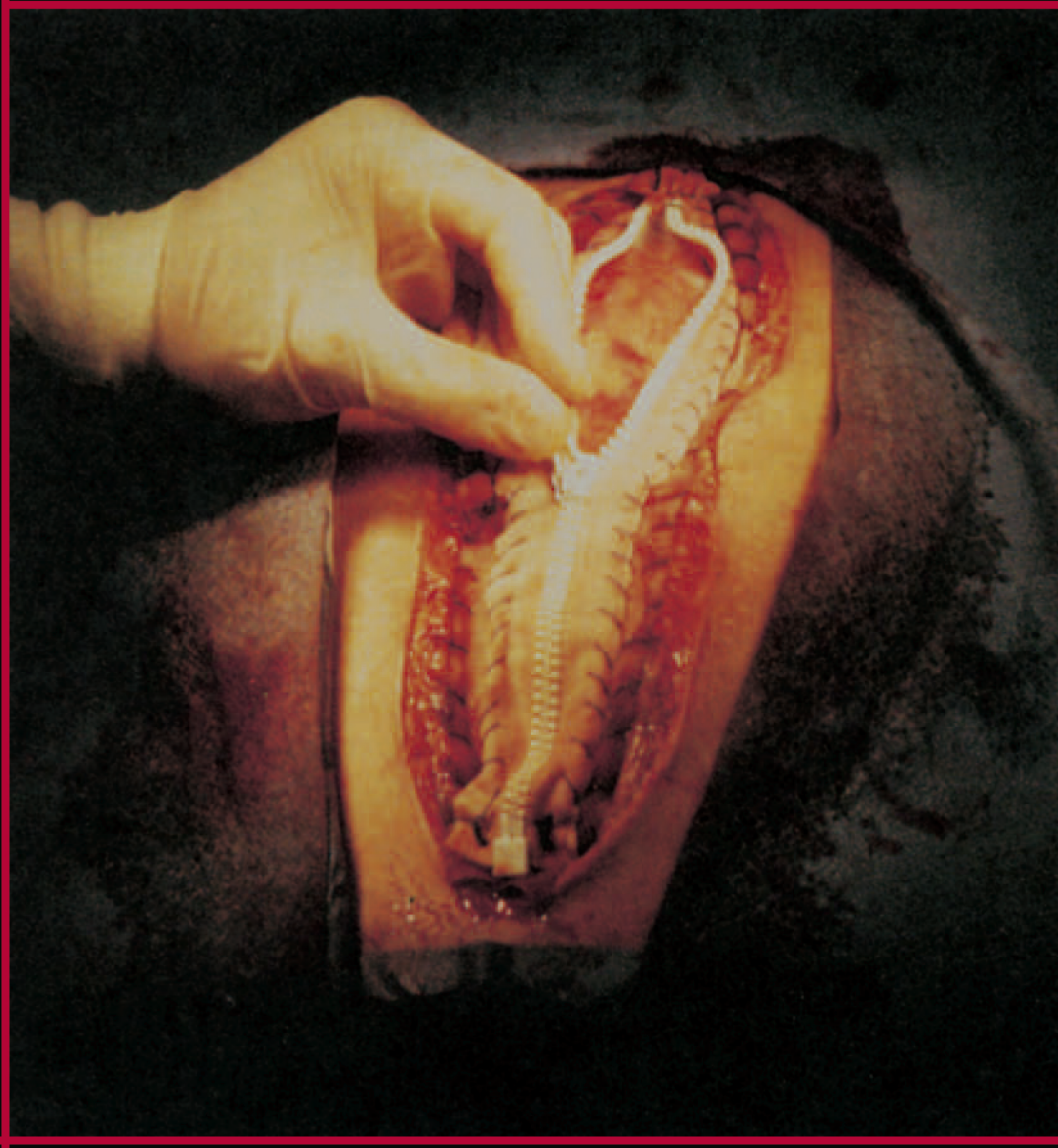
Antimicrobial pharmacokinetics in critically ill patients



Steven Buijk

ANTIMICROBIAL PHARMACOKINETICS IN CRITICALLY ILL PATIENTS

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Clinical studies to investigate pharmacokinetics of antimicrobial agents in critically ill patients

Klinische studies naar de farmacokinetiek van antimicrobiële middelen bij intensive care patiënten

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CHAPTER 1

INTRODUCTION AND OUTLINE OF THE DISSERTATION

Introduction

The intensive care unit (ICU) is an essential part of the surgical department, providing an environment for surveillance and treatment of the critically ill. Patients are admitted either with a life threatening condition due to a critical illness or they need observation and support after major surgery. In the Netherlands, approximately 60.000 patients are admitted to an adult ICU annually, which is 4% of total number of hospital admissions (Prismant 2002, Utrecht).

Infections are common in surgical ICU patients. An incidence of up to 40% of all admissions has been reported [1, 2]. Infections are a major indication for admission as in patients with generalised peritonitis or respiratory insufficiency due to a postoperative pneumonia. Furthermore, patients admitted for extensive trauma or after major surgery are susceptible to infectious complications. The host defences of the surgical patient are compromised by both extrinsic and intrinsic factors [3]. Normal barriers are breached by surgical incisions and by intravascular lines, wound drains, urinary catheters and endotracheal tubes. The integrity of the gastrointestinal epithelium is compromised by lack of enteral nutrition and periods of hypoperfusion, promoting bacterial translocation [4]. The protective indigenous microbial flora is changed by the use of broad-spectrum antibiotics. Furthermore, multiple alterations in the systemic immunity are seen [5]. Natural down-regulatory mechanisms for the inflammatory response exist, probably to limit autoimmune damage. Iatrogenic immune suppression is applied frequently following organ transplantation or with corticosteroids in pulmonary dysfunction. At last, there are pre-existent diseases associated with impaired host defences, including cirrhosis, renal failure, malignancy and diabetes [6].

The clinical presentation of an overwhelming infection is impressive. When local defence mechanisms are not able to contain the infectious source, a generalised inflammatory response develops triggered by bacteria or their toxins. This systemic response to infection is called sepsis and can be auto-destructive leading to septic shock and organ failure [7]. Infections and the accompanying organ failure are the main cause of mortality in surgical ICU today [1, 8]. For example, crude mortality associated with nosocomial bloodstream infection on a surgical ICU was 50% in a recent study [9], and the mortality directly attributed to this infection was 35%.

The treatment of sepsis and septic shock has evolved the past decades. Development of intensive care facilities, understanding of pathophysiological principles, improvement of surgical strategies and radiological interventions and introduction of potent antimicrobial agents, all contributed to an increased survival of the septic patient. A tremendous effort has been done to find immune-modulating agents to reduce the auto-destructive inflammatory response. All but one proved to be unsuccessful up to now [10]. Recently, activated protein C, a component of the anticoagulant system, was the first “magic bullet” to show reduced mortality in patients with severe sepsis [11]. Despite these advances in intensive care medicine the mortality of sepsis remains unacceptable high (approximately 25%-30%). Especially intra-abdominal sepsis, caused by a generalised peritonitis or necrotizing pancreatitis remains hard to concur, with mortality rates over 60% [12].

Since the beginning of the antimicrobial era in the early 1940s, antimicrobial therapy is the cornerstone in the treatment of severe infections. Their relevance in the treatment of the

critically ill is well established. Appropriate antimicrobial therapy decreases the frequency of shock and subsequently mortality with 50% in patients with severe infections [7]. Weinstein et al studied the epidemiology and outcome of bloodstream infection and found the lowest mortality in those patients who received appropriate antimicrobial therapy throughout the course of infection [13]. Nonetheless, treatment failure still occurs and there is the increasing prevalence of resistant pathogens [14]. So further research is necessary to optimise antimicrobial efficacy and to prevent the emergence of resistant mutants during therapy.

The outcome of antimicrobial treatment depends on different variables. Besides the susceptibility of the pathogens and the state of host defences, dosing schedules seem to play an important role in the efficacy and safety of the antimicrobial agent [15, 16]. Antimicrobials can be divided into different groups based on their pattern of bactericidal or bacteristatic activity [17]. For example, aminoglycosides, show a pattern of concentration dependent killing. The higher their concentration, the greater the rate and extent of bactericidal activity [18]. In contrast, beta-lactams, show a pattern of time dependent killing. Concentrations above 4 to 5 times the minimal inhibitory concentration (MIC) do not kill the organism any faster; bactericidal activity largely depends on the time of exposure [19, 20]. Attention for these pharmacodynamic properties of these different groups of antibiotics has resulted in higher efficacy and less antimicrobial resistance in vivo and vitro models [21]. Efficacy studies in patients regarding dosing schedules are scarce, because of the large sample sizes needed. But there are indications that there is clinical significance as well. Studies with once daily aminoglycoside regimens in patients suggest a small, non-significant trend towards better efficacy and significant less nephrotoxicity compared to multiple dosing [22].

Critically ill patients show aberrant and variable pharmacokinetics of drugs which are not easy to predict [23]. Disturbances in their circulation, extravasation of fluid (third spacing), renal and hepatic insufficiency, an altered metabolic condition and altered intestinal absorption are factors that influence the pharmacokinetic profile of the critically ill. To optimize antimicrobial therapy, both efficacy and safety, insight in the pharmacokinetics of these drugs in the critically ill is necessary.

In short, mortality due to severe infections and septic shock remains high on the surgical ICU. Furthermore, there is an increasing prevalence of resistant pathogens. Thus, antimicrobial therapy needs to be optimized. It is assumed that antimicrobial efficacy can be increased when modern insights in pharmacodynamics are complied. However, the critically ill patients show a deranged pharmacokinetic profile, which makes optimal dosing schedules difficult to design. Therefore, in this thesis we have studied the pharmacokinetics of several classes of antimicrobial agents in critically ill patients, administered in different dosing schedules or through different routes.

Outline of the thesis

This thesis consists of 4 sections. In section 1, **chapter 2** the deranged pharmacokinetic profile of the critically ill patient is described and it discusses the pharmacodynamic principles of different groups of antimicrobials.

In section 2, the scope of the infectious problem on the SICU of a referral centre is given. **Chapter 3** describes the epidemiology and clinical outcome of infections in surgical intensive care patients and the antimicrobial use and susceptibility patterns of the pathogens on the SICU. In **chapter 4** a dramatic case of streptococcal toxic shock syndrome is described to illustrate the overwhelming force of surgical sepsis.
In section 3 the pharmacokinetic studies are presented. Ceftazidime is a beta-lactam antibiotic frequently used for the treatment of gram-negative infections. As mentioned above, ceftazidime shows time-dependent killing. In **chapter 5** the pharmacokinetics of ceftazidime in serum and peritoneal fluid are compared during continuous and intermittent infusion in patients with severe intra-abdominal infections.
Enteral administration of drugs can simplify drug administration and reduce costs significantly. Fluconazole is an antifungal used for the treatment of fungal infections. It has an excellent enteral bioavailability in healthy volunteers. Whether enteral administration of fluconazole is safe in critically ill patients with a compromised enteral function was unknown. Therefore, we studied the pharmacokinetics of sequential intravenous and enteral fluconazole in critically ill surgical patients with invasive mycoses. The results are described in **chapter 6**.
Aminoglycosides show concentration dependent killing and are used frequently in the hemodynamic unstable patient. **Chapter 7** describes our experience with a once-daily dosing program of aminoglycosides in critically ill patients.
Ciprofloxacin is an antibiotic with a good enteral bioavailability in healthy persons as well. In **chapter 8** the bioavailability of enteral ciprofloxacin is described in patients with abdominal sepsis.
Liver transplantations are frequently complicated by infections. Peri-operative translocation of bacteria is believed to be an important factor in the pathophysiology of infectious complications after liver transplantation, especially during the anhepatic phase of liver transplantation when the hepatic clearance of the endotoxin by Kupffer cells is absent. Therefore, the broad- spectrum antibiotic cefotaxime, a beta-lactam, is used as prophylaxis. In **chapter 9** the peri-operative pharmacokinetics of cefotaxime in serum and bile during are studied during continuous and intermittent infusion in liver transplantation patients.

Section 4 contains the general discussion. In **chapter 10** the future directions in the treatment of tertiary peritonitis, a complex nosocomial infection representing the current limit of severe surgical infection, are described. In **chapter 11** the content of the above-mentioned chapters is summarized.

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CHAPTER 2

CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS OF ANTIMICROBIAL AGENTS IN CRITICALLY ILL PATIENTS

SE BUIJK, IC GYSSENS, HA BRUINING AND JW MOUTON

Submitted to Clinical Pharmacokinetics

Abstract
The concentration course of antimicrobial agents in time plays an important role in the efficacy and safety of the antimicrobial therapy. To optimise the pharmacodynamics, knowledge of the deranged pharmacokinetics of critically ill patients is necessary.
Despite the fact that enteral absorption in ICU patients is compromised by motility disturbance, mucosal atrophy and chemical interactions, the bioavailability of several antimicrobials is adequate. Caution is necessary in case of less susceptible pathogens in which higher dosage or combination therapy might be needed. The volume of distribution is increased and variable during critically illness. This is caused by third spacing and a decrease in serum protein for the highly protein bound antimicrobials. These factors can lead to suboptimal serum and tissue concentrations. During stress hepatic metabolism can be increased up to 50%. However, during critically illness, hepatic metabolism is more often impaired by pre-existent causes or acute causes including infection or shock induced failure. The pharmacokinetics of several antimicrobials are influenced by a variable liver function, but the extent of liver function is difficult to quantify in the clinical setting. Furthermore, in a multiple drug setting like an ICU, several drug-drug interactions involving antimicrobial agents are possible. Approximately one third of all critically ill patients develop renal failure. As most antimicrobials are eliminated from the body through the kidneys, this has a serious impact on the pharmacokinetics of these drugs.
To determine the optimal antimicrobial regimen the different parameters of antimicrobial activity are important. The in vitro activity tests (MIC, MBC) are predictors of the potency of the drug, but do not give information on the antimicrobial effect of the concentration-time profile in serum and at the site of infection. Antimicrobial agents either show concentration dependent activity, in which the rate and extent of bactericidal activity correlates with the magnitude of the concentration. In contrast, others show time dependent killing, in which activity largely depends on the time of exposure, not the magnitude. Knowledge of the pharmacodynamic efficacy parameters of antimicrobial agents (T>MIC, Cpeak/MIC, AUC/MIC) can help to determine the optimal dosing schedules. Individual therapeutic drug monitoring (TDM) combines, the serum concentrations of a certain drug with the pharmacokinetic profile of a patient in order to optimize dosage regimens according to modern pharmacodynamic insights. A positive impact of TDM has been documented on clinical outcome, reduction of hospital stay and toxicity. In critically ill patients with a deranged pharmacokinetic profile with wide inter- and intra patient variability, TDM can be of particular benefit in guiding the physician to the optimal dosing schedule. The different methods available for TDM in critically ill patients including a nomogram, the Sawchuk and Zaske method and Bayesian monitoring are reviewed.

1 Introduction

Antimicrobial agents are an essential part of the treatment of severe infection in the critically ill patient. For effective antimicrobial therapy, bactericidal concentrations of the drug are needed in blood and at the site of infection. The science that refers to the disposition of drugs in the body is called pharmacokinetics and includes absorption, distribution, metabolism and elimination of the drug. These factors, combined with the

dosage regimen, determine the time course of the drug concentration in serum and at the site of infection.
The systemic inflammatory response to infection, triggered by bacteria or their toxins, is called severe sepsis. It involves the release of inflammatory mediators, which can be auto-destructive leading to septic shock and organ failure [1]. During severe sepsis or septic shock, the pharmacokinetic profile of critically ill patients is influenced by factors such as a deranged circulation, organ dysfunction, fluid sequestration, an increased metabolic response and an altered gastro-intestinal absorption. Furthermore, often there are comorbid conditions adding further complexity to the physiological and metabolic picture of the patient. Therefore, critically ill patients show aberrant and variable pharmacokinetics of drugs.
Pharmacodynamics is defined as the relationship between the concentration profile and the pharmacological and toxicological effect of drugs. With respect to antimicrobial agents, the primary interest is the interaction between the concentration at the site of action and the antimicrobial effect. It has become evident from laboratory and clinical studies that the concentration course in time plays an important role in the efficacy and safety of the antimicrobial [2-4]. Thus, the interaction between pharmacokinetics and pharmacodynamics is important to determine the optimal dosing regimens of different classes of antimicrobial agents.
This review describes the pharmacokinetics of antimicrobial agents in critically ill patients. We focused on adult intensive care patients; neutropenic patients were excluded. Furthermore, this review discusses the basic pharmacodynamic principles of different groups of antimicrobials in use on the ICU and the different strategies for therapeutic drug monitoring.

2 Clinical pharmacokinetic principles in the critically ill

In general, the pharmacokinetics of antimicrobial agents are best described by a two compartment open model (figure 1). After infusion or absorption into the central (blood) compartment, the drug is distributed to the peripheral (tissue) compartment, while simultaneously (hepatic) metabolism and (renal) elimination occur. Gradually, the central and peripheral compartment reach an equilibrium and from this point/phase on the concentration in the central compartment decreases below the concentration in the peripheral compartment. This initiates a re-diffusion process from the peripheral to the central compartment resulting in elimination of the drug from both compartments [5].

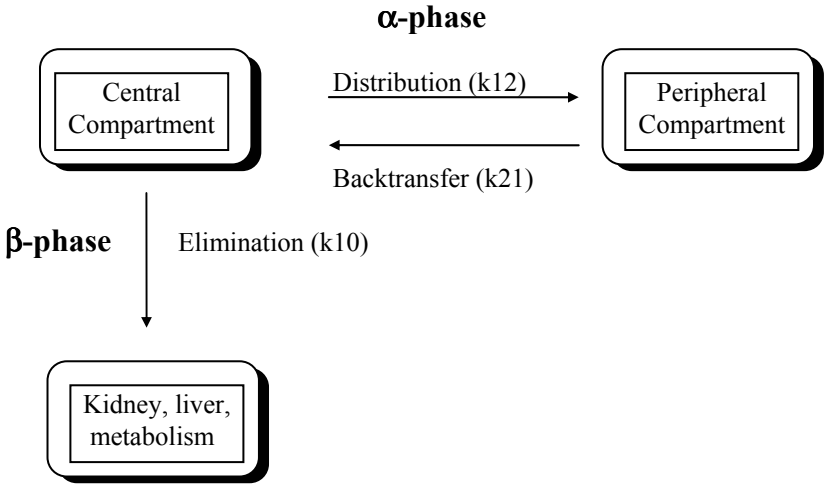

Figure 1. Open two-compartment model

2.1 Absorption

The main routes of antimicrobial drug administration in critically ill patients are intravascular or enteral. After intravenous administration full absorption and rapid attainment of therapeutic concentrations in serum are guaranteed. However, intravenous drugs are more expensive and the use of intra-vascular catheters is associated with a higher incidence of nosocomial infections [6]. In case of enteral dosing distribution and elimination are concurrent events resulting in a delay in time to reach the maximum concentration (Tmax) as well as lower serum peak concentrations (Cmax) [5]. Enteral absorption can be incomplete therefore, the bioavailability, defined as the fraction of a dose which reaches systemic circulation, is often lower after enteral administration compared to intravenous administration. Additionally, some orally administered drugs are metabolised before they reach systemic circulation, but this so called first pass metabolism is thought to be negligible in antimicrobials in use on the ICU [4].

To obtain a maximal bioavailability, absorption has to be optimal. Major factors affecting absorption from the gut are motility, the integrity of the mucosa and the blood supply. In critically ill patients, there are numerous factors, which can compromise enteral absorption (Table 1).

Table 1. Enteral absorption compromising factors in surgical ICU patients

Compromising factor	Causes
Decreased intestinal motility	Paralytic, mechanical ileus, opioids
Loss of mucosa	Starvation, shock, inflammatory bowel disease, chemotherapy
Decreased splanchnic blood flow	Shock
Edema of gut wall	Peritonitis, congestive heart failure
Decreased gastric acidity	Stress ulcer prophylaxis, gastric feeding
Chemical interactions	Iron preparations, enteral feedings, antacids

2.1.1 Motility

The electrical activity motility patterns of the GI tract are disrupted postoperatively [7, 8]. It is thought to be caused by sympathetic hyperstimulation, invoked by the stress of an operation. Under normal circumstances motility is restored within 48 to 96 hours, but additional factors like peritonitis, electrolyte imbalance (hypokalemia), opiate analgesics and anesthetics can prolong this period [9]. Studies on the therapeutic action of prokinetic drugs like erythromycin, cisapride and metoclopramide in critically ill patients are not conclusive [10, 11]. There is an improvement in gastric motility, but a lack of association between changes in gastric emptying times and improvements in symptoms [12]. Furthermore, some prokinetic drugs are associated with cardiac arrhythmias [13].

In the presence of an intestinal obstruction whether mechanical (e.g. tumors, adhesions) or paralytic (e.g. peritonitis, opoids), as much as 5 L of fluid may sequester proximal to the obstruction daily. It would be expected that this is associated with a diminished absorption of drugs [14], but reports on this subject are lacking.

2.1.2 Mucosal factors

Absorption from the bowel is also influenced by mucosal factors including the integrity of the brush border microvilli, the surface area, active or passive transport pathways and blood flow in the capillaries [15]. The integrity of the microvilli is changed by multiple factors including lack of enteral feedings, shock, injury, infection, inflammatory bowel disease and chemotherapy [16-20]. The effect of this mucosal atrophy on permeability and subsequent translocation of endotoxins and bacteria across the mucosa is well known [21, 22]. The effect of these mucosal changes on drug absorption is not clear. As most antimicrobials are absorbed by passive diffusion, an increased intestinal permeability may enhance absorption. On the other hand, there can be a retardation of diffusion caused by edema of the bowel wall as in congestive heart failure or peritonitis [23].

Surgery for abdominal sepsis often involves resection of bowel. As most drugs, antimicrobials are absorbed from the duodenum and jejunum and no site-specific regions for absorption are known. So only after extensive resection of small bowel residence time and surface area can be dramatically reduced, causing a decreased absorption of antimicrobials [24].

2.1.3 Interactions

Chemical interactions may hamper absorption. Changes in gastric acidity caused by H2 antagonist, proton pump inhibitors and antacids, influence the absorption of drugs depending on low gastric acidity for dissolving such as cefuroxime-axetil, cefpodoxime, and itraconazole. Cation containing enteral feedings, antacids, iron preparations and sulcralfate can impair absorption of quinolones and tetracyclines through chelation [25].

2.1.4. Clinical experience

Despite many absorption compromising factors, there is substantial clinical evidence that the gastro-intestinal tract is capable of absorbing nutrients early in the postoperative course or during critical illness [26, 27]. These results have eased the reservation against using the GI tract during critical illness. Studies on the absorption of antimicrobials in these phases are promising (Table 2).

The fluoroquinolones ciprofloxacin and levofloxacin and the anti-fungal fluconazole have proven to have an adequate bioavailability in critically ill patients, even in patients with peritonitis [28-33]. Other drugs with good bioavailability are clindamycin, rifampicin, metronidazole, co-trimoxazole and the newer quinolones (levofloxacin, moxifloxacin) [34], the new ketolide antibiotic telithromycin [35] and the new oxazolidinone antibiotic linezolid [36]. Nowadays, sequential dosing of antimicrobial agents in critically ill patients is propagated [28, 37]. During the initial severe sepsis or septic shock episode the patient is treated with intravenous antimicrobials, but as soon as enteral feeding is given successfully (retentions < 200mL/day) the course is completed enterally. However, the reported bioavailability of ciprofloxacin is variable, so with less susceptible pathogens such as *Staphylococcus aureus* or *Pseudomonas aeruginosa*, higher dosages than 750 mg q12h might be necessary [38, 39].

Table 2. Enteral absorption of ciprofloxacin, levofloxacin and fluconazole in critically ill patients

Antimicrobial	Reference	No patients Type ICU	Daily Dose	Cmax (mg/L)	Vd (L or L/kg)	T1/2β (h)	CL (L/h)	Comments
Ciprofloxacin	Cohn[40]	N=7 Mixed	750mg q12h PO	PO 2.3 (1.2-3.1)	A	A	A	AUC/MIC insufficient for higher MICs
Ciprofloxacin	De Marie[28]	N=5 Surgical	400mg q12h IV 750mg q12h PO Crossover	IV 6.8 (3.9-9.8) PO 3.2 (1.8-4.6)	1.2 (0.8-1.6)	5.2 (4.4-6.3)	17.0 (10.3-23.7)	F 53.1% AUC/MIC insufficient for higher MICs
Ciprofloxacin	Mimoz[39]	N=12 Surgical	400mg q12h IV 750mg q12h PO Crossover	IV 4.1 (1.5-7.4) PO 2.3 (0.7-5.8)	2.1 (1.1-4.9)	3.2 (1.3-5.9)	3.9 (12-120)	F 44% AUC/MIC insufficient for higher MICs
Ciprofloxacin	Debon[38]	N=20 Medical	500 mg q12h PO versus 750 mg q12h PO	PO 2.6 (1.2-4.3) versus PO 3.5 (1.5-5.9)	A	A	A	AUC/MIC insufficient for higher MICs
Levofloxacin	Rebuck[33]	N=28 Medical	500 mg q24h IV	7.5±0.8	1.2±0.3	8.0±1.7	8.1±2.1	F 95% (n=10) AUC/MIC insufficient for higher MICs
Fluconazole	Nicolau[30]	N=7 Mixed	100-200 mg q24 Crossover	PO 7.9±6.8 IV 9.9±6.2	A	PO 34.5±23.2 IV 38.5±31.9	PO 2.3±1.5 IV 1.8±0.9	F 85±19%
Fluconazole	Rosemurgy [31]	N=18 Surgical	100 mg q24 8 PO and 10 IV	PO 1.55±0.47 IV 1.48±0.36	A	PO 31±9.7 IV 30±11.0	A	Relative F 77%
Fluconazole	Buijk[29]	N=14 Surgical	400 mg q24 h Sequential	IV 24.7 (21.7-27.8) PO 20.4 (16.5-24.2)	0.58 (0.45-0.7)	IV 53.4 (36.9-68.9) PO 51.1 (31.7-69.8)	1.1 (0.8-1.4) both	Relative F 124%
Fluconazole	Pelz[32]	N=121 Surgical	400 mg q24 po	Ctrough 14.4 (0-69.8)	A	A	A	Ctrough above common MIC C.albicans

Data are means ±SD or (range); PO = enteral administration; IV = intravenous administration; Cmax = maximum serum concentration ; F = bioavailability; AUC = aera under the concentration curve; MIC = minimal inhibitory concentration.

In conclusion: Despite the fact that enteral absorption in ICU patients is compromised by motility disturbance, mucosal atrophy and chemical interactions, the bioavailability of several antimicrobials is adequate. Caution is necessary in case of less susceptible pathogens in which higher dosage or combination therapy might be needed.

2.2 Distribution

To kill bacteria, or at least inhibit their growth and enhance killing by host defence mechanisms, antimicrobial drugs have to be distributed to the site of infection. A quantitative measure for the spread of a drug throughout the body is the volume of distribution (Vd). This is a hypothetical volume of body fluid that would be required to dissolve the total amount of drug at the same concentrations as that found in the plasma, assuming no elimination. It does not necessarily refer to an actual body compartment, so it is more precisely termed as the apparent Vd. A large Vd (>550 mL/kg) indicates widespread tissue penetration, while a small Vd (< 60 mL/kg) represents complete retention within the plasma. A Vd of approximately 240 mL/kg indicates distribution intravascular and in the extravascular fluid (i.e. not intracellular; ≠ tissue).
The distribution of antimicrobials is influenced by the amount of tissue penetration and the sizes of the different body compartments.

2.2.1 Tissue penetration

Tissue penetration is promoted by high lipid solubility, non polarity and low plasma protein binding [41]. Only unbound drug is assumed to be capable of diffusing into tissue and be effective [4, 42]. An altered amount of free drug in plasma can have its effect on the pharmacokinetic profile of the drug. If the unbound fraction increases by depletion of binding proteins, tissue penetration and, subsequently, Vd increase. On the other hand, drugs that bind to acute phase reactants (e.g. alpha 1-acid glycoprotein) show a decreased unbound fraction and consequently a decreased tissue penetration and Vd. However, these effects of altered plasma protein binding on pharmacokinetics will only be substantial if the drug is protein bound for 80% or more [43]. For drugs with a plasma protein binding of less than 80%, the total amount of free drug in the body is hardly affected by changes in protein binding, because this is buffered by the much larger extravascular volume. Highly protein bound (>80%) antimicrobials frequently used on the ICU are listed in Table 3.

Table 3. Highly protein bound antimicrobial agents frequently used on the ICU.

Antimicrobial agent	Protein binding (%)
Flucloxacillin	96
Ceftriaxone	95
Teicoplanin	95
Erythromycin	84
Clindamycin	90
Rifampicin	80
Amphotericin	91-95
Itraconazole	99

References [41, 43-45].

Albumin is the binding protein for most antimicrobials (= acidic drugs). An exception is erythromycin, which binds to alpha 1-acid glycoprotein (= basic compounds) [41]. Significant changes in binding are not observed until the serum protein concentration is reduced by at least 60% [43]. Thus, extremely low concentrations of albumin (less than 20g/L) are required to markedly reduce the degree of protein binding. Hypoalbuminemia of this magnitude occurs in critically ill patients as part of the acute phase response, by sequestration and dilution in septic shock, by increased turnover or losses (burns, haemorrhage, catabolic states, nephrotic syndrome) and decreased synthesis (malnutrition, hepatic failure). Furthermore, endogenous competitors for binding sites include molecules like bilirubin and urea which can be elevated in hepatic and renal failure or other concomitant drugs may displace antimicrobials from the scarce binding sites [4]. Joynt et al found a 90% increase of the volume of distribution of the highly bound antimicrobial ceftriaxone in critical patients in comparison with normal subjects [46]. A decrease in available albumin caused an increase in unbound ceftriaxone and subsequently an increased distribution. This increased Vd caused subtherapeutic concentrations in the critical ill patient group.

2.2.2 Body compartments

The sizes of the different body compartments influence the volume of distribution. An established endocrine response to surgery is an increased secretion of antidiuretic hormone (ADH) and aldosterone [14]. Consequently, postoperative patients retain salt and water and have an expanded extracellular fluid space.

As a part of the systemic immune response to critically illness several mediators are circulating. These mediators increase the capillary permeability causing fluid accumulation in the extracellular fluid space, a phenomenon called third spacing. Clinical examples of third space fluid sequestrations are peripheral edema by congestive heart failure, septic shock and extensive fluid administration; massive ascites in liver failure and septic fluid sequestration as in peritonitis and pancreatitis [42]. A well known example is the increase in Vd of aminoglycosides in septic patients [47-60]. In general, all antimicrobials with poor or moderate protein binding and predominant distribution into the extravascular space are sensitive to third spacing. In critically ill this is described, besides the above mentioned

aminoglycoside studies, for vancomycin [61], aztreonam [62-64], carbapenems [65-68] and cephalosporins [69-74]. On the other hand, fluoroquinolones [28, 33, 39, 75-78], fluconazole [29] and the new antibiotic linezolid [36] distribute throughout the total body water compartment (large Vd) and are therefore less sensitive to fluid changes.
An important application of Vd is determination of the loading dose. A loading dose can be used to achieve a target concentration immediately (loading dose = Vd * target concentration), rather than waiting for steady state to occur. Loading doses should always be used in severe infections and in case of continuous infusion [25, 79]. Although the apparent Vd can give information about the extent of tissue distribution, it does not necessarily indicate in which tissue the drug penetrates. Furthermore, the drug may not be necesarily active, because of binding or trapping in cell lysosomes [80]. Finally, the perfusion of tissue can be hampered by tissue necrosis (pancreatitis, critical limb ischemia), a decreased blood flow (shock) or as in abscesses, a large distance between the vascular surface area and the infected site (diffusion distance) [81]. Thus, information about concentrations reached at the site of infection is important.
In conclusion: The volume of distribution is increased and variable during critical illness. This is caused by third spacing and a decrease in serum protein for the highly protein bound antimicrobials. These factors can lead to suboptimal serum and tissue concentrations.

2.3 Metabolism

Drug metabolism provides a mechanism for clearing the body of toxic compounds and drugs. Furthermore, it can produce active metabolites of the compound administered. The primary metabolising organ is the liver, but the kidneys, intestines (enterohepatic circulation), lungs and skin are also involved in this process.

2.3.1 Biotransformation

Routes of biotransformation are phase I reactions including oxidation, reduction and hydrolysis, which are usually catalysed by cytochrome P450 enzymes. The main function of phase I is to generate functional groups that can participate in phase II reactions. Phase II conjugation usually biotransforms compounds into larger, more polar molecules to hasten their excretion in urine or bile. Not cytochrome P450 enzymes, but microsomal transferases are involved in this process [5].
Hydrophilic antibiotics such as aminoglycosides, glycopeptides and most beta-lactam agents undergo little or no metabolic degradation since no molecular change is necessary for renal elimination [41]. Antimicrobial agents in use on the ICU with significant hepatic metabolism are listed in Table 4. Some antimicrobials have active metabolites i.e. cefotaxime, ciprofloxacin, rifampicin and flucloxacillin [44].
During stress, like in critical illness, there is a 10 to 50% increase of basal metabolic rate, depending on the severity of disease [14]. It can be anticipated that this hypermetabolic state has its effect on drug metabolism. However, during critically illness, hepatic metabolism is more often impaired by pre-existent causes like cirrhosis, chronic hepatitis or congestive liver failure or acute causes including infection or shock induced failure. Hepatic failure often occurs late in the course of the multi-organ-failure syndrome. Approximately 6% of all patients with severe sepsis develop hepatic failure [82].

In the literature, a few studies are available on the effect of liver failure on the pharmacokinetics of antimicrobials with significant hepatic clearance. For example, cefotaxime is partly metabolised in the liver to 3 metabolites of which one, desacetylcefotaxime has a bactericidal effect. Clinical studies have shown that in various degrees of liver failure and/or after liver transplantation the production of desacetylcefotaxime is hampered [83, 84]. Mann et al found a decreased hepatic clearance of clindamycin in 10 critically ill patients with sepsis [85]. Plaisance et al. found the lowest clearances of metronidazole in patients with obstructive liver disease. The presence of obstructive liver disease or renal impairment appeared to prolong the elimination of the hydroxymetabolite [86].

Table 4. Antimicrobial agents in use on the ICU with significant biotransformation.

Antimicrobial agent	Percentage of biotransformation (%)
Cephalosporins	
• Cefotaxime	50
• Ceftriaxone	44
Carbapenems	
• Meropenem	20-50*
• Imipenem	95 (in kidney)
Clindamycin	75-85
Metronidazole	80
Erythromycin, clarithromycin, azithromycin	50
Ciprofloxacin	18-33
Quinupristin-dalfopristin	20
Itraconazole	>90

References [44, 87, 88]. * = increased non-renal clearance in renal failure.

Besides indirect liver enzyme measurements or the Child-Pugh classification [89], antipyrine metabolism measurement can be used to quantify mixed cytochrome P450 mediated drug metabolism [90]. Carcillo et al. investigated antipyrine metabolism in children with sepsis and organ failure on a pediatric ICU. Children with persistent failure of three or more organs had a fourfold reduction in antipyrine clearance. Antipyrine clearance was inversely correlated to the number of organ failures [91].

2.3.2 Interactions

Another concern regarding metabolism in the critical care setting is the possible drug-drug interactions involving antimicrobial agents. This subject has been reviewed recently by Pea and Furlanut [92]. These data, completed with recent literature [93, 94] are summarized in Table 5. In these cases of multi-drug administration, therapeutic drug monitoring might be needed.

In conclusion: During stress hepatic metabolism can be increased up to 50%. However, during critical illness, hepatic metabolism is more often impaired by pre-existent causes or acute causes including infection or shock induced failure. The pharmacokinetics of several

antimicrobials is influenced by a variable liver function, but the extent of liver function is difficult to quantify in the clinical setting. Furthermore, in a multiple drug setting like an ICU, several drug-drug interactions involving antimicrobial agents are possible.

Table 5. Drug-drug interactions involving antimicrobial agents on the ICU.

Inhibitors of cytochrome P450
Macrolides (erythromycin, clarithromycin, azithromycin)
Ketolide (telithromycin)
Fluoroquinolones (ciprofloxacin, levofloxacin)
Quinupristin-dalfopristin
Azole anti-fungals (fluconazole, itraconazole, voriconazole)

↓ Decreased clearance

Drugs with decreased or enhanced clearance
Benzodiazepines (especially midazolam and triazolam)
Immunosuppressive agents (cyclosporin, tacrolimus)
Brochodilatators (theophylline)
Opoid analgesics (alfentanil)
Anticonconvulsants (phenytoin, carbamazepine)
Calcium antagonists (verapamil, nifedipine)
Anticoagulants (warfarin)

↑ Enhanced clearance

Inducer of cytochrome P450
Rifampicin

2.4 Excretion

In general, the total body clearance of a drug is the sum of the renal clearance and the metabolic clearance. Other minor pathways include the biliary, the pulmonary and gastro-intestinal clearance. Clearance is influenced by the function of the clearing organ (extraction ratio), amount of free drug in plasma and the blood flow.

2.4.1 Renal function

Most antimicrobials are eliminated from the body through the kidneys by glomerular filtration and/or tubular secretion. In generals, beta-lactam antibiotics and aminoglycosides are excreted largely unchanged by the kidneys [41]. Antimicrobials with extensive metabolism are listed above (Table 4). Some antimicrobials in use on the ICU are mainly excreted in bile. These include clindamycin, rifampicin and itraconazole [41, 44]. The excretion in bile of ciprofloxacin and meropenem is increased in renal failure. The fate of most of a dose of amphotericin B is unknown [45].

Acute renal failure is common in the surgical ICU. Causes include septic shock, major surgery, (multi) trauma, major burns and nephrotoxic drugs such as aminoglycosides,

vancomycin, amphotericin B, cyclosporin, ACE inhibitors, furosemide >160 mg/day, chemotherapy and contrast dye [95-97]. Approximately 30% of all patients with severe sepsis develop renal failure of which one third needs renal replacement therapy [82]. To determine renal function the creatinine clearance over 24 h can be calculated. In practice, the creatinine clearance is estimated by using the Cockroft and Gault equation [98]. This equation takes into account the patient's age, weight and gender and is therefore more accurate than simple assessment of serum creatinine. However, serum creatinine can be sub-normal in critically ill patients due to muscle wasting. Therefore, a minimal serum creatinine concentration of 85 μmol/L can be used to avoid an overestimating of renal function [99].

2.4.2 Protein binding

In general, antimicrobials show a restrictive clearance, which means that only free drug is eliminated [41]. The clearing organ shows a low to moderate extraction ratio depending on the amount of plasma protein binding. In this case clearance is sensitive to changes in protein binding, but again, significant changes are to be expected only with highly bound drugs [43]. On the other hand, there can be a non-restrictive clearance, in which the drug is stripped from its binding sites as it passes through the eliminating organ (=high extraction ratio). In this case clearance is insensitive to changes in protein binding, but dependent on the blood flow through and function of the clearing organ (for example cefotaxime). Burchart et al found an impaired clearance of cefotaxime after orthotopic liver transplantation, which was not fully explained by variation in creatinine clearance or transplant dysfunction [100]. Perhaps a diminished renal blood flow attributed here to.

2.4.3 Blood flow

Cardiac output can vary extremely during critical illness. Well known is the hyperdynamic circulation in severe sepsis with a cardiac output of >10L/min [101]. On the other hand, in the patient with congestive heart failure, the cardiac output can be as low as <2L/min. Besides the effect of the cardiac output, renal blood flow can be compromised during shock, hypovolemia and high intra-abdominal pressure (>25mmHg) [102]. Drugs like dopamine, dobutamine and diuretics are frequently used in critically ill patients to support the perfusion of the kidney. By stimulating the urinary output and/or the cardiac output they can enhance renal clearance of antimicrobials and cause under dosing. Pea et al. investigated the influence of some drugs with important hemodynamic effects (dopamine, dobutamine, furosemide) on vancomycin pharmacokinetics in 18 critically ill patients [103]. They found in some patients that the withdrawal of co-treatment with hemodynamically active drugs was followed by a sudden substantial increase in the vancomycin serum concentration, despite no major change in bodyweight or estimated creatinine clearance being observed.

Rate of elimination is described by the elimination rate constant, from which the elimination half-life (T½) is derived. T½ is defined as the amount of time necessary to decrease the serum concentrations by one half, and is dependent on the total body clearance and the volume of distribution. T½ can be used to determine when steady state will occur. When successive doses of a drug are administered, they accumulate until equilibrium is reached. At that point the amount administered equals the amount eliminated, a condition known as steady state. Steady state can be assumed to occur after four to five half lives of the drug.

Only when the dosing interval is 5 times longer than T½, accumulation and consequently steady state will not occur.
In conclusion: Approximately one third of all critically ill patients develop renal failure. As most antimicrobials are eliminated from the body through the kidneys, this has a serious impact on the pharmacokinetics of these drugs.

3 Pharmacodynamic principles

To determine the optimal antimicrobial regimen the following parameters of antimicrobial activity are important. The activity against the infecting pathogen in vitro, the persistent effects and the pharmacodynamic activity of antimicrobial agents in vitro and vivo and the local factors at the site of infection.

3.1 MIC and MBC

The antimicrobial activity against the infecting pathogen in vitro is usually quantified by the minimal inhibitory concentration (MIC) or the minimal bactericidal concentration (MBC). The MIC is the minimal concentration needed to suppress bacterial growth in vitro. The MBC is the minimal concentration needed to kill the pathogens in vitro. Although these parameters are reasonable predictors of the potency of the drug, they are static in vitro concentrations. They do not provide information on the rate of killing and whether this is enhanced by increasing the drug concentrations [104].

3.2 Persistent effects

Persistent effects of antimicrobial agents are inhibitory effects that persist after exposure to an antimicrobial drug. These persistent effects include the postantibiotic effect, the postantibiotic sub-MIC effect and the postantibiotic leucocyte enhancement [105-107].
The postantibiotic effect (PAE) is defined as persistent suppression of bacterial growth after exposure to an antimicrobial in vitro [108]. This effect is probably the result of sublethal damage to the micro-organism and persistence of antimicrobial at its binding site after the drug is removed. The PAE is influenced by the microorganism, the type and concentration of the antimicrobial and the time of exposure. In vitro, all antimicrobials produce PAEs for gram-positive bacteria lasting 1 to 2 hours. PAEs of approximately 2 hours for gram-negative organisms are observed after exposure to fluoroquinolones, aminoglycosides, macrolides, rifampicin and tetracyclines [109]. Beta-lactam antibiotics show no PAEs for gram-negative bacilli. An exception to this rule are the carbapenems imipenem and meropenem [110].
PAEs determined in vitro do not reflect the in vivo PAE, and therefore has little clinical importance. The PAE tends to be longer in vivo than in vitro. Exception to this are in vitro PAEs for streptococci exposed to penicillins and cephalosporins, which are lost in vivo. Furthermore, in vitro PAEs for aminoglycosides disappear with multiple dosing or a prolonged dosing interval (repair of sublethal damage), while in vivo PAEs appear to continue [104, 111]. PAEs determined in vivo may have some clinical relevance, but they are probably primarily caused by the postantibiotic sub-MIC effect (PAE-SME) and the postantibiotic leucocyte enhancement (PALE) [107, 112, 113]. In vivo, sub-MIC concentrations can be physiological at the end of the dosing interval. Subsequent exposure of organisms to sub-MIC concentrations of the antimicrobial, is known to produce

morphological changes, to slow growth of organisms and can increase the duration of the PAE in vivo by 40 to 100% [104]. PALE refers to the observation that bacteria in the postantibiotic phase are more susceptible to killing by leucocytes. In the presence of leucocytes the PAE of aminoglycosides and fluoroquinolones for gram-negative bacteria can be doubled [114]. However, PALE is not observed for gram-negative bacteria exposed to beta-lactams.

3.3 Pharmacodynamic activity

The effect of the concentration-time profile in serum and at the site of infection on the bactericidal activity is important. Antimicrobial agents can be divided into different groups based on their bactericidal activity [108, 115, 116]. Some show concentration dependent killing, in which the rate and extent of bactericidal activity correlates with the magnitude of the concentration. In contrast, others show time dependent killing, in which concentrations above 4 to 5 times the MIC do not kill the organism any faster; bactericidal activity largely depends on duration of exposure above the MIC. In Table 6 the antimicrobials are listed depending on their pattern of antimicrobial activity.

Table 6. Pharmacodynamic indices of antimicrobial agents predictive for efficacy.

Time dependent activity T>MIC	Concentration dependent activity AUC (Cpeak)/MIC
Cephalosporins	Aminoglycosides
Penicillins	Fluoroquinolones
Carbapenems	Metronidazole
Monobactams	Ketolides
Clindamycin	Azithromycin
Linezolid	Fluconazole
	Amphotericin B

3.3.1 Concentration dependent killing

In Table 6 the antimicrobials that have been classified as concentration dependent drugs are listed in the right column. Their optimal antimicrobial activity has been associated either with high ratio of peak drug concentration to MIC or the ratio of AUC to MIC. These antimicrobials have a substantial in vivo post-antibiotic effect for many organisms as well. Therefore, extending the dosing interval is rational with these agents. By obtaining high peak concentration/MIC ratios bactericidal activity is optimised and emergence of resistance is minimized.

In vitro, animal and clinical studies of extended interval dosing of aminoglycosides have shown that optimal bacterial activity is achieved when the peak concentration (Cpeak) is at least 10 times the MIC of the causative gram-negative pathogen [117, 118]. In addition, this Cpeak/MIC ratio of at least 10 may prevent the emergence of aminoglycoside-resistant subpopulations [119]. Data from animal models and clinical trials suggest that these extended interval regimens are as effective as conventional regimens for the treatment of gram-negative infections [120, 121], but reduce the oto- and nephrotoxicity associated with

aminoglycoside therapy [122]. Once daily dosing of aminoglycosides may not be desirable in all situations. For instance, one experimental study of enterococcal endocarditis indicated a greater efficacy when an aminoglycoside is administered in a multiple dosing regimen [123]. In other gram-positive infections no difference in efficacy compared to conventional dosing regimen has been found [117]. Furthermore, some patient groups have a relatively high total body clearance, such as patients with cystic fibrosis [124], resulting in suboptimal concentrations. In these patients twice daily dosing might be mandatory [125].
A recent survey of once-daily aminoglycoside dosing in the United States revealed that 75% of the hospitals adopted this strategy for the treatment of gram-negative infections, while 25% of the hospitals preferred conventional multiple dosing [126]. Dosages used varied between 5-7 mg/kg for gentamicin and tobramycin [117] and 20-25 mg/kg for amikacin and icepamicin [59, 127, 128]. In critically ill patients an increased volume of distribution of aminoglycosides is well known [47, 48, 50] especially in patients with septic shock [51]. Consequently, the maximum concentration reached is lower in patients with septic shock. Given an infection caused by *P. aeruginosa* with a MIC of 2mg/L (MIC90 = 2mg/L), the frequently used dose of 5 mg/kg is insufficient to obtain a Cmax/MIC ratio of 10. Delays in attaining therapeutic levels of aminoglycosides have been associated with persistence of infection and treatment failure [129]. Therefore, an initial high dose of 7mg/kg is necessary in this patient group, even in patients with renal impairment, to assure an adequate serum concentration. This initial high dosage needs to be continued in case of a *P.aeruginosa* infection. On the other hand in ICU patients with an infection caused by Enterobacteriaceae with lower MICs, this high dose is unnecessarily high in most of the cases. So in prolonged therapy, lowering the dose as soon as the MIC is known would be the best strategy [51]. By minimising the dose, there is less accumulation in the renal tubuli, which prevents nephrotoxicity [122].

For the fluoroquinolones the Pk/Pd index that best correlates with efficacy is the 24-hour AUC/MIC ratio. Forrest et al. found that a 24-hour AUC/MIC ratio >125 was associated with satisfactory outcome for seriously ill patients treated with intravenous ciprofloxacin [130]. Ratio's >250 resulted in faster elimination of the micro-organisms. Lower values resulted in clinical and bacteriological cure rates of less than 50%. In critically ill patients the fluoroquinolone ciprofloxacin is most often used. Ciprofloxacin is distributed throughout the total body compartment [88] and the Vd is therefore relatively insensitive to fluid overload and third spacing in the critically ill [28, 77]. Because of its good bioavailability, ciprofloxacin can be administered enterally in critically ill patients [38, 40, 75, 131] even in patients with a compromised absorption [28]. This can simplify the administration and reduce costs compared to intravenously administered ciprofloxacin. De Marie et al. showed that the AUC achieved by ciprofloxacin 750 mg bid via the enteral route appeared to be equivalent to that achieved by intravenous ciprofloxacin 400 mg bid. The regimen of 750 mg bid used in this study may be insufficient in some severe Pseudomonas infections for which an i.v. regimen of 400 mg tid is the standard treatment at this moment [132]. In such infections it is probably more appropriate to start with i.v. combination therapy and, if possible, to switch to oral/enteral ciprofloxacin with a daily dosage of 1500-2250 mg.

New antimicrobials like quinupristin-dalfopristin [133], ketolides [134] and linezolid [135], were recently introduced on the ICU to treat infections with emerging resistant gram-positive micro-organism. Sander et al. investigated the efficacy and safety of quinupristin-dalfopristin (Q-D) therapy in 12 critically ill patients with severe infections caused by methicillin-resistant staphylococci unresponsive to vancomycin treatment. Patients received, intravenously, Q-D 7.5 mg/kg body weight 3 times daily. Eradication of pathogen(s) was achieved in 7 of 12 patients (66%). Adverse events related to Q-D were not observed and neither renal nor liver function was adversely affected [133]. Pharmacokinetic studies with Q-D, ketolides or linezolid in critically ill are not yet available in the literature.
Metronidazole is often used on the SICU as a part of the treatment of intra-abdominal infections [136, 137]. Maximal killing of anaerobes is achieved with Cpeak/MIC ≥10 in vitro [138]. But in critically ill, where dosages of 750-1500 mf q8h are used, this has not been confirmed.
The antifungal agents fluconazole, itraconazole and amphotericin B show maximal killing with Cpeak/MIC ratio ranging between 8 and 2 [139]; an AUC/MIC ratio of 12-25 for fluconazole is described as well [140]. Studies on fluconazole in critically ill patients showed that peak concentrations reached intravenously were not significantly different than after enteral administration [30, 31] and that a dosage of 400 mg q24h is needed to reach an adequate AUC to treat *C.albicans*, especially at the side of infection [29]. *C.glabrata*, often resistant to Fluconazole, is treated with amphotericin B. Heinemann et al. investigated the pharmacokinetic characteristics of the liposomal formulation of amphotericin B (AmBisome) applied to 10 patients at a dose of 2.8 to 3.0 mg/kg of body weight and compares them to the pharmacokinetics observed in 6 patients treated with amphotericin B deoxycholate at the standard dose of 1.0 mg/kg. Liposomal amphotericin B significantly reduced the volume of drug distribution, thereby increasing the peak concentration 8 fold [141].

3.3.2 Time dependent killing

Beta-lactam antibiotics and possibly vancomycin and some macrolides show time-dependent killing, which means that maximal efficacy is achieved when the concentration at the site of infection exceeds the MIC of the pathogen for most of the dosing interval. For example, maximal efficacy for cephalosporins is achieved when serum levels are above the MIC for 60%-70% of the dosing interval for organisms without a PAE (such as Enterobacteriaceae, streptococci) and 40%-50% of the dosing interval for organisms that do have a PAE (such as staphylococci). These percentages are slightly lower for penicillins and the lowest for carbapenems, which might reflects the variations in rate of killing as this is possible faster with carbapenems. Besides the time during which the serum concentration exceeds the MIC (T>MIC), the actual serum level does influence outcome. The results from in-vitro and in-vivo experiments indicate that 4 x MIC for the infecting bacterium would be the target concentration for optimal effect. These observations have led to the proposition to administer beta-lactam antibiotics by continuous infusion [79].
Several studies have investigated the continuous infusion of ceftazidime in critically ill patients (Table 7). These studies showed variable serum concentrations of ceftazidime

depending on the total body clearance. In one study of critically ill medical patients, a mean steady state serum concentration of 30 mg/L was reached with an infusion of 3 g/24h, while the total body clearance was approximately 4 L/h [69]. In another study in patients with nosocomial pneumonia using the same regimen (3g/24h), the total body clearance was twice as high (± 8 L/h), and therefore a mean steady state concentration of 17 mg/L was reached [142]. Lipman et al. showed that a dose of 6g/24h is needed in mixed critically ill patients with a total body clearance of approximately 6 L/h to maintain a concentration of 40mg/L in serum with continuous infusion [143]. Hanes et al. studied continuous infusion in critically ill trauma patients with a total body clearance of 11.3 L/h using a regimen of 60 mg/kg. They found a mean steady state serum concentration of 19.2 mg/L [71]. In case of Pseudomonas infection with an MIC of 8 mg/L, a target concentration of ≥ 32 mg/L is needed. Buijk et al. found in a critically ill surgical population with a total body clearance of approximately 5.1 L/h, serum concentrations of ≥ 32 mg/L only for approximately 70% of the dosing interval after continuous and intermittent infusion (4.5 g/24h). In peritoneal exudates this was much lower [73]. When the concentration falls below the threshold concentration re-growth of pathogens and development of resistance can occur.

Ceftriaxone, a 3th generation cephalosporin, has different pharmacokinetic properties than ceftazidime. Studies in adult volunteers show that it is protein bound for >90%, it is mainly distributed in the central compartment, it has a low total body clearance (1.2-1.3 L/h) [144, 145] and therefore once daily administration is possible. In critically ill patients however, Joynt et al. showed that 20-30% decrease of available binding albumin caused a 90% increase in Vd and 100% increase in total body clearance [46]. This caused subtherapeutic concentrations in serum after a daily dose of 2g q24h. Therefore, evaluation of continuous infusion in this patient group is warranted.

The recommended 2 g twice daily dosing of cefpirome, a 4th generation cephalosporin, was evaluated in critically ill patients by Lipman et al [72]. They found lower and more variable serum cefpirome concentrations compared to concentrations in adult volunteers. A pharmacokinetic simulation showed that a continuous infusion of 6 g/24h is needed to assure T>4xMIC of *P.aeruginosa* for at least 60% of the dosing interval in this patient group.

The carbapenems (imipenem/cilastin and meropenem) demonstrate time dependent killing, but in contrast with the other beta-lactams do exhibit some PAE effects [146]. Maximal killing is achieved when serum concentrations are maintained above the MIC for 40% of the dosing interval [68]. Pharmacokinetic data in critically ill are limited. Thalhammer et al. compared in a crossover study the pharmacokinetics of meropenem by continuous infusion (2 g iv loading dose, followed by a 3 g / 24 h) and by intermittent administration (2 g iv / 8 h) in 15 critically ill patients. In both treatment groups, meropenem serum concentrations remained above the MICs throughout the dosing interval for most common bacterial pathogens [66]. Kitzes-Cohen et al. investigated the pharmacokinetics and pharmacodynamics of meropenem in 14 critically ill patients with sepsis. Patients received 2 g daily (creatinine clearance < 50mL/min) or 3 g daily (creatinine clearance >50mL/min). Meropenem serum levels exceeded 4 times the MIC for 50-100% of the dosing interval [147].

The current data on vancomycin suggests that bacterial killing is concentration independent [148, 149]. Continuous infusion of this potentially nephrotoxic drug [150] limits the amount of drug used and subsequently accumulation. Furthermore, continuous infusion may reduce the emergence of resistant bacterial strains [151]. Wysocki et al. compared intermittent and continuous infusion of vancomycin in 119 critically ill patients with MRSA infections [152]. CI patients reached the targeted concentrations faster and fewer samples were required for treatment monitoring than with intermittently dosed patients. The 10-day treatment cost per patient was significantly lower in the CI group due to less use of the drug per patient.

Table 7. Studies on continue infusion of beta-lactam antibiotics in critically ill patients.

Antimicrobial	Reference	No patients Type ICU	Daily Dose #	Cserum (mg/L)	Vd /kg)	T1/2β (h)	CL (L/h)	Comments
Cephalosporins								
Ceftazidime	Benko[69]	N=12 Medical	CI 3g/24h (2g) IB 2g q8h iv	Css 29.7±17.4 Cmax 124.4±52.6	18.9±9.0 L	3.5±1.6	N/A	T>MIC >100% CI T>MIC >100% IB
Ceftazidime	Lipman[143]	N=18 Mixed	CI 6g/24h (1g) IB 2g q8h iv	Target 40 mg/L	N/A	N/A	± 6.0	T>40 mg/l 100% CI T>40 mg/l 30% IB
Ceftazidime	Nicolau[142]	N=34 Medical	CI 3g/24h (1g) IB 2g q8h iv	Css 17.4±6.1 Cmax 106.5±34.6	N/A	3.2±2.5	8.6±3.5	T> MIC 100% CI T> MIC 56-100% IB
Ceftazidime	Hanes[71]	N=31 Trauma	CI 60mg/kg (2g) IB 2g q8h iv	Css 19.2±8.6 Cmax 90.9±44.3	0.32±0.14	1.72±0.71	11.7±4.3	T>MIC ≥ 92% both
Ceftazidime	Buijk[73]	N=18 Surgical	CI 4,5g/24h (1g) IB 1.5g q8h	Css 47 (21-93) Cmax 89 (58-125)	0.28 (0.15-0.44)	4.2 (1.3-12.3)	5.1 (2.3-8.9)	T>32 mg/l 67% CI and 69 IB in serum T>32 mg/l 45% CI and 6% IB in exudate
Carbapenems								
Meropenem	Thalhammer [66]	N=15 Medical	CI 3g/24h (2g) iv IB 2g q8h iv	Css 11.9±5.7 Cmax 110.1±6.9	0.32±0.04	2.4±0.7	7.7±1.4 CI 9.4±1.2 IB	CI adequate T>MIC, For *P.aeruginosa* 4g/24h proposed

Data are means ±SD or (range); CI = continuous infusion; IB = intermittent bolus infusion; Css = serum concentration at steady state after CI; # = loading dose between brackets; Cmax = maximum serum concentration after IB.

3.4 Tissue concentrations and local factors

Besides bloodstream infections and endocarditis, a bacterial infection site originates mostly from a certain tissue interstitium. Therefore, besides adequate plasma concentrations, sufficient tissue concentrations are needed. In critically ill patients tissue concentrations can be determined in various body fluids [29, 64, 65, 73], from tissue biopsies during surgery [137] and by microdialysis [74, 153-155]. These studies showed that despite effective antibiotic concentrations in serum, concentrations at tissue level were consequently lower than in serum. Possible explanations are an increased interstitial edema by capillary leakage (dilution) in septic shock [153] or for example incomplete passage through the blood-peritoneum barrier in peritonitis [73]. Inadequate target site concentrations may account for therapeutic failure.

Local factors at the site of infection may differ significantly from the in vitro or in vivo test conditions. Large inocula can allow resistant mutants to predominate under selective pressure of an antimicrobial agent. In a large inoculum organisms may grow slower, which can decrease the efficacy of the antimicrobial. Furthermore, the dense population can produce large amounts of beta-lactamases that can inactivate a beta-lactam antimicrobial. Additionally, the optimal test conditions do often not represent the local conditions at the site of infection and therefore test results can be misleading. For example, in an abscess with a low pH, low oxygen concentration and protein rich exudate, activity of the antimicrobial can be totally different. Furthermore, thrombotic masses and prosthetic material protect micro-organisms from host defences and antibiotics[81].

4 Monitoring and modelling

Historically, monitoring of antimicrobial drugs was reserved for drugs with a narrow therapeutic range such as aminoglycosides, vancomycin and amphotericin B in order to prevent toxicity. In the last decade, individual therapeutic drug monitoring (TDM) has evolved, in which the serum concentrations of a certain drug are combined with the pharmacokinetic profile of an individual patient to optimize dosage regimens according to modern pharmacodynamic insights. Several studies with aminoglycosides have documented a positive impact of TDM on clinical outcome, reduction of hospital stay and toxicity [156-158].

In critically ill patients with a deranged pharmacokinetic profile with wide inter- and intra patient variability, TDM can be of particular benefit in guiding the physician to the optimal dosing schedule. Most experience with TDM of antimicrobial agents is gained with aminoglycoside dosage regimens and the different methods available were recently reviewed [159]. The methods applicable for critically ill patients are listed below.

4.1 Once daily aminoglycoside nomogram

The once daily aminoglycoside (ODA) or Hartford Hospital nomogram is a widely used method to monitor extended interval aminoglycoside dosing [160]. Given a fixed dose (7 mg/kg of gentamicin, tobramycin or netimicin and 21 mg/kg of amikacin or isepamicin), the dosage interval is determined based on a single serum concentration drawn 6 to 14

hours after the start of infusion plotted on the nomogram. This method has been validated in a large hospital wide population but does not work for patients with high aminoglycoside clearance (burns of >20% of total body surface area or cystic fibrosis) or a deep compartment (ascites) [159, 160]. In our own experience, the ODA nomogram did not apply to critically ill patients as the recommended dosing interval was correct in only 62% of all 109 cases [51].

4.2 Sawchuk and Zaske method

The prototype of the non-Bayesian least-squares method was described by Sawchuk and Zaske [161]. The main assumption of the method is that disposition obeys a linear one-compartment open model. Two or more serum samples are taken in the post-distributive phase during a single dosage interval to measure the drug concentration. From the fitted serum-time concentration curve the area under the concentration curve (AUC) and the elimination rate constant (Kel= lnC1- lnC2/Δt) are calculated. Calculation of the AUC enables estimation of the total body clearance (CL=Dose/AUC), which is defined as the volume of blood or plasma from which the drug is removed per unit of time (L/h). Clearance is therefore independent of the volume of distribution. From Kel the elimination half-life (T½) can be obtained (T½=ln2/Kel) and by dividing CL through Kel an estimation of the volume of distribution (Vd) can be made.

This method has validated with gentamicin in different populations [162] and proved to be robust even in patients with extreme parameter values [159]. The method is applicable even if there is no prior knowledge about the pharmacokinetic profile of the population. The only drawback is the requirement for at least two or more serum samples. This can be overcome with Bayesian methods.

4.3 Bayesian methods

Bayesian methods combine prior information on a population with actual data on measured serum concentrations in estimating the individual patient's pharmacokinetic parameters [163, 164]. The incorporated prior information on the specific population includes the structure of the pharmacokinetic model (one, two or three compartments), the distribution of the pharmacokinetic parameters (means and variances), the value of the covariates (for example age, bodyweight, renal failure / serum creatinine, septic shock) and the residual error model [159]. A number of software packages are available for Bayesian forecasting [165]. Bayesian forecasting has been evaluated in critically ill patients for different antimicrobial agents. Several authors have demonstrated that the Bayesian method is capable in estimating the individual pharmacokinetics of aminoglycosides in ICU patients with a low bias and a good precision [57, 166-170]. However, predictive performance of the Bayesian forecast is dependent on the accuracy of the assumptions made about the population. Polard et al. reported a poor predictive performance of a Bayesian forecasting program of vancomycin in ICU patients [171]. Vancomycin pharmacokinetics in their ICU population was too variable during the course of therapy, preventing accurate concentration predictions. By identifying the potential sources of variability in the population, and incorporating these in the model, the predictive performance can be optimised [172-174].

In general, the intraindividual variability of the pharmacokinetic parameter has to be low (coefficient of variance <20%), otherwise the forecast will have a large prediction error

[159]. Critically ill patients with a rapidly changing physiological status (unstable renal function and /or hemodynamic status), uncertainty of the predictions may considerably increase irrespectively of the method used [163]. If the variability cannot be explained by covariates daily monitoring may be mandatory.

5 Conclusion

In critically ill patients, a disturbance of numerous physiological responses provokes a pharmacokinetic profile with wide inter- and intra patient variability. As differences in pharmacodynamic activity of antimicrobial agents have implications for optimal dosage regimens, knowledge of the deranged pharmacokinetics is mandatory. As this profile is hard to predict, therapeutic drug monitoring is necessary to guide the physician to the optimal dosing schedule.

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CHAPTER 3

INFECTION ON THE SURGICAL INTENSIVE CARE OF A REFERRAL CENTER: EPIDEMIOLOGY, ANTIMICROBIAL USE AND OUTCOME

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Abstract
Background: Infections represent a major source of morbidity, mortality and hospital costs in surgical intensive care patients. Antimicrobial use and the subsequent development of resistance among pathogens, influences the outcome of the treatment.
Objectives: To study the epidemiology and clinical outcome of infections in surgical intensive care patients and to describe the antimicrobial use and susceptibility patterns of the pathogens.
Design: A prospective 9 months cohort study.
Setting: A surgical intensive care unit (SICU) in a university referral hospital in The Netherlands
Patients: 182 admissions staying ≥ 48 hours were studied prospectively.
Results: One hundred and four episodes of infection and 155 infection sites (90% CDC defined) were documented. Overall, the incidence density of infection was 61 episodes per 1000 patient days. The majority of primary infections were localised in the abdominal cavity (40%), whereas ICU-acquired infections were more often pulmonary (43%). In primary infections, three-quarters of the gram-negative pathogens reflected normal predominant endogenous flora (*E. coli*, Klebsiella, Proteus) whereas, in ICU-acquired infections, the majority of gram-negative pathogens were selected Enterobacteriaceae or Pseudomonas spp. Among gram-positive pathogens, staphylococci rather than streptococci were present in ICU-acquired infections. Eight percent of the *P.aeruginosa* strains were multiple resistant. No multiple resistant Acinetobacter spp or Enterobacter spp were causing infections in our population. The incidence of MRSA and VRE was low. The total use of antibacterial agents on our SICU in 1999 was three times as high as the overall use in our hospital and five times greater than the use in Dutch hospitals in 1996. Patients with an episode of infection, either primary or ICU-acquired, had a significant higher in-unit mortality rate. Eighty-one out of 104 episodes (78%) were successfully treated. Inadequate antimicrobial therapy was associated with a significant increase in treatment failure and infection related death.
Conclusions: In long-stay SICU patients the incidence of infection is high. Insights into the susceptibility patterns of pathogens, antimicrobial utilization and treatment outcome on a local level are necessary to periodically evaluate the quality of care.

Introduction
The presence of a life threatening infection is a common reason for admission of a patient to a surgical intensive care unit (SICU) [1]. Due to several well-established risk factors [2], surgical patients are prone to develop an infection during their stay in the SICU[2]. Furthermore, infections in the SICU represent a significant source of morbidity, mortality and increased hospital costs [3].
Antimicrobial therapy plays an important role in the treatment of severe infections. Appropriate antimicrobial therapy will reduce mortality due to severe septic shock by 50% [4]. However, data on the epidemiology of infections, the microbiological spectrum of pathogens and the use of antimicrobial drugs are essential for appropriate antimicrobial prescribing. Antimicrobial selection pressure is a major determinant in the spectrum and

susceptibility of pathogens isolated in a SICU [5] and antimicrobial use may be very high in the ICU of a referral center with a complex patient population [6]. Establishment of a standardized method to quantify the use of antimicrobial agents would therefore allow the comparison of data with other hospital units and ICUs. In addition, the assessment of the success rate of antimicrobial therapy should be part of a hospital's quality of care control program.
This study describes the infections of long-stay patients admitted to the SICU of a Dutch university referral hospital, focusing on epidemiology, identity and susceptibility of the pathogens, antimicrobial use and clinical outcome.

Methods

Patients and methods

From March until September 1999, all consecutive patients admitted for > 48 hours (long-stay population) to the 18-bed (single room) SICU of the Erasmus MC in Rotterdam, The Netherlands, (1237 beds) were studied prospectively. Patients who were expected to stay > 48 hours but who died within 48 hours of admission were also included in the analysis. Excluded were (postoperative) patients who were transferred after ≤48 hours, organ transplant patients and patients admitted for monitoring during fibrinolysis treatment. On admission at the SICU, demographic data including age, sex and type and reason of admission were collected. The hospital admission date, the pre-admission American Society of Anaesthesiology (ASA) score [7] and inter or intra ward/ICU transfers were documented. The Acute Physiology And Chronic Health Evaluation II (APACHE II) score [8] was chosen to classify the severity of illness. The Sequential Organ Failure Assessment (SOFA) [9] score was used to express the extent of organ failure. For all patients the APACHE II was calculated over the first 24 hours of admission of their ICU stay. In patients with an infection, the APACHE II and SOFA score were calculated daily.
With respect to infections, diagnosis according to CDC criteria [10, 11] and causative pathogens were determined by a researcher (J.B) and an infectious diseases physician (I.G.) who evaluated clinical and laboratory data.

Definitions used

Infection sites were defined according to the CDC definitions for nosocomial infections [10] and the CDC definitions of surgical site infections [11], hereafter named CDC-defined infection sites. Secondary bloodstream infection was defined as a positive blood culture directly related to another infection site [10]. Blood cultures growing positive for coagulase negative staphylococci were considered to be contaminants unless they were isolated out of two or more blood cultures in a two-day period. Suspected or probable infection sites were infections meeting the CDC criteria only because antimicrobial therapy was initiated although supportive data for diagnosis of infection were lacking. Episodes of infection were defined as periods during hospitalisation in which one or more infection sites were diagnosed. Episodes of infection in the ICU were divided in primary and ICU-acquired infections. A primary infection was defined as an infection present at admission to the SICU or developing within the first 48h of the SICU stay. Primary infections could be community acquired or nosocomial. Community acquired infection was defined as an infection present at time of admission to the hospital or developing within 48 hours of the

hospital stay, therefore most likely present or incubating at time of admission. Nosocomially acquired infection was defined as an infection developing after 48 hours of hospital stay, thus most likely not present or incubating at time of admission. An ICU-acquired infection was defined as an infection developing after 48 hours in the ICU, not present or incubating at time of ICU admission. The incidence of episodes of infection was calculated per 100 admissions. The incidence density of episodes of infection or infection sites was calculated per 1000 patient days. Super-infection was defined as a repeat infection episode caused by another pathogen in the same body site.

Septic shock (e.g. sepsis-induced hypotension) was defined as a systolic blood pressure below 90 mmHg persisting for more than 60 minutes and not responding to a fluid challenge of 500 ml per hour or hypotension requiring continuous infusion of vasopressor agents, excluding dopamine infusion less than 5 μg/kg/min [12].

Microorganisms

Microbiological sampling was done only when clinically indicated. Susceptibility was determined with the Vitek susceptibility test (BioMérieux, Marcy l'Etoile, France). MICs were interpreted in three categories: resistant (R), intermediate (I), and susceptible (S) according to standard criteria for specific antimicrobial agents [13-15]. Multiple resistance of Pseudomonas aeruginosa, Acinetobacter spp and Enterobacter spp was defined according to the definition of the American CF Foundation: resistance to all agents in at least two of the following groups of antibiotics: beta-lactams, aminoglycosides, and fluoroquinolones [16].

Antimicrobial drug use was expressed as the number of Defined Daily Doses (DDD) per 100 patient days for systemic antimicrobial agents. DDDs of antimicrobial agents for systemic use listed in the ATC Index of 2002 were used [17]. The number of patient days was obtained by subtracting the number of admissions from the number of days spent in the SICU.

Clinical outcome was assessed per episode of infection and divided into resolution, failure and indeterminate. Resolution was defined as disappearance of all signs and symptoms related to the infection with further antibiotic therapy unnecessary. Failure was defined as death related to the infection or worsening of the signs and symptoms of infection so that antibiotic treatment had to be empirically changed (adding an antimicrobial agent to empirically broaden the spectrum was not considered a failure per se). Indeterminate was reserved for the cases in which the patients succumbed to an underlying disease during antimicrobial treatment. In-unit mortality was assessed per patient.

Statistical Analysis

Continuous data were analysed with the Student's t test. Categorical data were analysed by the Fisher's exact test. Statistical significance was assumed when $p<0.05$.

Results

Demography

In 7 months, 475 patients were admitted to the SICU of which 175 patients (124 M/ 51F) with a mean (± sd) age of 61 (18) years met our criteria and were the subject of this study. Seven patients were admitted twice. Demographics of the 182 admissions are shown in Table 1.

Table 1. Demographics of 182 long-stay admissions to the SICU*

Type of admission#	- elective surgery	94
	- emergency surgery	50
	- medical	38
Transfers	- from home	48
	- from a ward of Erasmus MC	97
	- from another hospital	37 (13 ICU, 24 ward)
ASA score§		3 (1-5)
APACHE II at admission		16 (4-35)
Median length of SICU stay (days)		4 (1-115)
Total patient days		1706

*SICU indicates surgical intensive care unit; APACHE, Acute Physiology And Chronic Health Evaluation; ASA, American Society of Anaesthesiology; long-stay, > 48 hours. Data are median (range) if applicable. #Types of surgery leading to admission were 58% gastro-intestinal surgery 58%, vascular surgery 23 % and trauma procedures 10%. §The ASA distribution was 21 admissions with a score of 1; 60 with 2; 68 with 3; 29 with 4 and 4 with 5.

Episodes of infection

Overall, 79 patients out of 175 had some infection during 84 admissions (46%). These 79 patients developed 104 episodes of infection. Fifty-nine patients had one episode and 20 patients had two episode of infection. This corresponds to an incidence of infection of 104/182 (57%) and an incidence density of 61.0 episodes of infection per 1000 patient days. Septic shock was present in 58% of all episodes of infection.

Primary infection was the reason of admission to the SICU in 22/182 cases (12%). In addition, another 39 admissions were diagnosed with a primary infection on the first day, bringing the total incidence of primary episodes of infection to 61 (33%). Seventy-three percent of the primary infections were nosocomial and 27% were community-acquired. In 43/182 (24%) admissions an ICU-acquired infection developed.

Infection sites

Of 84 admissions with infection, 43 (51%) had only one and 41 (49%) had two or more infection sites in the same infection episode, totalling 155 infection sites and an incidence density of 90.8 infection sites per 1000 patient days. The 61 admissions with a primary infection had 77 infection sites; while the total of ICU-acquired infection sites was 78. One hundred and forty infection sites (90%) could be categorised according to CDC criteria.

Fifteen infection sites (10%) were categorised as probable infections. No causative pathogens were cultured in these cases. The distribution of all infection sites is displayed in Table 2.
Surgical site infections, especially the intra-abdominal sites, dominated the primary spectrum whereas pneumonia was the most frequent ICU-acquired infection site. Blood cultures were taken in 74 of the 104 episodes of infection (71%). Thirty (41%) blood cultures grew positive for one or more pathogens. Primary bloodstream infection (catheter-related) occurred 13 times. The incidence density of catheter related BSI was 7.6 times per 1000 patient days. Secondary bloodstream infection occurred 17 times (incidence density 9.9 times per 1000 patient days); 14 times the source was an abdominal infection, twice an arterial / venous infection and once a respiratory tract infection. The incidence density of UTI was low.

Table 2. Infection sites in the SICU Erasmus MC (n=155)

	Total	**Primary infection**	**ICU-acquired infection**
Pneumonia	56 (32.8)	22 (12.9)	34 (19.9)
SSI#			
- Intra-abdominal	44 (25.8)	31 (18.2)	13 (7.6)
- Mediastinitis	7 (4.1)	4 (2.3)	3 (1.8)
- Vascular	3 (1.8)	1 (0.6)	2 (1.2)
- Other	3 (1.8)	1 (0.6)	2 (1.2)
Secondary BSI*	17 (9.9)	5 (2.9)	12 (7.0)
BSI*	13 (7.6)	5 (2.9)	8 (4.7)
Skin and Soft tissue infection	10 (5.9)	7 (4.1)	3 (1.8)
Urinary tract infection	2 (1.2)	1 (0.6)	1 (0.6)
Total	155 (90.8)	77 (45.1)	78 (45.7)

Between brackets is the incidence density of the infection site per 1000 patient days given.
= Surgical site infection; * = Bloodstream infection; other SSI include pleural empyema and sinusitis

Pathogens
One or more pathogens were cultured in 118 out of the 140 CDC-defined infection sites (84%), totalling 220 pathogens. From 22 CDC-defined infection sites no pathogen was cultured or no cultures were done. In Table 3, the distribution of 220 causative pathogens according to type of infection site is shown. Gram-negative aerobic bacteria represented 50% (111/220) and gram-positive bacteria 28% (61/220) of all pathogens. Overall, 44% of the infection sites were poly-microbial. In primary infection, the predominant gram-negative pathogens cultured were Enterobacteriaceae (n=45) of which 73% consisted of *E.coli*, Klebsiella spp and Proteus spp. In ICU- acquired infections, gram-negatives consisted of Pseudomonas species (n=23) and Enterobacteriaceae (n=27) of which 67% were identified as *Serratia marcescens*, Enterobacter spp and *Citrobacter freundii*. *S.*

aureus and coagulase negative staphylococci accounted for one third of the gram-positive bacteria in primary infection and two thirds in ICU-acquired infection while *E. faecalis* was determined in 75% of the primary and 80% of the ICU-acquired infections. Candida species constituted 9% (20/220) of all isolates; *Candida glabrata* was cultured in 1 out of 8 primary Candida infections and in 6 out of 12 ICU-acquired Candida infections.

A super-infection developed after treatment in 20 infection sites (14%) from which 36 causative pathogens were identified. Again, gram-negative bacteria were the predominant isolates (61%; n=22/36). Enterobacteriaceae were isolated 11 times (Enterobacter spp 3, *Serratia marcescens* 3, *Morganella morgagni* 1, *Citrobacter freundii* 1, *E. coli* 1, Klebsiella spp. 2). Pseudomonadaceae were responsible for one third of the isolates, with Pseudomonas species isolated 8 times and *Stenotrophomonas maltophilia* 2 times. Acinetobacter spp was isolated once. Gram-positive pathogens causing super-infection were coagulase negative staphylococci (5) and *E. faecalis* (4). Four out of five Candida isolates were *Candida albicans*.

Table 3. The causative pathogens* cultured in 140 CDC-defined infection sites

Pathogens	Primary infection sites (n= 77)	ICU-acquired infection sites (n= 78)
Enterobacteriaceae	45	27
• *E.coli*, Klebsiella spp and Proteus spp	33	9
• Other Enterobacteriaceae¶	12	18
Pseudomonas spp	14	23
• *P. aeruginosa*	8	17
• Other Pseudomonas	6	6
Acinetobacter spp	1	4
Staphylococci	11	20
• *S. aureus*	5	10
• Coagulase negative staphylococci	6	10
Enterococcus spp	8	10
• *E.faecalis*	6	8
• *E.faecium*	2	2
Streptococcus spp	11	1
Anaerobes	7	5
Other#	4	9
Candida spp	8	12
• *C.albicans*	7	6
• *C.glabrata*	1	6

* first isolate of a given species for a given infection site ¶ = Other Enterobacteriaceae include Serratia spp., Enterobacter spp. and Citrobacter spp.
# = Other bacteria include Corynebacterium spp., *Moraxella catharralis*, *Haemophilus influenzae*, Leuconostoc spp. and Bacillus spp.

Antimicrobial resistance

Table 4 shows the resistance rates of six specific pathogens cultured in our long-stay SICU population (first isolates per species per infection site). Data are compared to ICU data (first isolates per species and per patient) from French ICUs in 1991 [18], from other European ICUs in 1996 [19], and from the National Nosocomial Infections Surveillance (NNIS) system report from the USA, June 1999 [20].

Two strains of *P.aeruginosa* resistant to all beta-lactams and ciprofloxacine were cultured out of sputum of two patients (=multiple resistance). Those patients were treated with tobramycin. No multiple-resistant Acinetobacter spp or Enterobacter spp were identified in our population. The incidence of methicillin resistant *S. aureus* (n=1/15) and vancomycin resistant enterococci (n=1/18) was low compared to the ICUs in United States hospitals [20].

Antimicrobial drug use

In the long-stay population the median (range) duration of antimicrobial treatment was 6 (1-45) days. Table 5 shows the total antimicrobial drug use in Defined Daily Doses (DDD) per 100 patient days of the total patient population hospitalised in our SICU in 1999. Data are compared to the overall use of antimicrobial agents in our hospital in 1999 and to a survey on antimicrobial drug use in Dutch hospitals in 1996 [21].

The overall use of systemic antimicrobial drugs on our SICU in 1999 was 235 DDD per 100 patient days. This use was three times as high as the overall use in our hospital and five times greater than the mean use in Dutch hospitals in 1996. Most antibacterial drugs were used two to five times more in the ICU compared to the total of the hospital of Erasmus MC. Penicillins accounted for 63% and cephalosporins for only 7%. Flucloxacillin was used as sole antistaphylococcal penicillin, whereas amoxicillin was the first choice to treat infections caused by Enterococcus spp. Amoxicillin-clavulanic acid was mostly used for primary intraabdominal infections and empirical treatment of pneumonia. The exposure of patients to piperacillin/tazobactam and the carbapenems was, respectively, 11-fold and 6-fold that in the hospital overall. Piperacillin/tazobactam and carbapenems were used mainly in the empirical treatment of ICU-acquired infections, nosocomial polymicrobial infections or based on culture results. Aminoglycosides (in combination with a betalactam) were administered in a 7mg/kg dose as empirical treatment of clinical sepsis with hemodynamic instability [22]. Fluoroquinolones (ciprofloxacin) were used as sequential intravenous and enteral regimens for directed therapy of intra-abdominal infections [23]. Vancomycin was used only for the treatment of MRSA, MRSE and penicillin resistant enterococci or in patients who presented anaphylactic reactions to penicillins. Fluconazole was used for treatment of Candida infections. Only in cases of (presumed) azole resistance or when the fungus was determined as *C. glabrata*, was this therapy converted to amphotericin B.

Table 4. Resistance of specific ICU pathogens.

Pathogen	Antimicrobial drug	Erasmus MC Surgical ICU 1999	French ICU 1991 [18]	European ICUs* 1994-95 [19]	NNIS ICUs 1999 [20]
		Resistant isolates / total of isolates (% resistance)			
S.aureus	oxacillin	1/15 (7%)	A	A	476/865 (55%)
CNS¶	oxacillin	14/16 (87%)	A	A	686/789 (87%)
Enterococci	vancomycin	1/18 (6%)	A	A	15/58 (26%)
E.coli	ceftazidime	0/27 (0%)	18/611 (3%)	124 (1-4%)	10/316 (3%)
	ciprofloxacine	4/27 (15%)	18/611 (3%)	124 (1-14%)	A
P.aeruginosa	piperacillin-tazobactam	4/25 (16%)	126/634 (20%)	107 (5-20%)	42/350 (12%)
	ceftazidime	5/25 (20%)	120/634 (19%)	107 (2-16%)	96/480 (20%)
	ciprofloxacin	8/25 (32%)	203/634 (32%)	107 (8-37%)	110/480 (23%)
	tobramycin	0/25 (0%)	228/634 (36%)	A	39/350 (11%)
	imipenem	7/25 (28%)	139/634 (22%)	107 (16-24%)	57/298 (19%)
Enterobacter spp	ceftazidime	5/12 (42%)	38/158 (24%)	56 (26-48%)	A
	ciprofloxacin	0/12 (0%)	A	56 (0-31%)	A
	cotrimoxazole	0/12 (0%)	A	A	A
	imipenem	0/12 (0%)	A	56 (2-3%)	A

*= in this column only the total number of isolates and the range of % resistance in 5 different countries is given.

¶ CNS = coagulase negative staphylococci. A = not reported.

Table 5. Antimicrobial drug use in 3 different hospital settings in the Netherlands (DDD/100 patient days)

Antimicrobial agents for systemic use	Erasmus Medical Center Surgical ICU 1999	Erasmus Medical Center All inpatient areas 1999	54 Dutch hospitals All inpatient areas 1996 [21]
		DDD / 100 patient days	
Antibacterials total	195	61.2	42.5
Flucloxacillin	8.8	4.4	3.3
Amoxicillin	20.5	5.0	7.3
Amoxicillin-clavulanic acid	87.8	21.7	12.5
Piperacillin/tazobactam	5.9	0.5	0.3
Cephalosporins (2nd-3rd)	14.6	4.2	2.5
Carbapenems	10.3	1.7	0.1
Aminoglycosides *	14.0	2.9	1.9
Fluoroquinolones	12.7	8.0	3.3
Vancomycin	3.7	1.1	0.2
Metronidazol	5.7	0.9	1.0
Other antibacterials	10.8	10.8	10.1
Antimycotics total	39.8	7.1	A
Fluconazole	28.2	3.6	A
Amphotericin B	10.2	2.1	A
Other antimycotics	1.4	1.4	A

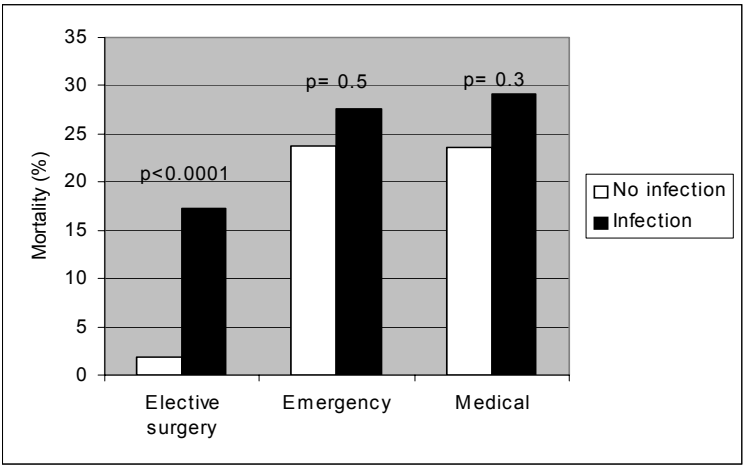
DDD = Defined Daily Doses; A = not reported. * = tobramycin and gentamicin.

Clinical outcome

Overall in-unit mortality was 17% (30/175). Eleven (20/175) percent of the patients died with an infection. In 18 patients, death was infection-related and 2 patients succumbed to an underlying disease during antibiotic treatment (infection-related mortality 60%). An episode of infection was associated with increased mortality. Patients without an episode of infection had a mortality rate of 10.8 %. Patients with episodes of infection either primary or ICU-acquired had a mortality rate of 24.4 % ($P<0.05$).

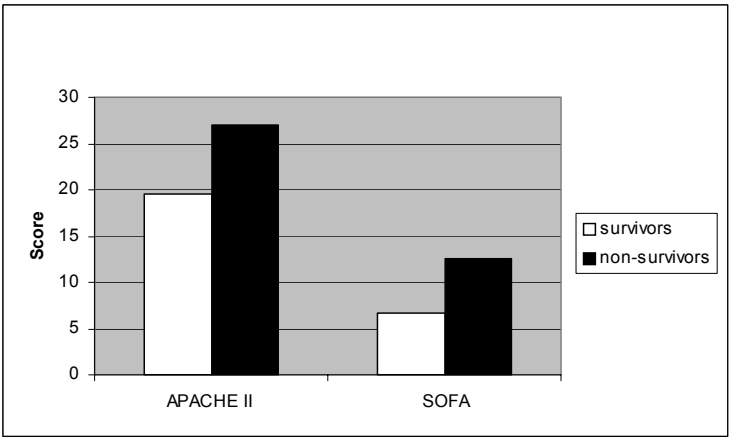
In Figure 1, mortality is plotted against the admission type; a distinction is made between the infected (black bars) and non-infected (white bars) patients. The distribution of ASA and APACHE scores at admission was not significantly different between groups. This figure shows that the impact of infection was significant in patients who were admitted after elective surgery (n=84). In patients admitted after emergency surgery (n=50) and for medical reasons (n=41), the a priori risk on fatality was also high although the contribution of an infection was not significant (at least in these numbers of patients). Elective surgical patients have a high a priori chance on survival, therefore, the impact of an infectious complication was considerable in this group.

Figure 1. Type of admission versus mortality during SICU stay in 175 long-stay patients



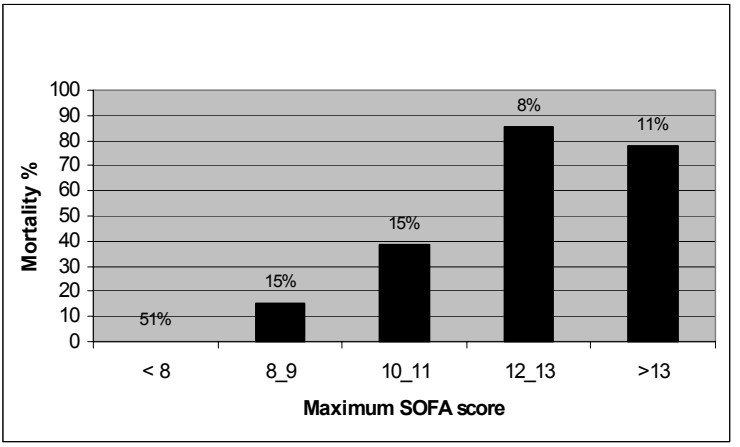
In Figure 2, the impact of systemic response (as expressed by the maximum APACHE score and the SOFA score) on mortality is shown in 79 patients with an infection. Mean maximum APACHE II for survivors (white bars) was 19.5 ± 1.2 and for non-survivors (black bars) 27.0 ± 1.1 ($P < 0.001$). Mean maximum SOFA score for survivors was 7.6 ± 0.7 and non-survivors 12.5 ± 0.8 ($P < 0.001$).

Figure 2. Mortality during SICU stay according to mean maximum APACHE and SOFA scores in 79 long-stay patients with an infection



In Figure 3 the distribution of in-unit mortality broken down by categories of mean maximum SOFA scores is displayed for 79 patients with an infection; 49% of the infected patients had significant organ failure (SOFA scores $\geq$8). Incidence percentages of the different SOFA scores are displayed above the bars. Mortality increased significantly as SOFA scores increased, ranging from 0% for patients with a score of less then 8 to 78% for patients with a score $\geq$12 ($P < 0.001$).

Figure 3. Maximum SOFA versus in-unit mortality in 79 long-stay patients with an infection



The treatment outcome of 84 admissions (79 patients, 104 episodes of infection) was evaluated (Figure 4). Eighty-one out of 104 episodes (78%) were successfully treated; 82% of the primary infections and 72% of the ICU-acquired infections. An episode of infection was associated with a prolonged ICU stay. Admissions without an episode of infection had a mean (±sd) length of stay of 4.1 ± 0.4 days. Admissions with episodes of infection either primary or ICU-acquired had a mean (±sd) length of stay of 17.7 ± 2.2 days ($P < 0.05$).

Causative pathogens with concomitant susceptibility tests were determined in 67 patients, forming 85 of the 104 episodes of infection. Table 6 shows the relationship between the adequacy of the antimicrobial therapy (causative micro-organisms susceptible) and the clinical outcome of the treatment in these 67 patients. Inadequate antimicrobial therapy (at least one of the causative micro-organisms not susceptible) was observed in 28/85 (33%) episodes of infection; treatment failure was seen in 15 of these episodes. Inadequate antimicrobial therapy was associated with a significant increase in treatment failure ($p<0.001$). Eighteen of the 67 patients died of infection, 12 of them had non-susceptible and 6 had susceptible pathogens. Table 6 shows that infections with non-susceptible pathogens were associated with infection-related death ($p<0.01$).

Figure 4. Clinical outcome diagram in 79 long-stay SICU patients with an infection

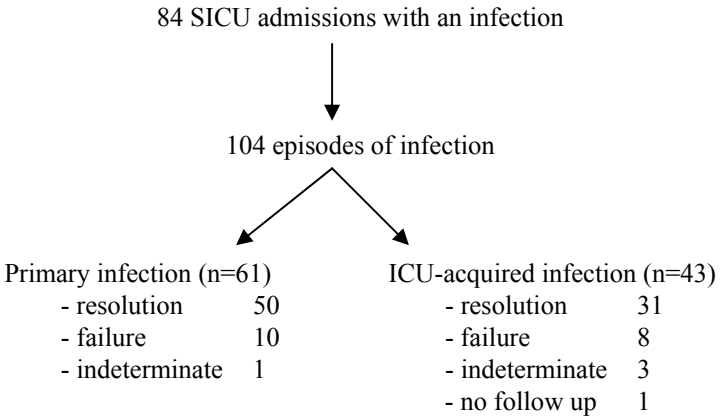


Table 6. Effect of adequacy of antimicrobial therapy (susceptibility of causative pathogen) on outcome of infection in 85 episodes of infection and on mortality in 67 long-stay SICU patients

Clinical outcome	Causative pathogen susceptible	Causative pathogen not susceptible
Treatment failure	3/57 (5%)	12/28 (43%)
Infection related deaths	6/42 (14%)	12/25 (48%)

Discussion

More than half (57%) of our long-stay (>48 hours) surgical ICU admissions were diagnosed with an infection at some time during their SICU stay. In 33%, a primary infection was present at or on the day of admission whereas, in 24% of admissions, the infection was acquired during SICU stay. Alberti et al. reported an incidence of primary infections varying between of 18.2-47.7% and ICU acquired infections varying between 11.2-20.7% in patients staying >24 h in surgical ICUs across Europe with the highest incidence in medical and emergency surgery patients [24]. In our selected patient group, the incidence density of infection, overall, was 61 episodes per 1000 patient day. Mintjes-de Groot et al. reported an incidence density of 42 episodes per 1000 patients in a surveillance study in patients staying ≥48 h on 16 Dutch ICUs [25]. In SICUs, Price et al. reported an incidence density of infection of 11.5 episodes in all patients admitted to their 20-bed SICU during a 34 days period [26]. Kollef et al found an incidence density of 47.2 episodes per 1000 patient days in all patients admitted to a cardiac SICU [27]. Therefore, depending on the type of ICU (medical, surgical, pediatric or mixed), the population studied (all admissions versus a selected group) and the type of surveillance (prospective or retrospective), the incidence density of infection reported in the literature varies between 10.6-57.1 episodes per 1000 patient days [28]. Our high incidence density of 61 per 1000 patient days can be explained by the fact that we selected long-stay patients (≥ 48 h), who were followed prospectively and the high proportion of admissions after emergency surgery and medical admissions (27% and 21% respectively).

Overall, 90% of the infection sites were CDC defined infection sites. Compared to the 61 admissions with a primary infection, the 43 admissions with an ICU-acquired infection had more often multiple infection sites. The occurrence of multiple infection sites is considered an independent risk factor of mortality [29] since every infection adds to the duration of stay which, in turn, increases the risk of acquiring another infection. The majority of primary infections in our SICU were localised in the abdominal cavity (40%), whereas ICU-acquired infections were more often pulmonary (43%). The bloodstream was involved in 13% of the primary infection sites and in 26% of the ICU-acquired infection sites. These figures are in concordance with other surveillance studies [2, 24, 30]. Overall, only 41% of all blood cultures were positive for one or more pathogens; in 56% this was secondary to another infection site. The focus of secondary sepsis was abdominal in most cases. The other 44% bloodstream infections were primary (catheter-related). Our incidence density of 7.6 BSI per 1000 patient days is comparable with data from other ICUs [28]. In contrast with other studies [28, 31, 32], our incidence density of urinary tract infections was low (1.2 UTI per 1000 patient days). On an ICU, catheter-related bacteriuria is often present however, due to permanent drainage, symptomatic infection develops in only 25% of the cases [25].

Causative pathogens were isolated from 84% of the CDC-defined infection sites. Although the proportion of gram negatives and gram-positives was approximately the same in primary and ICU-acquired infections, the strains of Enterobacteriaceae and gram-positive

micro-organisms identified were different. In primary infections, three-quarters of the gram-negative pathogens reflected normal predominant endogenous flora (*E. coli*, Klebsiella and Proteus spp) whereas, in ICU-acquired infections, the majority of gram-negative pathogens were selected Enterobacteriaceae or Pseudomonas spp. Among gram-positive pathogens, staphylococci rather than streptococci were present in ICU-acquired infections. *E.faecalis* was the predominant Enterococcus. In contrast with large surveillance studies, we did not record as many CNS infections [2, 24, 33]. This lower incidence could not be explained by a lower incidence density of catheter related bloodstream infection since this was comparable with other data [28]. In our opinion, these staphylocci are often contaminants rather than pathogens such as superficial surgical site infections or blood contaminated with CNS. By determining the causative pathogens per infection site by two of the researchers, we could make a clear distinction between infection and contamination thereby reducing the overestimation of CNS infections. Fungi were identified in 9% of all isolates and involved in one quarter of all super-infections. Comparable incidences have been reported [2, 24, 28]. However, one-third of all Candida isolates were *Candida glabrata*, a species resistant to fluconazole. In our SICU population, the use of broad-spectrum antibiotics, intra-vascular and intra-peritoneal catheters and the abundant use of fluconazole are all risk factors for selection of these strains [34].

Antimicrobial prescribing policies may play a very important role in the epidemiology of infections in the SICU [35]. Our hospital has a restrictive antimicrobial policy and severe infections are monitored by infectious diseases consultants. The total use of antibacterial agents on our SICU in 1999 was three times as high as the overall use in our hospital and five times greater than that reported in other Dutch hospitals in 1996 [21]. However, only 4 out of 54 hospitals in the report by Janknegt et al. were university hospitals such as ours (university, tertiary, referral). The use of most antibiotic classes in the SICU was approximately four to sevenfold higher compared to the overall use in the Erasmus MC. However, benchmarking antibiotic use among ICUs is only possible if a standardised measurement unit is used and if comparable ICU populations are studied. The DDD/100 patient days has been chosen by the WHO Drug Utilization Research Group to compare inpatient use on all levels [17]. Sleimann-Petersen et al. analysed the antimicrobial drug consumption in 30 Danish ICUs using this measurement unit [6]. They recorded a median value of 124 DDD/100 patient days (range 49-264). In Sweden, a mean use of antimicrobials in 8 ICUs approximated 125 DDD/100 patient days [36]. Compared to the data of these Scandinavian ICUs, the consumption of 195 DDD/100 patient days in our SICU population could be considered as moderately high. However, Scandinavian countries also consume the least antibiotics [37]. Compared to other countries, the SICU consumption reported here is relatively low due to restrictive Dutch prescribing patterns[37]. Lemmen et al. reported a decline in antimicrobial use in a German neurosurgical ICU from 346 to 210 DDD/100 patient days after implementation of an infectious diseases consultant [38]. Antimicrobial use in ICUs in the United States was reported recently by Fridkin et al [20]. Unfortunately, the reported data are not entirely comparable with this study since the authors defined their own DDD. In future studies, a

standardised unit of measurement should be employed to compare antimicrobial use among different ICUs and the impact of antimicrobial drug control policies on rates of antimicrobial resistance [39].

Antimicrobial use is the most important factor in the development of antimicrobial resistance [40, 41]. Previous exposure to antimicrobials may favour the emergence of (multi-) resistant pathogens by two mechanisms. Firstly, antimicrobials modify the endogenous flora leading to colonisation with resistant pathogens. Secondly, antibiotics may select or induce beta-lactamase producing gram-negative bacilli such as *P.aeruginosa*, Enterobacter spp, Serratia spp en Acinetobacter spp. There was a considerable consumption of antimicrobial drugs (and therefore selection pressure) on our SICU. Three-quarters of the primary infections were nosocomial and many patients were hospitalised before undergoing major elective surgery, were admitted from hospital wards or were referred from another hospital with a complication after surgery. These patients might have been colonised, therefore, with selected nosocomial micro-organisms.
Compared to data from other European hospitals, the percentages of resistant gram-negative bacteria were comparable to rates in the higher range of ICUs in Europe (Sweden) [18, 19]. The resistance rates of *P. aeruginosa* were comparable for piperacillin-tazobactam, ciprofloxacin and imipenem, but lower for ceftazidime and tobramycin. Eight percent (n=2/25) of the *P.aeruginosa* strains were multi-resistant. No multi-resistant Acinetobacter spp or Enterobacter spp were identified in our population. The incidence of MRSA and VRE was low compared to the ICUs in United States hospitals [20] and some other European countries. In Europe, the prevalence of MRSA varies according to geographical location with percentages of up to 80% in Southern European countries [5, 42].
A number of studies have evaluated the impact of antimicrobial resistance on morbidity, mortality and costs [43]. Compared to data from the USA, the percentages of VRE and MRSA were much lower in our ICU [20]. MRSA and VRE infections can lead to excess length of stay and increased cost of care [42, 44]. In critically ill patients, MRSA bacteremia has a higher attributable mortality than MSSA bacteremia [45] and patients with SSI caused by MRSA had a greater 90-day mortality rate than patients with SSI caused by MSSA [46]. Infection with resistant Gram-negative bacteria is known to have an adverse impact on outcome with excessive mortality being seen in patient groups infected with Acinetobacter spp and *P. aeruginosa* [47, 48].

Overall, 78% of all episodes of infection resolved clinically; 82% of the primary infections and 72% of the ICU-acquired infections. This is comparable with data from others [49, 50]. Two-thirds of the non-survivors died with an infection and, in 60%, death was considered infection related.
Inadequate antimicrobial therapy was associated with a significant increase in treatment failure and infection- related death. This has been previously described in the literature and applies to a wide variety of ICU patients [51, 52]. In 33% of the episodes of infection in our study, at least one of the causative pathogens was not susceptible to the antimicrobial

therapy; this was associated with clinical failure in half of these cases. Knowledge of the predominant causative pathogens and up-to-date unit-specific resistance patterns will increase the likelihood of choosing an effective empiric regimen [39]. As soon as the clinical situation and culture data allow, streamlining to a narrow spectrum of antibiotics is advised. However, microbiological information is often lacking in the clinical situation. Microbiological data were present in 84% of the CDC defined infection sites in our study. Alberti et al. reported microbiological documentation in only 63% of all infections [24]. Furthermore, during therapy the accessibility of infection sites often disappears making it impossible to obtain follow up culture data. This lack of information hampers the selection of the right antimicrobial agent.

Early survival in the SICU depends on different factors. First, the patients' co-morbidity determines the a priori risk on mortality after major surgery. The ASA scoring system has proven to estimate the a priori risk on mortality adequately [7, 53]. The worse the preoperative condition the higher the risk on postoperative complications and fatal outcome. A knowledge of risk factors can lead to optimisation of the patients' preoperative condition which can reduce per-operative morbidity and mortality [54]. Also, the type of admission has an effect on survival. Emergency surgical and medical admissions have higher fatality rates compared to patients admitted after scheduled surgery [29, 31, 32] because the underlying disease itself is life threatening. Furthermore, the development of postoperative (infectious) complications and their impact on the host is a major factor. An infection triggers an immune response in every host but the impact of the response is not uniform. However, the extent of the immune response does determine outcome [29, 31]. In our data, the severity of the systemic response, quantified by the APACHE score and the extent of organ failure expressed by the SOFA score, were significantly associated with mortality. Finally, the success of treating these infectious complications and the organ failure they provoke also influence survival.

Insights into the susceptibility patterns of pathogens, antimicrobial utilization and treatment outcome on a local level are necessary to periodically evaluate the quality of care. One of the limitations of this study was that the study population was surgical, long-stay and the number of patients was relatively limited. The data were, therefore, not entirely representative for other types of ICUs. Other limitations were the availability of data on antibiotic use at the ward level rather than at the patient level and the fact that infections were documented only by microbiological data collected in routine patient care. Despite these limitations, the concurrent approach of clinical data collection, the in depth approach of standardising the diagnoses of infection and differentiating relevant causative pathogens from colonising micro-organisms by the researcher with the help of an expert in infectious diseases contributed to the quality of the observational data presented. Finally, the use of standardised measurement units of antimicrobial use allow for international comparison of antimicrobial drug use in ICUs.

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CHAPTER 4

AN INSIDIOUS CASE OF STREPTOCOCCAL SOFT TISSUE INFECTION

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Introduction

Streptococcus pyogenes produces a pyrogenic toxin that is responsible for a wide variety of infectious diseases including scarlet fever, rheumatic fever, and soft tissue infections. During the past decade its pathogenicity and virulence have increased [1, 2] causing a syndrome of severe soft tissue infections and pronounced systemic toxicity. This streptococcal toxic shock syndrome is associated with a mortality of roughly 30%. Because of the dramatic course of the syndrome, early recognition followed by radical operative debridement and antimicrobial treatment are essential [3, 4].

We describe a case that illustrates the insidious character of the streptococcal toxic shock syndrome, and plead for vigilance in the diagnosis of *S. pyogenes* soft tissue infection.

Case report

A 65-year old vicar was referred to our clinic for evaluation of cellulitis of the left shoulder. He had been in good health until a week before, when he developed redness and pain in the left shoulder after an episode of sore throat, fever and chills, which were treated by his general practioner with non-steroidal anti-inflammatory drugs (NSAID).

Shortly after admission he became hypotensive and disorientated. Core temperature was 39.3§C, pulse rate 130 bpm and he needed mechanical ventilation to achieve adequate oxygenation (PaO2 = 10.1 kPa and FiO2 = 100%). He had a leucopenia (1,0 x 109/L) with a rise of 20 % in immature bands and thrombocytopenia (73 x 109/L), as well as oliguria (15 ml/hour) despite adequate fluid challenge and metabolic acidosis (plasma lactate = 12.9 mmol/L). Vasopressor drugs were needed to sustain cardiovascular function. His APACHE II score on admission to the intensive care unit (ICU) was 30.

The skin of the left neck, shoulder, and trunk was diffusely swollen, erythematous, and warm. There was necrotic epidermolysis with bullae formation on the left arm (Figure 1). The left hand was oedematous and cyanotic. No pulse was palpable in the left radial artery.

Gram stain of the bullous fluid showed gram-positive cocci in chains. Antibiotics including ceftriaxone 4 g twice a day and penicillin G 2 x 106 IU three times a day were given intravenously. Fasciotomy of the affected areas showed no necrotic fascia, only regions of swollen subcutaneous tissue. The surgeon therefore refrained from debridement.

When cultures of throat, blood, urine, operatively biopsied soft tissue, and fluid from the bullae grew *S. pyogenes* sensitive to clindamycin and penicillin ceftriaxone was replaced with clindamycin 400 mg four times a day intravenously. This drug is known for its excellent tissue penetration, but the patient's condition deteriorated during the next few days. Dependence on vasopressor drugs increased and the skin lesions progressed to necrotic epidermolysis of both upper extremities and necrosis of several phalanges (Figure 2). As there was still no clinical evidence of deep soft tissue infection, only superficial necrotomy was done. Multiorgan dysfunction developed rapidly, including acute respiratory distress syndrome, liver dysfunction, primary peritonitis with *Enterococcus faecium*, coagulopathy, and renal dysfunction that required continuous arteriovenous hemodialysis.

He was resuscitated several times before he died of multiorgan failure, 10 days after admission to hospital.
The necropsy report mentioned overwhelming pneumonia, culture from the bronchial secretions growing *Pseudomonas aeruginosa*, ischaemic hepatitis, splenic infarction, massive acute tubular necrosis of both kidneys and complete necrosis of all fingers and toes. Parts of the ileum and colon were necrotic and ischaemic. Gram- positive cocci, later identified as *S. pyogenes*, were found in large areas of skin where suppurative panniculitis was diagnosed.

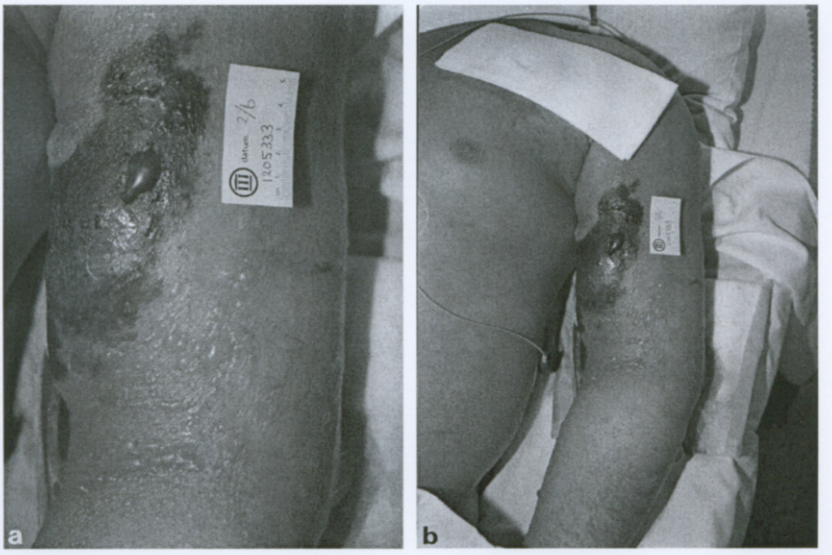

Fig. 1. (*a*) and (*b*) The diffusely swollen and erythematous skin of the neck, shoulder, and trunk with necrotic epidermolysis and bullae formation.

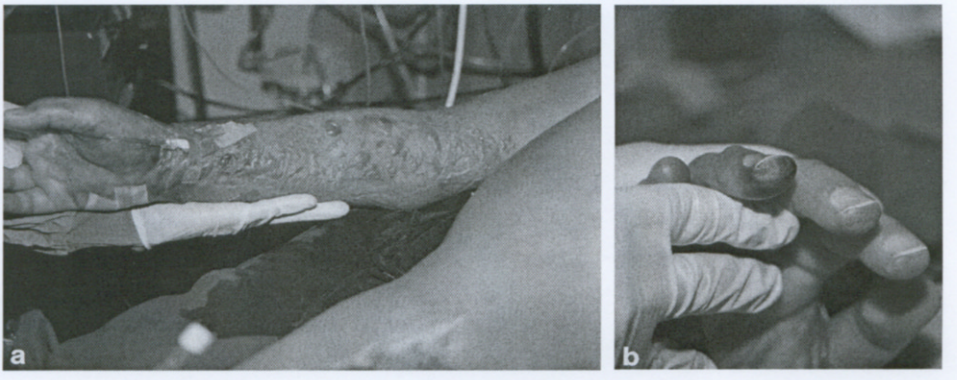

Fig. 2. (*a*) and (*b*) Profound necrotic epidermolysis with phalangeal necrosis.

Discussion

Streptoccal soft tissue infections can occur at dermal, fascial, or muscle level and the essential question is whether prompt surgical intervention is necessary in addition to antimicrobial drugs. Treatment guidelines are based on the anatomical level and the presence or absence of necrosis: superficial soft tissue infections without necrosis are treated with antibiotics alone, and operation is needed if there is deep infection (fasciitis or myositis) or necrosis at any level [5]. *S. pyogenes* soft tissue infections are notorious for their profound systemic toxicity. The pathophysiological mechanism is not yet fully elucidated but thought to be complex. Group A streptococci produce a large number of extracellular products including streptolysins, streptokinase and pyrogenic exotoxins. These exotoxins damage host tissue, promote the spread of infection, and may initiate the complex cascade that leads to septicaemia and the multiorgan dysfunction syndrome [6, 7]. Additionally, bacteraemia itself may result in activation of the complement cascade, disseminated intravascular coagulopathy, and shock mediated by active endogenous mediators. General features of this streptococcal toxic shock syndrome include fever, hypotension, rashes, desquamation, and multiorgan system dysfunction [6, 8]. The mortality is 30%, with most deaths secondary to shock and respiratory failure.

Because of the rapidly progressive and lethal course of the syndrome, early recognition and aggressive treatment are essential. Unfortunately, insidiously mild signs of soft tissue infection can hamper medical decision-making.

In the case described, inspection and exploration of the affected areas showed only cellulitis characterised by superficial necrosis, epidermolysis, and swollen subcutaneous tissue. Because treatment guidelines recommend antibiotic treatment without operation when lesions are superficial, we refrained from aggressive debridement. This proved to be fatal. As we learned from the necropsy report, large areas of subcutaneous tissue were infiltrated with *S. pyogenes*. When a bacterial inoculum is continuously producing such large quantities of exotoxin, antibiotic treatment alone is insufficient.

In summary, when a streptococcal soft tissue infection is associated with fulminant septicaemia, extensive surgical debridement or even amputation is essential to terminate toxin production, even when lesions are superficial.

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CHAPTER 5

PHARMACOKINETICS OF CEFTAZIDIME IN SERUM AND PERITONEAL EXUDATE DURING CONTINUOUS AND INTERMITTENT INFUSION IN PATIENTS WITH SEVERE INTRA-ABDOMINAL INFECTIONS

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Abstract
Background: Ceftazidime demonstrates time-dependent killing, which is maximal at 4 or 5 times the MIC for the organism and continuous infusion (CI) has been proposed to ensure adequate ceftazidime concentrations for the entire course of therapy. Severe intra-abdominal infections (IAI) are infections in which (repeated) surgical or percutaneous drainage is required for management and ceftazidime is frequently used in their treatment. Cardiovascular and metabolic changes, renal and liver dysfunction alter drug pharmacokinetics during critical illness. No data exist on concentrations of ceftazidime reached in the peritoneal fluid in patients with severe IAI.
Objectives: 1) To determine the pharmacokinetics of ceftazidime in serum during continuous and intermittent infusion in patients with severe IAI. 2) To determine the concentrations of ceftazidime reached in the peritoneal exudate.
Methods: 18 surgical patients with severe IAI and a calculated creatinine clearance of > 30 ml/min were studied. A non-randomised pilot study of 6 patients treated with continuous infusion alone was followed by a prospective, randomised comparative study of 12 patients. Pilot study patients received ceftazidime 1 g iv followed by a 4.5 g continuous infusion over 24 h. Randomised patients received either ceftazidime continuously as above or 1,5 g tds. Samples for pharmacokinetic analyses were collected on day 2 and 4. Ceftazidime concentrations were determined by HPLC.
Main results: Continuous infusion resulted in a mean concentration in serum above 40 mg/L and a time above 4 x MIC of most pathogens encountered in severe IAI for >90% of the course of therapy in serum and peritoneal exsudate. Eight-hourly administration resulted in time above 4 x MIC of most pathogens encountered in severe IAI for >90% of the dosing interval, but in peritoneal exudate only for 44% of the dosing interval. During continuous infusion, AUCs in the peritoneal exudate were approximately 60% of the concomitant serum AUCs.
Conclusions: In critically ill surgical patients with severe intra-abdominal infections, continuous infusion of ceftazidime resulted in more favourable concentrations in serum and peritoneal exudate than eight-hourly bolus infusion.

Introduction
Despite increased understanding of the pathophysiological principles, improved surgical techniques, the use of broad spectrum antimicrobial agents and advances in life support facilities, severe intra-abdominal infections (IAI) continue to have mortality rates between 30% and 76% which are dependent on a number of factors [1]. These include the magnitude of the systemic immune response, age, malnutrition, immune suppression, pre-existing disease, the source and extent of infection, delay to operation and the virulence of the causative pathogens. Therefore, treatment must be optimised to improve outcome.
IAI are almost always polymicrobial and contain a mixture of Gram-negative enteric bacteria, as well as obligate anaerobic bacilli. The antimicrobial treatment should cover these micro-organisms [2]. During the course of treatment antimicrobial selection pressure may change the spectrum of isolates to more resistant Enterobacteriaceae and *Pseudomonas*

aeruginosa [3]. Ceftazidime is a β-lactam with activity against this selected Gram-negative flora.

From a pharmacodynamic point of view, continuous infusion may be preferable to intermittent dosing. The bactericidal activity of ceftazidime depends on the time that the concentration is above the minimal inhibitory concentration (MIC) of the causative pathogen [4, 5] and maximal killing is achieved at concentrations of 4 or 5 times the MIC [6]. Furthermore, ceftazidime does not possess a post-antibiotic effect against Gram-negative bacilli [5]. Continuous infusion has the advantage of avoiding the unnecessarily high peak and sub-MIC trough concentrations found with intermittent dosing [7, 8]. From a pharmacokinetic point of view the advantages are less clear. A faster total body clearance after continuous infusion of piperacillin at high doses has been described [9]. Furthermore, the drug concentration profiles in the peritoneal cavity after either method of administration have never been compared.

Cardiovascular and metabolic changes as well as renal and liver dysfunction can markedly alter the pharmacokinetics of ceftazidime during critical illness [10-12]. To our knowledge, the pharmacokinetics of ceftazidime in serum of critically ill patients with severe IAI has not been documented, nor have concentrations in peritoneal exudate been measured.

Materials and methods

The study protocol met the standards of the hospital's medical ethical committee. Informed consent was obtained from the patient or a first degree relative (parents, partner or children).

Patient population

Patients who were admitted to the Surgical Intensive Care Unit of University Hospital Rotterdam between January 1997 and May 1998 and who met the following criteria were eligible for enrolment in the study: 1) over 18 2) severe IAI defined as an IAI accompanied by a systemic inflammatory response, necessitating repeated laparotomies, open abdominal treatment or percutaneous drainage and intensive care support; 3) suspected or proven Gram-negative infection.

Exclusion criteria were: 1) known allergy to ceftazidime; 2) creatinine clearance < 30 mL/min and/or urinary output < 10 mL/h over the preceding 12 h and/or hemofiltration or dialysis; 3) severe granulocytopenia defined as <500 PMN/μL; 4) APACHE II score ≥ 30; 5) use of selective decontamination of the digestive tract; 6) causative pathogens resistant to ceftazidime.

All patients were classified according to the Acute Physiology and Chronic Health Evaluation (APACHE II) score [13]. Use of concomitant drugs and the causative pathogens and their MIC of ceftazidime were documented.

The following parameters were assessed: demography data including age, sex, weight and cause of the IAI; the number of surgical interventions and the amount of rinse fluid used in case of postoperative continuous lavage (i.e. maximum of 2L 0.9% NaCl/24 h). Serum creatinine, alanineaminotransferase (ALAT), aspartateaminotransferase (ASAT), bilirubin, albumin, platelets and neutrophils were assessed daily. Creatinine clearance was estimated

from the serum creatinine concentration using the Cockroft-Gault equation [14]. Adverse events were documented during the treatment period.

Study design

The study consisted of two parts:

The first part was a prospective, non-randomised, non-comparative pilot study in which 6 patients received ceftazidime as a 1 g iv loading dose followed by a 4.5 g iv continuous infusion. This regimen was based on an apparent Vd of 300 mL/kg and a target concentration in serum of at least 40 mg/L. The second part was a prospective, randomised, comparative study in which 12 patients were randomised to receive either ceftazidime 1 g iv (loading dose) followed by a 4.5 g iv continuous infusion or as a 1.5 g iv bolus tds. Treatment was continued for up to 10 days.

Ceftazidime administration and dosage modulation

Normal renal function: for the continuous infusion, ceftazidime (GlaxoWellcome, The Netherlands) was diluted in 250 mL 0.9% NaCl and infused with an electronic pump (Ivac Medical System, Hampshire, England). The loading dose and the intermittent bolus infusions were prepared according to the manufacturer's guidelines and infused over 20 min using an electronic pump.

If calculated creatinine clearance was between 49 and 30 mL/min, the total daily dose was reduced to 2 g. If creatinine clearance dropped below 29mL/min during the study period, the total daily dose was reduced to 1 g.

Pharmacokinetics

Blood, peritoneal exudate and urine samples for the determination of ceftazidime concentrations were drawn at day 2 and 4. Peritoneal exudate cultures were taken prior to start of therapy and repeated on indication. MICs of ceftazidime were determined by Etest^{R} (AB Biodisc, Solna, Sweden).

Blood samples were taken from the non-infusion arm at the following intervals: during CI samples were drawn twice daily at intervals ranging from 8 to 12 h; during intermittent therapy, samples were drawn pre (t=0) and at 20 min, 1h, 2h, 4h and 8h after the start of the infusion. After sampling, blood was allowed to clot on ice for 20 min and centrifuged at 1500G for 10min. The separated serum was stored at -70°C until analysis.

Peritoneal exudate samples were drawn from drainage catheters. During CI, samples were drawn at the same time as blood samples; after intermittent therapy samples were taken 1h and 8h after the start of the infusion. The total amount of peritoneal fluid drained was collected and a sample was taken for ceftazidime assay. Exsudate was stored at -70°C until analysis.

Urine was collected over 24 hours. The volume was measured and a sample was taken for ceftazidime assay and stored at -70°C until analysis.

Ceftazidime concentrations were determined by using high performance liquid chromatography (HPLC) [15]. The lower limit was 0.4 mg/L in both serum and exudate and the method was linear up to 250 mg/L.

The primary descriptive parameters were area under the concentration curve (AUC0-24h), the serum elimination half-life (T½β), the volume of distribution at steady state (Vdss), the total body clearance (CL) and concentrations in serum and exudate reached.

In the CI group, the AUC0-24h in serum and exudate was calculated by multiplying the mean concentration times 24 and the CL was calculated by dividing the infusion rate through the mean concentration over 24h. In the intermittent therapy group, the AUC0-24h, T½β and Vdss in serum were estimated with the MWpharm program (Mediware, Groningen, The Netherlands) using a two compartment model. The AUC was calculated using the trapezoidal rule (AUC0-24h). The CL was calculated using a non-compartmental equation (Clearance = Dosis / AUC (L/h)). The AUC0-24h in exudate was estimated by multiplying the mean concentration over 8 h times 24.
The AUCexudate/AUCserum ratio was calculated in patients with both sample ports available. Time above the minimal inhibitory concentration (T>MIC) was estimated from the individual curves. The peritoneal clearance of ceftazidime was calculated by dividing the concentration of ceftazidime measured in the collected drain fluid through the total amount of ceftazidime infused in the same time period.

Statistical analysis

The Mann-Whitney test and the Fisher's exact test or were used as appropriate to determine differences between the groups; a p-value <0.05 (two-tailed) was considered statistically significant. Correlation of ceftazidime clearance with creatinine clearance was determined by using the Spearman correlation statistic. Patients were eligible for analysis if they had completed day 2 of the treatment period.

Results

Eighteen patients were enrolled of whom twelve received continuous and six intermittent ceftazidime as part of an antimicrobial drug regimen. There were no statistical differences between the 6 CI patients of the pilot study and the 6 CI patients of the randomised study, therefore their data was pooled. In the CI group, 8 patients received 4.5 g/24h; 1 patient received 2 g/24h and 3 patients switched from 4.5 to 2 g/24h during treatment. In the intermittent therapy group 5 patients received 1.5 g tds and 1 patient switched from 1.5 g tds to 1 g bd during treatment. Patients were treated concomitantly with other antibiotics directed against pathogens not susceptible to ceftazidime.

Demographics: The demographic characteristics of the study patients are summarised in Table 1. The groups were comparable as regards to age, APACHE score and creatinine clearance. Severity of illness was reflected in a mean APACHE II score of 15 (= predicted mortality 24%) and an overall mortality on the ICU of 28%. The mean duration of treatment was 5 days.

Table 1. Demographics (n=18)

	Continuous (n=12)	Intermittent (n=6)	P
Age (yr)	62 (46-76)	64 (42-87)	
Male / female	7 / 5	4 / 2	
APACHE II	16 (10-23)	14 (7-19	0.3
Cause of peritonitis			
- postoperative leakage	n=6	n=3	
- pancreatitis	n=1	n=2	
- gastrointestinal perforation	n=5	n=1	
Open abdomen technique	n=5	n=3	
Number of operations per patient (range)	1-10	2-5	
Overall mortality (on ICU)	25%	33%	1.0
Creatinine clearance at inclusion (ml/min)	93 (36-215)	106 (59-160)	0.6

If applicable, data are means (range)

Pharmacokinetics in serum: Serum concentrations were measured in 12 patients after CI and in 6 patients after intermittent therapy. The fitted curves for mean concentrations in serum versus time of both regimens are shown in Figure I. The pharmacokinetic data on day 2 and 4 are shown in Table 2; only the randomised patients were statistically compared. The total body clearance, and subsequently the AUC0→24h, did not differ between groups. The mean steady state concentration in serum after CI was >40mg/L. The lowest serum concentration during CI was 21.1 mg/L and the lowest trough concentration was 5.6 mg/L during intermittent therapy. The serum elimination half-life ranged widely. The volume of distribution approached the extracellular volume. Correlation between the creatinine clearance and the total body clearance was 0.8 ($R^2 = 0.64$).

Pharmacokinetics in peritoneal exudate: Concentrations reached in peritoneal exudate were measured in 9 patients after CI and in 4 patients after BI. In 3 patients the planned relaparotomie was cancelled; in 2 patients the intra-abdominal drains were removed before sample day 2. The fitted curves for mean concentrations in peritoneal exudate versus time of both regimens are shown in Figure II.

Table 2 illustrates that, in peritoneal exudate, the calculated AUCs were higher in the CI group; on sample day 2 this difference was statistically significant. The mean AUCexudate/AUCserum ratio varied between 56-64% during CI and 33-35% during intermittent therapy. This difference did not reach statistical significance. The lowest concentration in the peritoneal exudate during CI was 5.5 mg/L and the lowest trough concentration was 1 mg/L during intermittent therapy. Peritoneal clearance was low.

Overall, fifty-seven percent of a dose was found unchanged in urine after 24 h.

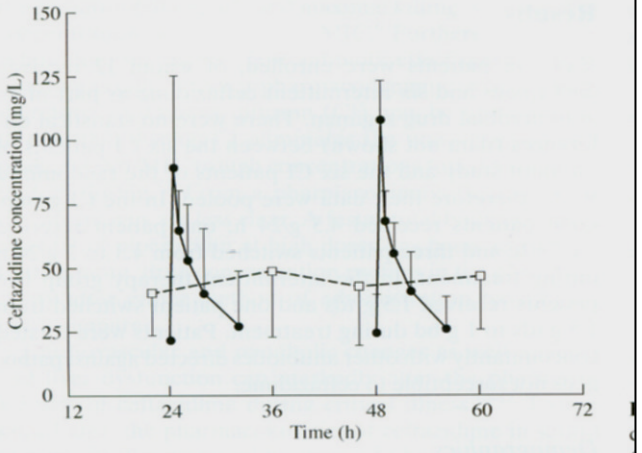

Figure 1. Concentration of ceftazidime in serum after continuous (n = 12; □) and intermittent (n = 6; ●) administration (mean ± S.D.).

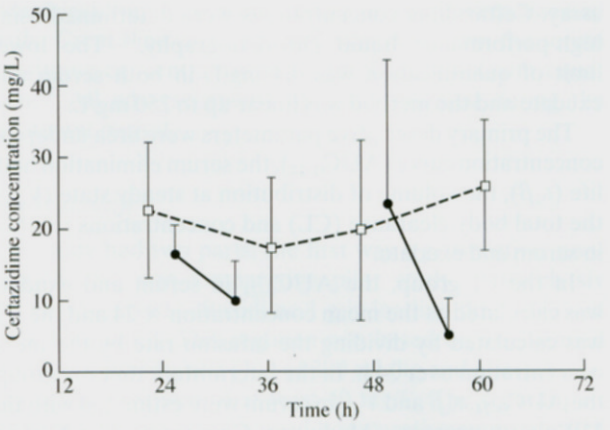

Figure 2. Concentration of ceftazidime in exudate after continuous (n = 9; □) and intermittent administration (n = 4; ●) (mean ± S.D.).

Table 2. Pharmacokinetic parameters of ceftazidime in serum and peritoneal exudates

PK parameter	Day 2			Day 4		
	CI (n=12)	**IB (n=6)**	**P***	**CI (n=12)**	**IB (n=6)**	**P**
Serum						
AUC0→24h (mg.h/L)	1131 (505-2230)	1064 (505-1950)	0.5	1098 (581-2233)	1166 (644-1496)	0.6
Cmean (mg/L)	47.1 (21.1-92.9)			45.1 (24.2-93.1)		
Cmax (mg/L)		88.7 (58.3-124.8)			104.4 (94.6-127.8)	
Ctrough (mg/L)		19.4 (5.6-68.4)			23.7 (7.1-41.3)	
Vdss (L/kg)		0.279 (0.146-0.443)			0.240 (153-339)	
T½β (h)		4.2 (1.3-12.3)			3.0 (1.3-3.9)	
CL (L/h)	4.1 (1.4-8.9)	5.1 (2.3-8.9)	0.2	4.2 (1.6-7.7)	4.0 (2.0-7.0)	0.3
Renal excretion (%)	59 (18-127)	51 (23-81)	0.5	59 (18-102)	69 (39-74)	0.5
	CI (n=9)	**IB (n=4)**	**P**	**CI (n=9)**	**IB (n=4)**	**P**
Exudate						
AUC0→24h (mg.h/L)	522 (132-838)	316 (204-445)	0.01	637 (420-940)	346 (73-728)	0.1
Cmean (mg/L)	21.7 (5.5-34.9)			26.6 (17.5-39.2)		
C1h (mg/L)		15.9 (10.3-20.0)			24.7 (5.4-52.2)	
C8h (mg/L)		11.2 (5.2-17.1)			6.8 (1.0-10.8)	
Clearance by drainage (%)	1.2 (0.6-1.5)	1800 (100-2800)	0.8	1600 (100-4900)	1600 (200-3800)	0.6
AUCexsudate/AUCserum (%)	56 (19-112)	35 (19-45)	0.09	64 (27-94)	33 (5-61)	0.15

Data are means (range). * Statistically only the randomised patients are compared.

Pathogens: In Table 3 the cultured pathogens relevant to the study and their MIC of ceftazidime are displayed. In 18 patients, 26 ceftazidime susceptible Gram-negative pathogens were cultured. In one patient an intermediately susceptible (MIC ≥ 16/mg/L) *Enterobacter cloacae* was cultured for which the antibiotic regimen was adjusted. Non susceptible pathogens including anaerobes, coagulase negative staphylococci, enterococci and candida species were concomitantly treated with specific antimicrobial drugs.

Table 3. Pathogens cultured from the peritoneal exsudate and their MIC

Pathogen	n (%)	MIC[#]
Escherichia coli	11(42)	0.25 (0.125-2)
Pseudomonas aeruginosa	9 (34)	2 (2-4)
Klebsiella oxytoca	2 (8)	0.19-0.25
Proteus mirabilis	2 (8)	0.125
Stenotrophomonas maltophilia	1 (4)	1.5
Citrobacter species	1 (4)	0.5

= mean (range) if applicable

Table 4 shows that the minimum concentrations in serum exceeded 4 times the actual MICs for 100% of the dosage interval in both regimen groups. In exudate, this was 88% of the dosage interval in the intermittent therapy group. In addition, the continuous infusion regimen provided serum and exudate concentrations exceeding 16mg/L (4 x MIC for a susceptibility breakpoint of 4 mg/L) for >90%, while in the intermittent therapy group this was only 44% in exudate. In the case of 4 x MIC for a susceptibility breakpoint of 8 mg/L, both regimens reached a serum concentration of approximately 70% of the dosage interval; 5 of the 12 CI patients and 6 of the 6 patients on intermittent therapy had concentrations below 32mL/L. In exudate both regimens were insufficient for this target concentration.
No allergic reactions or elevated liver enzymes were observed during the study period.

Table 4. Time above the MIC in serum and peritoneal exudate

		Continuous infusion (%)	Intermittent bolus (%)
T >4x MIC(actual)	serum	100	100
	exudate	100	88
T > 16mg/L	serum	100	90
	exudate	92	44
T > 32 mg/L	serum	67	69
	exudate	45	6

%= percentage of the dosing interval in which the concentrations in serum or exudate exceeded the indicated concentrations

Discussion

This study shows that, from a pharmacokinetic and pharmacodynamic point of view, continuous infusion of ceftazidime results in favourable concentrations in serum compared to intermittent infusion of the same daily dose in critically ill patients with severe intra-abdominal infections. Animal models suggest that maximal efficacy of ceftazidime is achieved when concentrations in serum are maintained above 4 x MIC for at least 60% of the dosing interval for Enterobacteriaceae [16]. In the case of a Pseudomonas infection, sustained concentrations above at least 4 x MIC are recommended [6]. Since the MIC_{90} of *Pseudomonas aeruginosa* is 8mg/L in our institution (unpublished data, blood cultures in ICU patients), a ceftazidime concentration of at least 32 mg/L with an empirical regimen would be required until the causative pathogen and its MIC is determined. In this study, the continuous regimen of 4.5 g/24h after a loading dose of 1 g resulted in a mean steady state concentration in serum above 32mg/L. However, concentrations ranged widely, 5 of the 12 CI patients had concentration below 32 mg/L during therapy. The intermittent bolus regimen of 3 times 1.5 g per 24h resulted in a very high mean maximum concentration in serum that, generally, would not add to the bactericidal activity of ceftazidime, while the mean trough concentration in serum fell below the intended concentration of 32mg/L. All 6 patients had serum concentrations below 32 mg/L during therapy.

As critically ill patients are notorious for their variable pharmacokinetics, the actual time above the target concentration of 32mg/L per individual patient is more illustrative. In our critically ill study population, serum concentrations of ≥ 32 mg/L were reached only for approximately 70% of the dosing interval for both regimens. When the concentration falls below the threshold concentration re-growth of pathogens and development of resistance can occur. Therefore, a higher dosage is needed in cases of Pseudomonas infection with an MIC of 8 mg/L.

Other studies investigating continuous infusion of ceftazidime in critically ill patients found variable serum concentrations depending on the total body clearance. In a study of critically ill medical patients, a mean steady state serum concentration of 30 mg/L was reached with an infusion of 3 g/24h, while the total body clearance was approximately 4 L/h [10]. In another study in patients with nosocomial pneumonia using the same regimen (3g/24h), the total body clearance was twice as high (± 8 L/h), and therefore a mean steady state concentration of 17 mg/L was reached [17]. Lipman et al. showed that a dose of 6g/24h is needed in (not specified) critically ill patients with a total body clearance of approximately 6 L/h to maintain a concentration of 40mg/L in serum with continuous infusion [12].

To kill bacteria, or at least inhibit their growth and enhance killing by host defence mechanisms, antimicrobial drugs must act at the site of infection. Thus, in the case of severe intra-abdominal infections, the concentrations reached in the peritoneal exudate are informative. In this study, the continuous regimen resulted in a mean steady state concentration at the site of infection of >24mg/L, while the intermittent bolus regimen resulted in much lower mean maximum and trough concentrations in the peritoneal exudate. This resulted in the actual T>MIC at the site of infection during continuous infusion showing a more favourable concentration profile. However, for a target concentration of 32

mg/L in peritoneal exudate, both dosing regimen were insufficient and thus higher dosage will be necessary.
AUCs in the peritoneal exudate were approximately 60% of the concomitant serum AUCs after continuous infusion. Since the binding of ceftazidime to plasma protein is low (17%) [18], this can only partly explain this discrepancy. Another explanation would be an incomplete passage through the blood-peritoneum barrier. Corbett et al measured ceftazidime penetration into normal peritoneal fluid of patients undergoing elective abdominal surgery and found a concentration 62% of the concomitant serum level [19]. In our patient population, fast clearance through drains present in these spaces, may have prevented equilibration. An other explanation is that the peritoneal compartment fluid was diluted by continuous lavage. The AUCexudate/AUCserum ratio after intermittent therapy was lower (30%) than after CI, but this did not reach statistical significance. The difference between continuous and intermittent administration could be explained by the way of sampling. If the time to reach the maximum concentration in the peritoneal exudate is not the estimated 1h but shorter or longer, we measured a sub-maximal concentration and therefore calculated a smaller AUC. Mouton et al. measured concentrations reached in blister fluid after CI and intermittent infusion in healthy volunteers and found equal peak concentrations in blister fluid at 1h with both regimens [20]. Furthermore, the total amount of data points was low in the intermittent group.

Compared to data from healthy volunteers (Vd=180 mL/kg; T½ = 1.6h and CL=8.5L/h) [20, 21], the pharmacokinetic parameters in serum derived in this study revealed an increased volume of distribution and a decreased total body clearance resulting in an increased elimination half-life. In addition, the data showed considerable variance. Comparable variability of the pharmacokinetic profile has been observed in critically ill patients with pneumonia [10-12, 17]. Ceftazidime is not metabolised, has low protein binding and is almost entirely eliminated by glomerular filtration. The variability in clearance therefore mainly depends on renal function [22] and this varies widely among the critically ill. Approximately 30% of all patients with severe sepsis develop renal failure [23]. Furthermore, critical illness can be associated with a significant increase in the volume of distribution [11].
Variable pharmacokinetics result in a variable concentration profiles with unpredictable low trough concentrations after intermittent bolus dosing of ceftazidime [24]. Using continuous infusion it is easier to sustain a certain target concentration. Based on these data, a population model for patients with complicated intra-abdominal infections can be made. Routinely available clinical variables such as bodyweight, age, gender and serum creatinine can be used to predict ceftazidime clearance [25]. Using information about the individual pharmacokinetic profile and the MIC of the causative pathogen, the optimal dose of ceftazidime can be determined. This goal-oriented dosing of ceftazidime might result in a higher antibiotic efficacy. Extrapolating the available data to our situation (Vd =260mL/kg, CL 4 L/h and 60% penetration), the dose of ceftazidime must be between 1.5-4.5 g/24h after a loading dose of 1 g to achieve an optimal concentration in peritoneal exudate for most pathogens (MIC 2-6mg/L). In the case of peritonitis caused by *Pseudomonas* with a

MIC of 8 mg/L, the dose of ceftazidime must be at least 6 g/24h after a loading dose of 1 g. In critically ill patients with a total body clearance >4 L/h [17, 24], the dose has to be even higher. Although ceftazidime is a drug with low toxicity, mild hypersensitivity manifestations is the most common side effect [26], high doses of >80mg/kg/24h has not been tested in humans.

We conclude that from a pharmacokinetic and pharmacodynamic point of view, continuous infusion of ceftazidime renders favourable concentrations in serum and peritoneal exudate compared to intermittent bolus infusion in critically ill surgical patients with complicated intra-abdominal infections. In addition, with continuous infusion, concentrations can be reasonably predicted allowing a more accurate dose adjustment. The AUCexudate/AUCserum ratio after continuous infusion was approximately 60%. This has to be taken into account when treating pathogens with higher MICs.

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CHAPTER 6

PHARMACOKINETICS OF SEQUENTIAL INTRAVENOUS AND ENTERAL FLUCONAZOLE IN CRITICALLY ILL SURGICAL PATIENTS WITH COMPROMISED GASTRO-INTESTINAL FUNCTION

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Abstract

*Background***:** In surgical intensive care patients, the incidence of *Candida* infections is increasing and is associated with a high mortality. Especially patients with complicated intra-abdominal infections are at risk. Fluconazole has fungi-static activity against most species of *Candida* encountered in surgical intensive care patients. Fluconazole has excellent enteral bioavailability in healthy volunteers and ICU patients without recent GI-surgery and normal renal function. No data are available on the bioavailability of fluconazole in ICU patients with peritonitis and/or recent gastro-intestinal surgery. No data are available on the concentrations of fluconazole at the site of infection in this specific patient group.

*Objectives***:** 1) To determine the pharmacokinetics of sequential intravenous and enteral fluconazole in serum of surgical ICU patients with deep mycoses. 2) To determine the concentrations of fluconazole reached at the site of infection. 3) To determine if enteral administration of fluconazole, which has an important pharmacoeconomic advantage, is justified in this specific patient group.

*Design***:** Descriptive, sequential study as a part of a therapeutic drug monitoring program.

*Setting***:** Eighteen-bed surgical intensive care unit in a referral centre.

*Patients***:** Fourteen critically ill surgical patients with recent gastro-intestinal surgery and a deep mycosis caused by a fluconazole susceptible fungus and a calculated creatinine clearance of > 40 ml/min.

*Interventions***:** Fluconazole dosage regimen: 400 mg iv q24h with an extra dose of 400 mg iv after 12h on day 1. If the clinical condition allowed enteral administration on day 4, the content of 2 capsules of 200 mg was given via the feeding tube with concomitant enteral feeds.

*Measurements and main results***:** Serum, exudate from the site of infection and urine samples collected at assumed steady state (after ≥ 5 doses). Fluconazole concentrations were determined by HPLC.

The mean AUC0-24h in serum after enteral administration did not significantly differ from the AUC0-24h during intravenous treatment. The elimination half-life was lengthened compared to healthy volunteers. The mean (95% CI) estimated bioavailability was 124 (90-158)%. The mean (95% CI) area under the concentration time curves (AUCs) achieved in the exudate from the site of infection were 67 (55-79)% of the AUCs reached in serum for both regimens.

*Conclusions***:** In critically ill patients with recent gastro-intestinal surgery and/or peritonitis the bioavailability of enteral fluconazole was adequate. Concentrations of fluconazole reached in exudate were lower than in serum for both regimens, but adequate to treat most cases of deep mycoses in this specific patient group.

Introduction

Deep mycoses have become a major source of morbidity and mortality in the surgical intensive care unit nowadays[1, 2]. *Candida spp* are the most common yeast-like fungi isolated and account for 8% to 15% of all hospital-acquired bloodstream infections. In intensive care patients, *Candida* infections constitute up to 8% of all nosocomial infections[3]. Risk factors associated with development of deep mycoses include severity of illness (APACHE II score >10, ventilator use for >48 hours), the use of broad-spectrum antibiotics, indwelling central access catheters, total parental nutrition, immunosuppression and burns[1, 2]. The most frequently encountered deep mycoses in the surgical intensive care include complicated intra-abdominal infections (so-called tertiary peritonitis), and candidemias caused by intravascular catheter infections. *Candida albicans* is the predominately cultured pathogen[4].

Fluconazole is an imidazole with fungistatic activity against most species of *Candida*, including *C.albicans* and *C.tropicalis*. Potentially resistant strains include *C. glabrata*, *C. lusitaneae* and *C. krusei*. Its clinical use for deep mycoses is increasing, due to low toxicity and equivalent efficacy in comparison to the more toxic amphotericin B[5]. An additional advantage is the excellent bioavailability of fluconazole after oral administration in healthy volunteers[6, 7]. The latter can simplify drug administration and reduce costs significantly. Nicolau et al. demonstrated excellent bioavailability of fluconazole administered via a feeding tube in critically ill patients without recent gastro-intestinal (GI) surgery and normal renal and hepatic function[8]. Rosemurgy et al. found a bioavailability of 77% after a single dose of 100 mg in 4 patients with recent GI surgery[9]. To our knowledge no data are available concerning the bioavailability at steady state of enterally administered fluconazole in critically ill surgical patients with fungal peritonitis and/or recent GI surgery. It can be envisaged that infected viscera and repeated abdominal surgery compromise enteral absorption. Furthermore, no data exist on the concentrations reached in the exudate from the site of infection in this specific patient group.

Therefore, we conducted a descriptive, sequential study to investigate the pharmacokinetics of intravenous (400 mg) and enteral (400 mg) fluconazole treatment in patients with deep mycoses in the surgical intensive care unit.

Materials and methods

Patient population

The study was conducted as a part of a therapeutic drug monitoring program at the 18-bed surgical intensive care unit of a university hospital. Patients treated with fluconazole for deep mycosis following recent GI surgery were sampled. Deep mycoses were defined as organ/space infections in which *Candida* species was isolated from an aseptically obtained culture of fluid or tissue. Candidemia was defined as isolation of *Candida* species from one or more blood cultures[10].

Excluded were patients with superficial mycoses or colonisation; known allergy to fluconazole; severe renal impairment defined as a calculated creatinine clearance < 40 ml/min; liver disease defined as ALAT or ASAT > 150 U/L or total bilirubin > 137 µmol/L; severe neutropenia defined as <500 neutrophils per mm^3 and concomitant use of

rifampicin or hydrochlorthiazides. All patients were classified according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score [11] and the Therapeutic Intervention Scoring System (TISS) [12] at inclusion. Use of concomitant drugs was documented.

The following parameters were assessed: demographic data including age, sex, weight and site of infection; type and number of surgical interventions and type and rate of enteral feeding and gastric residual volume if applicable. Serum creatinine, ALAT, ASAT, bilirubin, albumin, platelets and neutrophils were assessed daily. Creatinine clearance was calculated over 24 hours by using the standard equation. Adverse events were documented during the treatment period.

Dosage regimens

In patients with normal renal function fluconazole (Diflucan®, Pfizer BV, Capelle a/d IJssel, The Netherlands) was administered intravenously at a dosage of 400 mg over 30 min by an electronic pump (Ivac Medical System, Hampshire, England) once daily. On the first day of treatment an extra dose of 400mg was given after 12 hours. If the clinical condition of the patient allowed enteral administration at day 4 of treatment (gastric residue <200 mL/day; presence of bowel sounds), fluconazole was administered enterally by GI tube. In tube-fed patients 2 capsules of 200mg were opened and their content was dissolved in 0.9% NaCl and instilled through the tube. For enteral feeding Nutrison® or Peptison® (Nutricia, Zoetermeer, The Netherlands) were used at a rate ranging between 30-100ml/h.

In case of renal impairment the dosage was adjusted as follows: if calculated creatinine clearance was < 40ml/min the total daily dose was set at 200mg. If creatinine clearance decreased to <20ml/min during the study period the total daily dose was diminished to 100mg. Only the data of patients with a calculated creatinine clearance > 40 mL/min are presented.

Pharmacokinetics

Blood, exudate from the site of infection and urine samples for the determination of fluconazole concentrations were drawn at assumed steady state (after ≥ 5 dosages). If treatment was switched to the enteral route at least 3 doses had to be administered before the second sampling period.

Blood samples were taken from the non-infusion arm. Sample times after intravenous administration were: prior to infusion (t=0) and at 30min, 1h, 2h, 4h, 8h and 24h after start of infusion. For enteral administration, samples were drawn prior to infusion (t=0) and at 30min, 1h, 1.5h 2h, 3h, 4h, 8h and 24h after start of infusion. After sampling, blood was allowed to clot on ice for 20 min and centrifuged at 1500G for 10min.

Exudate samples were drawn from drainage catheters in the peritoneal cavity or mediastinum prior to infusion (t=0) and at 2h, 3h, 4h, 8h and 24h after drug administration. The total amount of exudate drained from the site of infection over 24 hours was measured.

Urine was collected over 24 hours. The volume was measured and a sample of 4 ml was taken for analysis of creatinine and fluconazole concentrations.

Serum, exudate and urine samples were stored at -70°C until analysis. Fluconazole concentrations were determined by using high performance liquid chromatography (HPLC) [13]. The lower limit was 0.1 mg/L in serum and 1 mg/L in exudate and the method was

linear up to 100 mg/L. Pharmacokinetic parameters were estimated using the MWpharm program (Mediware, Groningen, The Netherlands) using a two compartment model for intravenous dosing and an one compartment (absorption) model after enteral dosing. Pharmacokinetic parameters were calculated using standard equations. The primary descriptive parameters were area under the concentration curve (AUC0-24h), the serum half-life (T½), the volume of distribution (Vd), the total body clearance and concentrations in serum and exudate reached. The bioavailability, defined as the faction of a dose of fluconazole which reaches systemic circulation following enteral administration, was estimated by calculating the AUCenteral/AUCintravenous ratio in the patients who received both administration routes.

Statistical analysis

The analysis and evaluation were performed in accordance with the following criteria:
Description of serum and exudate concentration profiles (i.e. plots, tables) after administration of fluconazole, using means and 95% confidence intervals of the mean. Mann-Whitney tests were used to determine differences between groups; a p-value <0.05 was considered statistically significant. Patients were eligible for analysis if they had completed day 4 of the treatment period.

Results

Fourteen patients were sampled; in ten patients, intravenous therapy was switched to the enteral route. Data of one patient who developed severe renal impairment (CLcreat < 10 mL/min) during enteral dosing were considered non evaluable.

Table 1. General characteristics of the study population (N=14)

Age (yr)		53 (45-61)
Weight (kg)		79 (73-86)
Male / female		10 / 4
APACHE II		13 (11-15)
TISS		41 (36-46)
Diagnosis	- peritonitis	n=12
	- mediastinitis	n=2
	- candidemia	n=2
Nr. of reoperations during study (range)		0-5
Overall mortality (on ICU)		43%

If applicable, data are means (95% CI)

Demographics: The demographic characteristics of all patients sampled are summarised in Table 1. Severity of illness is reflected in a mean APACHE II score of 13 (= predicted mortality 20%) and a mean TISS score of 41 (=intensive care patient). Twelve patients had fungal peritonitis of whom 9 were treated with the open abdomen technique[14]. Two patients suffered from fungal mediastinitis after esophagectomy with primary reconstruction. The infected cavities were lavaged continuously with approximately 2 L

saline / 24 h. This is a surgical technique used at our institute in which an infected space is irrigated continuously to dilute the bacterial load and debris. The number of operations during study ranged between 0-5 procedures per patient. Six patients had a gastric tube, 2 a duodenal tube and 2 an enterostomy. Feeding rate ranged between 30 to 100 mL/h. Two patients had an episode of candidemia, which occurred before the start of therapy in both cases. Six patients (43%) died on the ICU, all were infection related deaths. Five patients died while receiving fluconazole, 2 patients during intravenous therapy and 3 patients during enteral treatment.

The mean steady-state concentrations versus time in serum and exudate of both regimens are shown in Figure 1 and 2 respectively. Concentrations reached in serum were measured in 14 patients after intravenous dosing and in 9 patients after enteral dosing. Concentrations reached in exudate from the site of infection were measured in 11 patients after intravenous dosing and in 6 patients after enteral dosing. In table 2 the calculated pharmacokinetic parameters in serum and exudate are displayed for all evaluable patients. Mann-Whitney tests were done on the data of the patients who completed both regimens.

Pharmacokinetics in serum: Table 2 illustrates that the mean AUC0-24h in serum after enteral administration did not significantly differ from the AUC0-24h during iv treatment (p=0.4). The Cmax at steady state was not significantly higher after iv administration (p=0.5). The mean time to reach Cmax (Tmax) after enteral administration was less than an hour, which indicates that fluconazole is readily absorbed. The mean serum half-life was relatively long and highly variable. The overall mean volume of distribution was equivalent to 58% of body weight, approaching the volume of total body water.

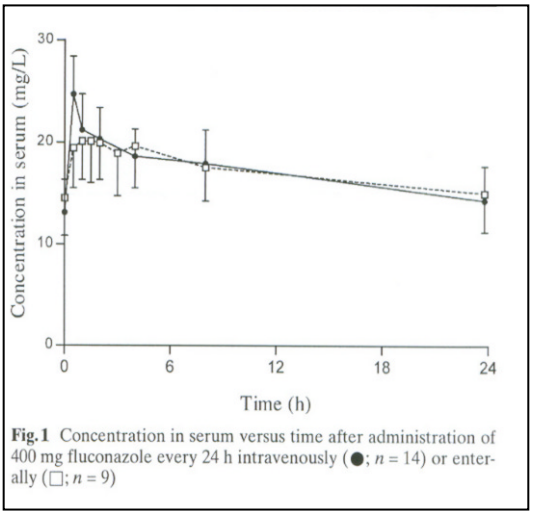

Fig. 1 Concentration in serum versus time after administration of 400 mg fluconazole every 24 h intravenously (●; $n = 14$) or enterally (□; $n = 9$)

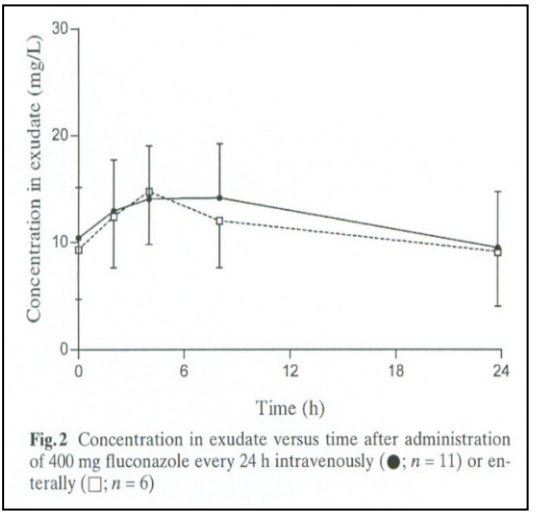

Fig. 2 Concentration in exudate versus time after administration of 400 mg fluconazole every 24 h intravenously (●; $n = 11$) or enterally (□; $n = 6$)

Table 2. Pharmacokinetic parameters of fluconazole in serum and at the site of infection of all patients studied.

PK parameter	intravenous 400 mg	enteral 400 mg	P-value[#]
Serum	**(n=14)**	**(n=9)**	
AUC0→24h (mg.h/L)	09 (336-482)	418 (319-516)	0.4
Cmax (mg/L)	24.7 (21.7-27.8)	20.4 (16.5-24.2)	0.5
Tmax (h)		0.8 (0.4-1.3)	
Vd (L/kg)	0.58 (0.45-0.70)		
T½ (h)	53.4 (36.9-68.9)[*]	51.1 (31.7-69.8)	0.5
CL (L/h)	1.14 (0.84-1.43)	1.09 (0.8-1.38)	0.4
Renal excretion (%)	63 (50-76)	65 (48-81)	0.8
CLcreat (mL/min)	96 (74-119)	123 (83-162)	0.6
Exudate	**(n=11)**	**(n=6)**	
AUC0→24h (mg.h/L)	292 (210-274)	222 (168-275)	0.6
AUCexudate/AUCserum (%)	69 (55-88)	62 (50-73)	0.5
Cmax (mg/L)	16.7 (11.6-21.7)	16.2 (11.5-21.0)	0.1
Ctrough (mg/L)	9.5 (5.3-13.7)	9.1 (3.1-15.1)	0.1
Volume exudate (mL/24h)	2300 (1800-2900)	1500 (1000-2000)	0.1

Data are means (95% CI)

AUC0→24h = area under the concentration curve (mg.h/L); Cmax = maximum concentration (mg/L); Ctrough = trough concentration (mg/L); Tmax = time to reach maximum concentration (h); T½ = elimination half life (* = β-phase) (h); Vd = volume of distribution (L/kg); CL = clearance (L/h); CLcreat = calculated creatinine clearance (mL/min)

[#]P-values are calculated for the patients who received both regimens, i.e. in serum n=9 and in exudate n=6

Pharmacokinetics in exudate: The mean (95% CI) amount of fluid drained from the site of infection (=exudate & lavage fluid) per 24 h tended to be higher in the IV group, but this difference was not significant (p=0.1).The mean AUC0-24h in exudate after enteral administration did not significantly differ from the AUC0-24h in exudate during iv treatment (p=0.6). The AUCexudate/AUCserum ratio was approximately 67%. The mean (95% CI) maximum and through concentrations did not differ as well.
Overall, sixty-four percent of a 400 mg dose was found unchanged in urine after 24 h.

In Table 3 the estimated bioavailability (F%) is given, reflected by the mean (95% CI) AUCent/AUCiv ratio of the 9 patients with an creatinine clearance > 40 mL/min who completed both dosing regimens. There was considerable variance between patients. The lowest F was 71%, but still resulting in an adequate AUC. On the average the estimated bioavailability was more than 100%, indicating complete enteral absorption of fluconazole.
No allergic reactions, elevated liver enzymes (ALAT or ASAT > 150 U/L) or elevation of total bilirubin (> 137 μmol/L) were observed during the study period.

Table 3. Pharmacokinetic parameters of fluconazole in serum (n=9) in patients who completed both regimens

Pt	Route of administration	Sample day	CLcreat (mL/min)	$AUC_{0\rightarrow24h}$ (mg.h/L)	F (%)
2	IV	9	180	146	
	NG	14	220	209	143
6	IV	5	115	421	
	Ileostomy	10	153	299	71
8	IV	6	61	626	
	NG	9	43	552	88
9	IV	5	122	221	
	ND	9	244	396	179
10	IV	6	110	409	
	NG	9	103	481	117
11	IV	5	130	273	
	NG	8	160	244	89
12	IV	5	70	406	
	Gastrostomy	10	45	435	107
13	IV	5	130	308	
	Jejunostomy	9	78	684	221
14	IV	6	61	450	
	ND	9	59	458	102
Intravenous			108 (83-134)	362 (269-455)	
Enteral			123 (74-172)	418 (319-516)	124 (90-158)
P-value			0.6	0.4	

Data are means (95% CI)

NG = nasogastric; ND = nasoduodenal; IV = intravenous; CLcreat = creatinine clearance (mL/min); AUC0→24h = area under the concentration curve (mg.h/L); F = estimated bioavailability (%)

Discussion

This study demonstrates that in critically ill surgical patients with recent gastro-intestinal surgery and/or peritonitis the bioavailability of enteral fluconazole is adequate. Enteral administration of fluconazole 400 mg q24 resulted in AUCs comparable to those obtained after 400 mg q24 intravenously. Despite the presence of factors compromising gastro-intestinal absorption such as visceral edema, impaired motility of the bowel, loss of mucosal surface after resection or enteral intake deprivation and cation-containing enteral feeds, the estimated bioavailability at steady state of enterally administered fluconazole was 100%. The draw back of a sequential study is that the bioavailability can only be estimated, as the AUC of the different dosing methods are not measured at the same time. To calculated the exact bioavailability a randomised cross-over study is needed. To be informed about the accuracy of our fluconazole policy, which is starting intravenously and switching to enteral as soon as possible, we did a sequential study. Our data imply that enteral administration of fluconazole is save as soon as enteral feeding is resumed successfully in this patient group.

The lowest bioavailability (71%) was found in a patient who's dose of fluconazole was administered in a distal enterostomy. It is possible that a shortage of bowel prevented full absorption. On the other hand, the smaller AUC in serum after enteral dosing in this patient can be explained by an increased creatinine clearance between the two measurement periods. Despite this low estimated bioavailability the AUCs in serum and exudate were adequate. In all other cases, no difference in absorption was observed between gastric and more distal segments of the gastro-intestinal tract. As fluconazole can be dosed up to 1600 mg/day without toxic effects[6], a dose >400 mg can be considered in case of shortage of bowel or fast clearance.

In three patients the estimated bioavailability markedly exceeded 100% (143%, 179% and 221% respectively). This can be explained by the fact that the total body clearance of these three patients was much higher (2.7 L/h, 1.8 L/h and 1.3L/h resp.) during intravenous dosing than it was during enteral dosing (1.9 L/h, 1.0 L/h and 0.6 L/h resp.). Two patients had a hyperdynamic circulation as seen in septic shock with a normal renal function during the iv sampling period, resulting in fast clearance of the drug. In the third patient there was a significant drop in creatinine clearance (130mL/min to 78mL/min) between both measurement periods. Another explanation would be that steady state was not reached at the time of the first measurement.

The main difference in pharmacokinetics of fluconazole in this patient group compared to healthy volunteers was an increase in elimination half-life. As described by others the absorption rate was not influenced by the different types of enteral feeding [8] and the maximum concentrations in serum were reached in less than an hour. The volume of distribution was large as described in studies in healthy volunteers[7] and implies distribution in all body fluids. The mean total body clearance of fluconazole in these patients was comparable to measurements obtained from healthy volunteers[7, 15]. On the other hand the mean serum half-life was lengthened considerably (T½ (mean ± sd) = 31.4 ± 5.5h). While fluconazole is mainly eliminated by renal clearance this increase in serum

half-life can be explained by accumulation in tissues and pooling in peripheral and central edema (deep compartment). Such a pharmacokinetic profile ensures the patient of a sufficient AUC throughout the dosing interval.

Concentrations of fluconazole reached at the site of infection were lower than in serum for both regimens, but adequate to treat most cases of deep mycoses in this specific patient group. In the exudate of the infected cavities the AUCs after enteral administration were comparable to those after intravenous dosing, but on average 33% lower than the AUCs measured in serum. As binding to plasma protein of fluconazole is low (12%)[7], this can only partly explain this discrepancy. Another explanation would be an incomplete passage through the blood-peritoneum barrier. A comparable ratio was described for peritoneal dialysate[16]. However, Rieder-Nelissen et al. found excellent penetration in pulmonary tissue after intravenous administration[17]. In our patient population, fast clearance through drains present in these spaces, may have prevented equilibration. A third explanation is that the peritoneal or mediastinal compartment fluid was diluted by continuous lavage. Although not significant, there was a trend towards lower AUCs and Cmax in the patients with the highest amount of fluid drained (data not shown). This suggests that this rinsing technique could compromise antimicrobial killing by fluconazole.
Efficacy studies in mice have shown that the efficacy of fluconazole is best predicted by the AUC/MIC ratio[18]. The height of the maximum concentration has no therapeutic consequences, as long as a minimal AUC is achieved. In this murine disseminated candidiasis infection model the magnitude of the AUC/MIC ratio to reach 50% of the maximal effect (ED(50)) ranged from 12 to 25. A susceptibility breakpoint for dosages of 400 mg fluconazole/day has been set at MIC ≤ 16 mg/L. In our study, the AUCs reached in serum and at the site of infection with both regimens were sufficiently high to treat deep *Candida* infections with a MIC ≤ 16 mg/L.

Several studies support the use of fluconazole as preferred therapy in the treatment of systemic infections caused by *Candida albicans*[5, 19-21]. In case of poorly susceptible *Candida* species like *C.krusei* or *C.glabrata* amphotericin B is the drug of first choice. Controlled trials are necessary to establish the optimal dose of fluconazole and duration of therapy in critically ill surgical patients with deep mycoses. As our study shows that the enteral absorption of fluconazole is sufficient even in the gastro-intestinal compromised patients, it is evident that it is save to use it in other prevalent ICU deep mycoses like catheter-related candidiasis and funguria. Current consensus agrees a loading dose of 600-800mg/day intravenously the first 3 days followed by 400 mg daily given either enterally or intravenously depending on the gastro-intestinal condition[1]. In case of candidemia a minimal treatment period of 10-14 days is recommended. In case of *Candida* peritonitis the duration of therapy depends on the eradication of systemic and local peritoneal response and normalisation of biochemical infection parameters. Given the high mortality associated with candidemia, early presumptive antifungal treatment with (enteral) fluconazole in patients at risk (i.e. neutropenic patients, transplant recipients, colonisation at multiple sites, severity of illness, the use of antibiotics, mechanical ventilation and intravascular catheters)

is a subject under discussion. Clinical studies are required to evaluate the efficacy of this strategy.
Patients with recent gastro-intestinal surgery with or without peritonitis are thought to have impaired absorption of drugs after enteral administration. Physicians are therefore reluctant to prescribe oral preparations of drugs to these patients and they are excluded from pharmacokinetic studies. Although our bioavailability data are based on 9 patients only and the confidence intervals were large, we advocate enteral administration of fluconazole in critically ill patients with peritonitis and/or recent abdominal surgery as soon as enteral feeding is possible. Subsequently, this treatment strategy will lower treatment costs, reduce workload and help prevent intra-vascular device related complications.

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CHAPTER 7

EXPERIENCE WITH A ONCE-DAILY DOSING PROGRAM OF AMINOGLYCOSIDES IN CRITICALLY ILL PATIENTS

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Abstract

Background: Aminoglycosides show concentration dependent killing, therefore once-daily aminoglycoside (ODA) regimens have been instituted. Data on experience with ODA regimens in critically ill patients are limited.

Objectives: 1) to evaluate the ODA-program in critically ill patients; 2) to describe the pharmacokinetics of aminoglycosides (gentamicin and tobramycin) and 3) to assess the incidence of nephrotoxicity associated with an ODA regimen in this specific patient group.

Design: a prospective, descriptive study

Setting: 18-bed surgical and 12-bed medical intensive care unit in a referral centre.

Patients: 89 critically ill patients with a suspected or confirmed infection for which gentamicin or tobramycin was indicated and a creatinine clearance >30 ml/minute were monitored. One hundred and nine pharmacokinetic profiles were gathered.

Interventions: A first dose of 7 mg/kg/24h of gentamicin or tobramycin was given to every patient independent of renal function. Subsequent doses were chosen on the basis of the pharmacokinetic results of the first dose.

Measurements: Serum samples were collected 1 and 6 hours after start of the aminoglycoside infusion. All samples were assayed by using immunofluorescence. Pharmacokinetic parameters were estimated using a one compartment model.

Main results: The volume of distribution of aminoglycosides was significantly higher in critical ill patients with septic shock than in those without. Consequently, the maximum concentration reached was significantly lower in patients with septic shock. In *P. aeruginosa* infections the mean (SD) estimated Cmax/MIC ratio was 10.3 (3.3). In n= 17 (49%) of the patients treated >24h (n=35), a dose adjustment or lengthening of interval was necessary. The recommended dosing interval based on the Hartford Hospital nomogram and one serum concentration at 6 hours was correct in only 62% of all cases. Signs of renal impairment occurred in n=12 (14%) of the patients; in all survivors renal function recovered completely, no haemofiltration was needed.

Conclusions: An ODA-regimen of 7mg/kg produced Cmax/MIC ratios >10 in the majority of critically ill patients in our population. Septic shock and renal dysfunction caused an aberrant pharmacokinetic profile of aminoglycosides in these patients. Therefore, individual therapeutic drug monitoring is warranted. Signs of renal impairment were common in the presence of shock, but appeared to be reversible.

Introduction

Data from in vitro studies and animal models have shown that an aminoglycoside's rate and extent of bacterial killing is concentration-dependent [1,2]. Optimum bacterial activity is achieved when the maximum concentration (Cmax) is at least 10 times the minimal inhibitory concentration (MIC) of the causative gram-negative pathogen [3]. In addition, this Cmax/MIC ratio of at least 10:1 may prevent the emergence of aminoglycoside-resistant pathogens [4]. Therefore, once-daily aminoglycoside (ODA) regimens have been instituted. Data from animal models and clinical trials suggest that these regimens are as

effective as conventional regimens for the treatment of gram-negative infections, but reduce the oto- and nephrotoxicity associated with aminoglycoside therapy [5].
The aminoglycosides currently in use on our Intensive Care Units (ICU) are gentamicin and tobramycin. Aminoglycoside resistance on the ICU in the Netherlands is low (2-7%) [6], therefore is safe to use them as empirical therapy. In our institution, gentamicin is used, combined with beta-lactams, as empirical therapy for suspected bacterial sepsis with gram-negative micro-organisms. Empirical therapy is streamlined as soon as possible to definitive therapy with less toxic agents. Tobramycin is used, combined with beta-lactams, for the definitive therapy of *P.aeruginosa* infections.
Aminoglycoside pharmacokinetics in critically ill surgical patients are extremely variable [7-10]. Changes in renal function can alter the rate and extent of aminoglycoside elimination with an increased risk of toxicity. An increased volume of distribution may result in sub-therapeutic serum concentrations. Delays in attaining therapeutic levels have been associated with persistence of gram-negative organisms, delayed therapeutic responses and treatment failure [11,12]. Therefore, high dosages of 7 mg/kg are recommended and therapeutic drug monitoring is warranted.
In 1997 we introduced a hospital wide once-daily aminoglycoside program with individual monitoring based on the pharmacokinetic profile of the first dose and the MIC of the causative pathogen.
The purpose of the study was 1) to evaluate the ODA-program in critically ill patients; 2) to describe the pharmacokinetics of aminoglycosides administered once-daily in critically ill patients and 3) to assess the incidence of nephrotoxicity associated with an ODA regimen in this specific patient group.

Materials and methods

Patient population

All patients admitted to the surgical and medical intensive care unit (ICU) of our hospital between January 1997 and March 1998 with a suspected or confirmed infection treated with gentamicin or tobramycin were monitored. Excluded from this analysis were patients with renal impairment at inclusion defined as a creatinine clearance <30ml/min and/or haemofiltration. All patients were classified according to APACHE II [13] and TISS [14] score.
Demographic data, the presence of septic shock and concomitant medication were documented. Septic shock was defined as hypotension caused by an infection requiring continuous infusion of catecholamines (excluding dopamine < 5µg/kg/min) [15]. Cultures were taken on indication. MICs of gentamicin and tobramycin were determined with the Vitek susceptibility test (BioMérieux, Marcy l'Etoile, France). MICs were interpreted in 3 categories: resistant (R), intermediate (I) and susceptible (S). For *P.aeruginosa* the breakpoints for tobramycin were: R >8, I 4-8, S ≤ 4 mg/L. For Enterobacteriaceae breakpoints for gentamicin were: R > 8, I 2-4, S ≤ 1 mg/L. Enterococci were interpreted into low (8 ≤ MIC < 500 mg/L) and high (MIC ≥ 500mg/L) level resistance. Serum creatinine and neutrophils were assessed daily. Creatinine clearance was estimated from the

serum creatinine concentration by using the Cockroft-Gault equation [16] with the actual and with a minimal serum creatinine concentration of 85 µmol/L [17].
Sites of infections were defined according to the Center for Disease Control definitions for nosocomial infections [18] and CDC definitions of surgical site infections [19].

ODA program

All patients received an initial dose of 7 mg/kg/24h of gentamicin or tobramycin. Dosage was based on latest actual body weight. Dosages were rounded off at multiples and quarters of vials (80 mg vials, 2mL). Aminoglycosides were administered in 30 minutes using a infusion pump (Ivac Medical System, Hampshire, England).
The following monitoring program was incorporated hospital wide. Serum samples were collected 1 and 6 hours after start of the first aminoglycoside infusion. On day 4 or in case of renal impairment, fluctuating renal function or prolonged therapy >1 week, the pharmacokinetic assay was repeated. The aim of the program was to achieve a Cmax/MIC ratio ≥10 and an aminoglycoside-free (<0.5 mg/L) interval of at least 4 h per administration period. The individual pharmacokinetic profile was calculated using a computer simulation model with a one-compartment intravenous infusion model and a fixed volume of distribution (Vd) of 333 mL/kg. The elimination rate constant (Kel) was calculated as follows: Kel (h-1) = (lnC6h - lnC1h) / Δtime. C1h and C6h are serum concentrations at 1h and 6h respectively. The elimination half-life (T½) was derived from Kel (T½ (h) = ln2 / Kel). Time to reach the trough concentration of 0.5mg/L after start administration (T0.5) was calculated by T0.5 (h) = ((lnC1h - ln0.5) / Kel) + Δ(t1h - t0h). Δ(t1h - t0h) is the time between start infusion and sample collection 1, usually 1h. The maximum concentration was calculated by dividing the dose by the volume of distribution (Cmax (mg/L)= Dose (mg) / Vd (L)). By this way, different doses could be simulated by various degrees of elimination rate constants to determine the dose and administration interval which produces the intended goals. All samples were assayed by using immunofluorescence (TDx, Abbott Laboratories, Illinois, USA).

Pharmacokinetics

Pharmacokinetic parameters including the Kel (h-1), the T½ (h), the Vd (mL/kg) and the total body clearance (CL, L/h) were estimated using the MwPharm program (Mediware, Groningen, The Netherlands) using a one compartment model.
The predicted performance of the hospital's monitoring system was evaluated using the method of Sheiner and Beal [20]. A 24 hour trough concentration (C24h) was estimated 1) using the elimination rate constant calculated from the obtained pharmacokinetic profile (C24h = e ((Kel x Δt) + lnC1h)) and 2) using an elimination rate constant (Kelcreat) calculated from the estimated creatinine clearance (Kelcreat = CLcreat/Vd and Vd=333ml/kg) and serum concentration at 1h (C24h = e ((Kelcreat x Δt) + lnC1h)). To estimate the creatinine clearance the Cockroft and Gault formula was used, either with the actual serum creatinine (method A) or with a minimum serum creatinine of 85 µmol/L (method B). All three estimated trough concentrations were compared with the measured trough concentration. Bias was determined as the mean prediction error, which is the mean difference between the predicted and the measured trough concentration. Precision was

calculated as the mean squared prediction error, which is equal to the mean of the sum of squared differences between the predicted and measured trough concentration.

Nephrotoxicity

Nephrotoxicity was assessed by serum creatinine in all patients receiving aminoglycosides. Nephrotoxicity was defined as a rise in serum creatinine of 45 μmol/L or more during the treatment period or within a week after the last dose.

Statistical analysis

For description of parameters means (± SD) were used. The Mann-Whitney test were used to determine differences between groups. For bias and precision a paired t-test was used. A p-value <0.05 was considered statistically significant.

Results

Patients

Eighty-nine patients were monitored (66 gentamicin, 23 tobramycin). N=53 were recruited from the surgical ICU and n=36 from the medical ICU. In that period approximately 1200 patients were admitted to both ICUs of whom 700 stayed ≥ 48h in the ICU. Demographic characteristics are listed in Table 1.

The mean (± SD) APACHE II score was 17 (4), which is associated with an estimated mortality of 35%. A mean (± SD) TISS of 33 (8) corresponds with a medium to severe critically ill patient population. Septic shock was present in 42% of the patients. Overall mortality on the ICU was 28%. Severe renal impairment (30-60ml/min) was present in 12%.

Sixty-one percent of the patients (n=54) were treated with a single dose, 19% (n=17) were treated for 48h, 11% (n=10) were treated for 72h and 9% (n=8) received aminoglycosides for >72h. The median (range) duration of therapy was 24 (24-192)h. The median (range) dosage administered was 480 (280-900) mg.

Table 1. Demographic characteristics.

	n=89
M/F	69/20
Age (mean, range) (yr.)	57 (87-20)
APACHE II (mean, SD)	17 (4)
TISS (mean, SD)	33 (8)
Presence of septic shock (%)	42
Overall mortality on ICU(%)	28
Creatinine clearance ≥ 60 ml/min (%)	78
Creatinine clearance 30-60 ml/min (%)	12

Sites of infection and microbiology

Forty-one percent of the patients had a respiratory tract infection, 38% had an deep surgical space infection and 6% had a primary bloodstream infection. In 13 patients (15 %) no source of infection could be established.

In Table 2 the cultured pathogens are listed. Eighty-three different gram-negative and 23 gram-positive isolates were cultured. Enterobacteriaceae (46/83; 55%) and *P.aeruginosa* (24/83; 29%) were the most frequent cultured pathogens. In 71 patients (80%) blood was cultured, of which 21 patients (30%) had positive blood cultures.

The Vitek system does not give the exact MIC, but the susceptibility is reported on the basis of breakpoints. Therefore, we could calculate the minimal Cmax/MIC ratio that was reached for the different pathogens. For the 23 susceptible strains of *P.aeruginosa* the Vitek MIC was ≤ 4 mg/L. For the 41 susceptible strains of Enterobacteriaceae the Vitek MIC was ≤ 1 mg/L. The minimal mean (SD) Cmax/MIC ratio reached based on the Vitek susceptibility results was 21.3 (7.2) susceptible Enterobacteriaceae and 5.5 (1.6) for the

susceptible strains of *P.aeruginosa*. To obtain a better estimate of the Cmax/MIC ratio of *P.aeruginosa* we performed E-tests (AB Biodisk, Solna, Sweden) on all (n=21) *P.aeruginosa* strains isolated from blood cultures of ICU patients in 1998 (non-published data). The MIC90 for tobramycin was 2 mg/L; all strains were sensitive. Using this MIC90 of 2mg/L and the measured maximum concentrations in the patients with a Pseudomonas infection, we also calculated the Cmax/MIC ratio. In this case, the estimated mean (SD) Cmax/MIC ratio was 10.3 (3.3) *P. aeruginosa* in our population.
During the course of treatment one *P. aeruginosa* and one *E.coli* became resistant to respectively tobramycin and gentamicin. None of the *Stenotrophomonas maltophilia* (n=8) cultured were aminoglycoside susceptible. Approximately 30% of the *E. faecalis* were highly resistant to aminoglycosides, all *S. aureus* cultured were susceptible.

Table 2. Pathogens, susceptibility and sites of infection.

	Susceptibility			**Site of infection**		
Gram-negatives (n=83)	**S**	**I**	**R**	**SS**	**BS**	**RT**
Pseudomonas aeruginosa (n=24)	23		1	9	3	9
Enterobacteriaceae (n=46)				23	9	14
E.coli (n=16)	12	3	1			
Klebsiella spp (n=9)	9					
Enterobacter spp (n=9)	9					
Proteus mirabilis (n=3)	3					
Citrobacter spp (n=3)	2		1			
Morganella morganii (n=2)	2					
Hafnia alvei (n=2)	2					
Serratia spp (n=2)	2					
Acinetobacter spp (n=5)	1	1	3	2	2	1
Stenotrophomonas maltophilia (n=8)		1	7	1	1	6
Gram-positives (n=23)						
E. faecalis (n=13)			9 LR 4 HR	11	1	1
S. aureus (n=10)	10			1	5	4

SS = surgical site; BS = blood stream; RT = respiratory tract. S = susceptible; I = intermediate; R = resistant; LR = low level resistance ($8 \leq$ MIC < 500 mg/L); HR = high level resistance (MIC ≥ 500 mg/L).

Pharmacokinetics

Gentamicin and tobramycin showed similar pharmacokinetic profiles, therefore data of both were pooled. A total of 109 profiles were gathered (77 gentamicin, 32 tobramycin). Table 3 shows the pharmacokinetic parameters obtained. A distinction was made between patients with an estimated creatinine clearance greater or less than 60mL/min 5. The mean dose given to patients was 6.3 mg/kg, the mean Cmax reached was 21 mg/L. There was a significant difference between the two clearance groups with respect to total body clearance (CL), elimination half-life and the time to reached a trough concentration of 0.5 mg/mL. Standard deviations were relatively large. The mean volume of distribution approximated the extracellular volume of intensive care patients 10.

Table 3. Pharmacokinetic parameters of an ODA-regimen of aminoglycosides in ICU patients

	Clcreat ≥ 60mL/min (n=96)	**CLcreat 30-60mL/min (n=13)**	**P-value**
Dose (mg/kg)	6.2 (0.9)	6.4 (1.2)	0.5
CLcreat (mL/min)	90 (25)	45 (7)	< 0.0001
Cmax (mg/L)	20.5 (6.9)	21.5 (5.8)	0.6
Vd (mL/kg)	317 (120)	302 (95)	0.7
CL (mL/min)	85 (40)	47 (15)	0.001
Kel (h^{-1})	0.22 (0.1)	0.15 (0.06)	0.01
T½ (h)	3.8 (1.8)	5.4 (2.2)	0.01
T0.5 (h)	20.3 (8.8)	29.1 (11.3)	0.01

Data are means (SD); Clcreat = estimated creatinine clearance; Cmax = maximum concentration; CL = clearance; Vd = volume of distribution; Kel = elimination rate constant; T½ = elimination half-life; T0.5 = time to reach a trough concentration of 0.5 mg/L.

Table 4 shows the significant difference in volume of distribution of aminoglycosides between patients with or without septic shock. While the total body clearances did not differ between patients groups, the elimination half-life increased significantly by this increase in Vd. The Cmax was significantly lower in the shock group as well.

Table 4. Pharmacokinetic parameters of an ODA-regimen of aminoglycosides in ICU patients with or without septic shock

	Shock (n=49)	No shock (n=60)	P-value
Dose (mg/kg)	6.3 (0.8)	6.1 (1.1)	0.2
CLcreat (mL/min)	79 (19)	83 (24)	0.3
Cmax (mg/L)	18.5 (5.6)	21.3 (7.2)	0.03
CL (mL/min)	80 (35)	85 (43)	0.5
Vd (mL/kg)	353 (128)	287 (100)	0.004
Kel (h^{-1})	0.19 (0.07)	0.24 (0.11)	0.01
T½ (h)	4.3 (2)	3.7 (1.9)	0.01

Data are means (SD); CLcreat = estimated creatinine clearance; Cmax = maximum concentration; CL = clearance; Vd = volume of distribution; Kel = elimination rate constant; $T_{1/2}$ = elimination half-life.

Thirty-nine percent of all patients (n=35) were treated >24h; in 17 patients (49%) an adjustment of the dose or an increase of the dosing interval was needed. All adjustments were based on an increased elimination half-life. In practice, if an elimination half-life was lengthened, the dosing interval was increased as long as a 7mg/kg dose was necessary. The T0.5 was calculated and the next dose was given 4h after this trough concentration was reached. If the MIC of the pathogen was known and a Cmax/MIC ratio of 10 could be reached with a lower dose, the dose was decreased to subsequently reach an earlier T0.5. We tested the Hartford Hospital nomogram on our data set as well [5]. The recommended dosing interval based on this nomogram and one serum concentration at 6 hours was correct in only 62% of all cases.

The predicted performances of the three monitoring methods was assessed in 44 of the 53 surgical ICU patients. In nine patients no trough sample was available. These nine patients had creatinine clearances within the normal range. Table 5 shows the results obtained by the hospital's monitoring system compared to the results by methods A and B in which the estimated creatinine clearance was used to calculate the elimination rate constant. The negative bias indicates that all three methods tended to over predict the elimination rate slightly. The hospital's two sample method showed the most accurate precision, but there was no significant difference with method B.

Table 5. Predicted performance of the three monitoring methods.

Monitoring method	Bias	Precision	P-value[1]
Two serum samples	-0.6 (-1.9 to 1.1)	0.8 (0-3.9)	
CLcreat (method A)	-0.8 (-2.7 to 0.8)	1.2 (0-7.1)	0.02
CLcreat (method B)	-0.7 (-2.7 to 0.8)	0.9 (0-7.1)	0.35

Data are means (SD); [1] method A and B are compared to the two sample method.

Nephrotoxicity

Eighty-seven out of 89 patients were assessable to evaluate potential nephrotoxicity. Two patients died within 24 h after start of therapy. During the study period, no other potentially nephrotoxic drugs such as ciclosporin, vancomycin, amphotericine B, cisplatin and high-dose (>200 mg/daily) furosemide were administered.

Twelve patients showed an increase in serum creatinine of 45 μmol/L or more during therapy or within a week after discontinuating aminoglycosides (14%). This rise occurred in six of 54 patients (11%) receiving only one dose of which all six had shock. In six of 35 patients (17%) treated for at least 48h this rise in serum creatinine occurred, four of them had shock as well. A relation with peak level or trough level was not assessable. Two of these 12 patients died due to septic shock, in all other cases the impaired renal function was temporary.

Among the patients with an initial creatinine clearance <60mL/min (n=13), three showed a rise in serum creatinine of >45 μmol/L, all of them had shock as well. Two of these 13 patients died during their stay on the ICU, in the 11 patients remaining the renal dysfunction was temporary. In none of the patients with renal dysfunction haemofiltration was needed.

Discussion

There is substantial evidence that ODA is as effective and less nephrotoxic as multiple dosing in the treatment of gram-negative infections. A recent survey of ODA dosing in the United States revealed that 75% of the hospitals adopted this strategy for the treatment of gram-negative infections, while 25% of the hospitals preferred conventional multiple dosing [21]. There is still concern about ODA dosing in patients with variable pharmacokinetics and reduced renal function such as intensive care patients [22]. In this study, we describe our experience with ODA dosing in this specific patient population.

In our ICU, aminoglycosides are frequently used combined with beta-lactams, as empirical therapy for suspected bacterial sepsis with gram-negative micro-organisms. This "up front" dosing is switched to less toxic alternatives, if the septic shock is reversed and/or if blood cultures are negative. Only in case of *P. aeruginosa* infection tobramycin is continued as part of a combination therapy. This restrictive policy is reflected in the fact that the majority of patients were treated with one single dose (61%). One could wonder if monitoring is necessary with such a restrictive usage. But our data do show that in almost 50% of the patients treated >24h, a dose adjustment or lengthening of interval was necessary. If we would have used the Hartford Hospital nomogram and one serum concentration at 6 hours 5, the recommended dosing interval would be correct in only 62% of all cases. The pharmacokinetic profile of ICU patients is apparently too variable to fit in this nomogram. Furthermore, using this strategy one is not informed about the Cmax. Therefore, we choose for individual monitoring. Knowledge of the individual variability is necessary, because goal-oriented dosing of aminoglycosides results in higher antibiotic efficacy and reduced incidence of nephrotoxicity [23]. Using a one compartment model and two serum samples, the Kel and the T0.5 were calculated. In this model the elimination rate constant was slightly overestimated, as reflected in the negative bias. When the estimated creatinine clearance (with a minimum serum creatinine of 85 µmol/L = method B) was used to calculate the elimination rate constant a similar predictive performance was seen. This means that with a single aminoglycoside serum sample and the estimated creatinine clearance an acceptable prediction of the individual pharmacokinetic profile can be made. Consequently, this can save one sample per patient. In our daily practice, we still use the two sample method as we feel that method B needs to be evaluated in a larger group of patients. We would recommend to assess a pharmacokinetic profile in all ICU patients after the first dose to be informed about the individual variability and the T0.5. A subsequent dose can be adjusted to the MIC of the pathogen if applicable and given after a aminoglycoside free interval of at least 4h.

An increased volume of distribution of aminoglycosides in critically ill patients is well known [7,9]. Our data demonstrate that there is a significant difference in the volume of distribution between patients with septic shock compared to those without. Peripheral fluid extravasation in combination with aggressive fluid challenges is causing this phenomenon. Consequently, the maximum concentration reached is lower in patients with septic shock. Delays in attaining therapeutic levels of aminoglycosides have been associated with persistence of infection and treatment failure [11]. Therefore, an initial high dose of 7mg/kg is necessary to assure optimal bacterial killing in this patient group, even in

patients with renal impairment. Our data show that the frequently used dose of 5 mg/kg would be insufficient in a patient with septic shock caused by *P. aeruginosa* with a MIC of 2mg/L to obtain a Cmax/MIC ratio of 10.
The hyperdynamic circulatory state often seen septic shock did not cause an increased clearance of the aminoglycosides, which is reflected in an equal total body clearance in both groups. This decrease in the elimination rate constant and consequently the increase in elimination half-life was largely caused by the increase in Vd and not by a decrease in renal function. The elimination half-life was within the normal range in ICU-patients with an estimated creatinine clearance ≥ 60 ml/min, but was significantly increased in patients with an estimated creatinine clearance 30-60 ml/min. Thus, the mean time to reach a trough concentration less than 0.5 mg/L was within twenty hours in the normo-clearance group, permitting daily dosing. Extension of the dosing interval is necessary in patients with an estimated creatinine clearance < 60 ml/min.
Although optimum Cmax / MIC ratios have not been clearly defined, there is moderate to strong evidence that in patients with gram-negative infections the Cmax needs to exceed the MIC by eight to ten-fold for optimal clinical response [5]. Enterobacteriaceae and *P.aeruginosa* were the predominant gram-negative pathogens in this study. These data show that with an aminoglycoside dosing schedule of 7 mg/kg, the mean Cmax/MIC ratio was theoretically adequate in patients with *P.aeruginosa* (MIC90 = 2/mg/L). This initial high dosage needs to be continued in case of a *P.aeruginosa* infection. On the other hand in ICU patients with an infection caused by Enterobacteriaceae, the Cmax/MIC ratio was unnecessary high in most of the cases. So in prolonged therapy, lowering the dose as soon as the MIC is known would be the best strategy. By minimising the dose, there is less accumulation in the renal tubuli which prevents nephrotoxicity [24].
Once daily dosing may not be desirable in all situations. For instance, experimental studies of enterococcal endocarditis have shown a greater efficacy when an aminoglycoside is administered in multiple dosing regimen [25]. In other gram-positive infections no difference in efficacy compared to conventional dosing regimen has been found [5]. Therefore, ODA is not our standard treatment policy in gram-positive infections in critically ill. However in practice, the empirical combination of a beta-lactam and an aminoglycoside is synergistic against possible gram-positive pathogens the first 24-48 hours. As soon as cultures are known and a gram-positive pathogen is present we streamline antimicrobial therapy.
Reported nephrotoxicity of aminoglycosides dosed once daily varies between 0-5% [26,27], while this occurs in up to 17% in multiple dosing [27]. Assessment of nephrotoxicity of aminoglycosides in ICU patients is hampered by presence of numeral other risk-factors, such as hypotension and concomitant use of other nephrotoxic drugs. Approximately 30% of all patients with severe sepsis develop renal failure [28]. In our study population, 14% of the patients showed signs of renal impairment. This hampers decision making on whether to continue aminoglycosides, because the exact cause of renal dysfunction is not known. However, aminoglycosides are powerful antibiotics, often needed in patients with septic shock. Therefore, close monitoring is necessary. In all survivors the renal impairment was reversible, no haemofiltration was needed.

Conclusions: An ODA-regimen of 7mg/kg produced Cmax/MIC ratios >10 in the majority of critically ill patients in our population. Septic shock and renal dysfunction caused an aberrant pharmacokinetic profile of aminoglycosides in these patients, which was not suitable for the Hartford Hospital nomogram. Therefore, individual therapeutic drug monitoring is warranted. Signs of renal impairment were common in the presence of shock, but appeared to be reversible.

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CHAPTER 8

BIOAVAILABILITY OF CIPROFLOXACIN IN INTENSIVE CARE PATIENTS WITH GRAM-NEGATIVE INTRA-ABDOMINAL INFECTIONS

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Abstract
Background: Oral formulations of ciprofloxacin have been used successfully in the treatment of severe Gram-negative infections but no data are available on enteral absorption of ciprofloxacin in ICU patients with severe intra-abdominal infections.
*Objectives***:** 1) to describe the pharmacokinetics of ciprofloxacine; 2) to calculated the absolute bioavalability of ciprofloxacine in this patient group.
*Design***:** a randomized cross over study.
*Setting***:** 18-bed surgical intensive care unit in a referral centre.
*Methods***:** Comparative steady state pharmacokinetics of 750 mg bid enteral and 400 mg bid iv bid ciprofloxacin was studied in 5 tubefed ICU patients with severe Gram-negative intra-abdominal infections
*Main results***:** After multiple dosing the calculated 24h area under the serum concentration versus time curve after 750 mg bid enteral dosing was equivalent to that after 400 mg bid iv. The mean bioavailability of enteral dosing was 53.1 (95% CI 43.5-62.8) %. In 7 additional ICU patients with intra-abdominal infections receiving enteral ciprofloxacin, the mean serum steady state concentration at 2 hrs after administration was 3.9 (95% CI: 1.9-5.9) μg/ml, not significantly different from that found in the crossover study (p=0.4).
Conclusion: In tubefed ICU patients with severe intra-abdominal infections the bioavailability of enteral ciprofloxacin is adequate.

Introduction
Ciprofloxacin is a potent antibiotic with activity against a wide variety of Gram-negative bacteria including multiresistant organisms responsible for nosocomial infections on the intensive care unit (ICU). Because of excellent penetration in the peritoneal cavity and the rapid killing properties, ciprofloxacin is an important antibiotic for the treatment of Gram-negative intra-abdominal infections (GNIAI) including peritonitis, cholangitis, and intra-abdominal abscesses [1,2]. In non-ICU patients, oral ciprofloxacin has a good bioavailability (56-78%) resulting in adequate serum and tissue concentrations; this can simplify the administration and reduce costs compared to intravenously administered ciprofloxacine [3,4]. A recent study in ICU patients with pneumonia showed serum levels well above MIC=s for many important pathogens [5]. However, in ICU patients with severe GNIAI no pharmacokinetic data are available of the use of orally or enterally administered ciprofloxacin, since these patients are usually excluded in pharmacokinetic studies [4]. Single dose studies performed in non-ICU patients receiving enteral feeding have shown impaired bioavailability with a reduction varying between 27 and 67% probably due to interaction with metallic cation-containing feeding products [6,7]. This had led to a warning against indiscriminate use of enteral ciprofloxacin in ICU patients with severe infections [8] In patients with severe GNIAI the absorption of ciprofloxacin may be even more compromised because of the malabsorption state of infected viscera and repeated surgical interventions [9]. In a recent randomized study, sequential intravenous/oral treatment with ciprofloxacin combined with metronidazol had equivalent efficacy as continued IV treatment with the same combination [2]. However, no pharmacokinetic data were

gathered, and the oral administration was allowed only after improvement of the patient. So, it is difficult to conclude from this study whether oral or enteral ciprofloxacin administration is appropriate in the treatment of severe GNIAI.
Therefore, we conducted a randomized crossover study to investigate the pharmacokinetics of enteral (750 mg bid) versus intravenous (400 mg bid) ciprofloxacin in patients with severe GNIAI while receiving continuous tube feeding.

Patients and Methods

Patients

Tube-fed ICU patients aged between 18 and 60 years were eligible if they had a GNIAI with a strain susceptible to ciprofloxacin. Patients were excluded if they had a contraindication for tube-feeding, a history of quinolone allergy, a history of seizures, an estimated creatinine clearance of less than 25 ml/min, abnormal hepatic function tests (ASAT or ALAT more than 90 U/L), or the concomitant use of any of the following drugs theophylline, caffeine, coumarine derivatives, antacids containing magnesium or aluminium salts, sucralphate, zinc salts, iron salts, calcium salts, NSAID=s, cyclosporin, metoclopramide, glibenclamide and probenicide. Females of childbearing potential were excluded if they had a positive urine pregnancy test. The study was approved by the Hospital Ethical Committee, and informed consent was obtained from the patients or their legal representatives.
In addition to the cross-over study, ICU patients with peritonitis were studied in a non-randomized manner if they received enteral ciprofloxacin treatment.

Study medication and collection of samples and clinical data

A randomized, two-sequence crossover design was used for each patient. Patients received ciprofloxacin at random either 400 mg intravenously every 12 hr or 750 mg via a nasogastric or nasoduodenal tube every 12 hrs. For intravenous use vials of 254,4 mg ciprofloxacin lactate were used corresponding to 200 mg ciprofloxacin. Reconstitued solutions were made within 90 minutes prior to the infusion and stored at +40 C until used. Infusion was performed with use of an infusor within 30 minutes. For enteral use tablets of 873 mg ciprofloxacinhydrochloride monohydrate were used corresponding to 750 mg of ciprofloxacin. Tablets were dissolved in 20 ml of a saline solution and added to the enteral feeding. Continuous enteral feeding (50 to 75 ml/hr NutrisonR or Nutrison E+ R, Nutricia, Netherlands) was maintained throughout the study. The contents of these nutritions included salts of calcium 50 mg, magnesium 20 mg, iron 1 mg, zinc 1 mg per 100 ml. Treatments were switched after 48 to 60 hrs. Samples of blood and urine for ciprofloxacin concentrations were drawn at least 36 hrs following the first dosage of each treatment sequence. Serial blood samples were collected before drug administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hr after dosing; urine samples were taken at 2,4,6, 8 and 12 hr after dosing. Samples of serum and urine were stored frozen at -800 C.
Bloodsamples from non-randomized patients were taken at least 36 hrs after initiating enteral 750 mg bid ciprofloxacine just prior to and 2 hours after dosing.
The following clinical data were documented during the crossover study: surgical diagnosis, APACHE II score at entry; the number of laparotomies prior to entry and during

administration of study medication and sample collection; the Gram-negative pathogen isolated from peritoneal cavity, type of enteral nutrition, rate of enteral feeding, duration of successful enteral feeding prior to entry, gastric residue at time of sampling, type of feeding-tube; biochemistry including creatinin, hepatic function tests, albumen and hematology tests at entry, prior to each second treatment sequence and within 48 hrs after stopping the study medication; creatinine clearance during sample collections.

Ciprofloxacin assay

Samples were assayed for ciprofloxacin by HPLC using an octyldecylsilane column (Chrompack, Middelburg, The Netherlands) with a 1.6% triethylamine solution (pH 2.15) containing 19.4% (vol/vol) acetonitril as a mobile phase. A 0.8 M perchloric acid solution was added to an equal volume of sample, centrifuged, and the supernatant analyzed. The lower limit of assay sensitivity was 0.5 mg/L. Samples were measured over a range of 0-16 mg/L and control samples were determined during every run. Between sample between day variation was less than 10%. All assays were performed in duplicate.

Data analysis and statistics

Serum concentrations were plotted versus time in a semilogarithmic plot. Pharmacokinetic parameters were estimated using the MWpharm program (Mediware, Groningen, The Netherlands) using a two compartment open model after iv dosing and a one compartment open model after enteral administration. The AUC0-12h was determined using the log-linear trapezoidal rule. Bioavailability was calculated by dividing the AUC0-12h after enteral dosing by that after iv dosing and correcting for the dose. The Wilcoxon matched pairs or the matched t-test was used to detemined the differences between treatments. The primary efficacy measure was defined as the AUC0-12h of both treatment regimens being at least equal. Testing was done by using a one-sided test procedure to assess equivalence of average bioavailability. Before the study was started it was determined that efficacy would be concluded if the lower bound of the 95% confidence interval for the average ratio of the intraindividual AUC fell above 80%. The following secondary parameters were determined: the maximum concentration of ciprofloxacin in serum during steady state (Cmax,ss); the time to reach Cmax,ss; the total clearance (CL) and the serum half life-time T1/2β.

Results

Seven patients enrolled, of which 6 completed the cross-over study. One patient developed a significant impairment of renal function during the IV regimen, resulting in non-evaluable data for this regimen. Five patients were evaluable for comparison of the primary endpoint parameter. The characteristics of these 5 patients are summarized in Table 1.

The mean steady-state serum concentrations of enteral and IV regimens are shown in Figure 1. The pharmacokinetic data are shown in Table 2. The mean (95% CI) creatinine clearance was 60.8 (28-93) mL/min for the enteral and 76.8 (30-124) mL/min for the intravenous regimen (p=0.5). The mean Cmax was 3.2 (95% CI: 1,8-4,6) µg/mL for the enteral and 6.8 (3,9-9,8) µg/mL for the IV regimen, the mean time to Cmax was 2.1 (95% CI: 0,4-3,8) and 0.6 (0,3-0,9) hrs, respectively. The mean AUC0-12h during enteral ciprofloxacin (19.1; 95% CI 10.8-27.5) did not significantly differ from the AUC0-12h during IV treatment (19.3; 95% CI 11.8-26.7). The mean bioavailability of enterally administered ciprofloxacin was 53.1 (95% CI 43.5-62.8) %.

In addition to the above enrolled two patients not evaluable for the crossover analysis, 5 other ICU patients with intra-abdominal infections received ciprofloxacin enterally (750 mg bid). In this group of seven patients the mean creatinine clearance was 85 ml/min (51-120). The steady state concentrations of ciprofloxacin at 2 hours after enteral administration were comparable to the mean at this time point in the five cross-over patients (mean 3.9, 95% CI 1.9-5.9 µg/ml; versus mean 3.2, 95% CI 1.8-4.6 µg/ml, p=0.4).

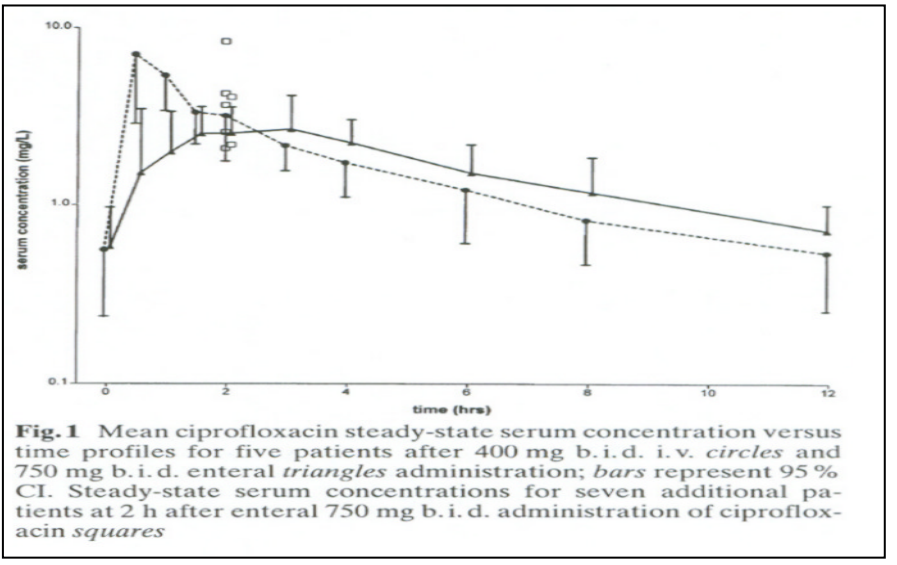

Fig. 1 Mean ciprofloxacin steady-state serum concentration versus time profiles for five patients after 400 mg b.i.d. i.v. *circles* and 750 mg b.i.d. enteral *triangles* administration; *bars* represent 95 % CI. Steady-state serum concentrations for seven additional patients at 2 h after enteral 750 mg b.i.d. administration of ciprofloxacin *squares*

Table 1. Characteristics at entry of five patients with severe GNIAI treated with enteral and parenteral administration of ciprofloxacin.

Characteristic	Patient A	Patient B	Patient C	Patient D	Patient E
Age (yr)	27	74	76	48	55
Weight (kg)	75	70	100	86	55
Diagnosis	Low anterior Resection	Postpyloric Perforation	Hysterectomy (cancer)	Cholecystectomy and pancreatitis	Crohn's disease
ICU stay (days)	14	60	27	12	16
Laparotomies - number - prior to entry	 n=7 4 days	 n=2 56 days	 n=7 2 days	 n=6 1 day	 n=7 0 days
Pathogen	Pseudomonas aeruginosa	Klebsiella Pneumoniae	Enterobacter aerogenes	Escherichia coli	Klebsiella pneumoniae
Open abdomen treatment	+	-	+	+	+
APACHE II score	16	26	18	13	12
Serum creatinine	37	43	57	110	37

Table 2. Pharmacokinetic parameters of ciprofloxacin after enteral and parenteral treatment.

Pharmacokinetic parameter	Mean value (95% CI) (n=5)
Intravenous administration	
AUC (mg.h/L)	19.3 (11.8-26.7)
Vdss (L)	95.1 (64.3-125.9)
Cl (L/h)	17.0 (10.3-23.7)
T1/2β (h)	5.2 (4.4-6.3)
Cmax,ss	6.8 (3.9-9.8)
Enteral administration	
AUC (mg.h/L)	19.1 (10.8-27.5)
Bioavailability (%)	53.1 (43.5-62.8)
Cmax,ss	3.2 (1.8-4.6)
AUC enteral / AUCIV (%)	99.6 (81.5-117.7)

AUC= area under serum concentration-time curve; Vdss = volume of distribution at steady state; Cl = total body clearance; T1/2β = elimination half-life; Cmax,ss = maximum serum concentration at steady state.

Discussion

In this study we demonstrated that enteral administration of ciprofloxacin 750 mg bid during tube feeding in ICU patients with severe GNIAI resulted in serum levels comparable to that of 400 mg bid iv administration. We excluded patients with significantly impaired renal function because these patients would have favourable serum druglevels [4,10]. We did not exclude patients after substantial small bowel resections, patients undergoing abdominal rinsing or laparotomies during ciprofloxacin dosing unless tubefeeding had to be discontinued. In our study we did not hold enteral feeding throughout dosing although it has been suggested that the presence of divalent cation-containing tubefeeding could impair absorption [6,7]. Despite the presence of these factors potentially influencing the bioavailability, we found a reasonable bioavailability for the enteral administered ciprofloxacin of 53%. Although Cmax after enteral administration was lower than after intravenous administration, the AUC achieved by ciprofloxacin 750 mg bid via the enteral route appeared to be equivalent to that achieved by intravenous ciprofloxacin 400 mg bid. Because the AUC is the most predictive pharmacokinetic parameter for clinical success, we believe that our results indicate that ciprofloxacin can be used successfully when administered orally or enterally in this patient population [11].

The regimen of 750 mg bid used in this study, may be insufficient in some severe Pseudomonas infections for which an IV regimen of 400 mg tid is the standard treatment at this moment [12]. Such an IV regimen would probably equal enteral ciprofloxacin 750 mg tid in ICU-patients with GNIAI. In such infections it is probably more appropriate to start with IV therapy and, if possible, to switch to oral/enteral ciprofloxacin with a daily dosage

of 2 gram. The use of enteral or oral use in ICU patients in initial or stepdown regimen, will result in considerable savings of costs.
In conclusion, our pharmacokinetic study demonstrated that enteral dosing of ciprofloxacin 750 mg twice a day resulted in adequate serum levels in ICU patients with severe Gram-negative intra-abdominal infections and can therefore be used in the treatment of patients.

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CHAPTER 9

PERI-OPERATIVE PHARMACOKINETICS OF CEFOTAXIME IN SERUM AND BILE DURING CONTINUOUS AND INTERMITTENT INFUSION IN LIVER TRANSPLANTATION PATIENTS

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Abstract
Background: Cefotaxime demonstrates time-dependent killing and continuous infusion (CI) has been proposed to ensure adequate cefotaxime concentrations for the entire course of therapy. Liver transplantations (LTX) are frequently complicated by bacterial infections and therefore peri-operative broad spectrum antibiotics are used.
Perioperative blood loss, fluid replacement and liver dysfunction alter drug pharmacokinetics during LTX. No data exist on concentrations of cefotaxime reached in the serum and bile in patients undergoing a LTX.
Objectives: 1) To determine the pharmacokinetics of cefotaxime in serum and bile during continuous and intermittent infusion in patients undergoing a LTX
Methods: 15 patients undergoing a LTX were included. The pharmacokinetics of cefotaxime and its active metabolite were studied after continuous infusion (CI) (4000 mg iv q24 following a loading dose of 1000 mg) and intermittent bolus infusion (BI) (1000 mg q6) in serum and bile. Samples for pharmacokinetic analyses were collected the first 48 h after LTX. Cefotaxime concentrations were determined by HPLC.
Main Results: During surgery, the mean concentration in serum after CI was 18.2 mg/L. The lowest serum concentration was 5 mg/L in the CI group and undetectable in the BI group. Serum concentrations of ≥ 4 mg/L were reached for 100% of the dosing interval during CI and approximately 60% during BI. There was no correlation between the amount of blood loss and the rate of total body clearance (R2=0.1).
Postoperatively, the mean concentration in serum after CI was 26.4 mg/L. The lowest serum concentration was 7.8 mg/L in the CI group and undetectable after BI. Overall, the mean (SD) amount of unchanged CTX found in urine was 51 (23)% of the administered dose, corresponding with a mean (SD) renal clearance of 91 (69) mL/min. The overall total metabolic clearance was 54 (43) mL/min and the partial metabolic clearance was 32 (31) mL/min.
The peri-operative pharmacokinetics of cefotaxime were deranged and variable in this patient group, mainly caused by an increased volume of distribution and a decreased hepatic clearance. Metabolism was hampered, but still AUCdctx/AUCctx ratios varying between 0.7-0.9 were reached peroperatively. Postoperatively, AUCdctx/AUCctx ratios were higher than peroperatively (1.1-1.4). Overall, the mean (SD) amount of DCTX found in urine was 24 (13)% of the administered dose.
The total amount of unchanged CTX found in bile was approximately 0.1% of the administered dose, leading to concentrations exceeding 4 mg/L throughout the dosing interval for both regimens.
Conclusion: Intermittent bolus infusion of cefotaxime of 1000 mg q6 produces insufficient serum concentrations during surgery in patients undergoing a liver transplantation. This can be avoided with continuous infusion. Postoperative, a decreased metabolic clearance in transplantated livers and a drop in renal function cause an impaired clearance of cefotaxime and accumulation of its metabolite. Subsequently, both regimen produce adequate concentrations in serum and bile postoperative.

Introduction
Orthotopic liver transplantations (OLT) are frequently complicated by bacterial infections of the abdomen, the lower respiratory tract and the bloodstream. Up to 83% of the patients

become infected at some stage [1] and overall, 79% of all infection in the ICU are bacterial [2]. Peri-operative translocation of Gram-negative bacteria is believed to be an important factor in the pathophysiology of infectious complications after OLT, especially during the anhepatic phase of liver transplantation when the hepatic clearance of endotoxin by Kupffer cells is absent [3]. Therefore, perioperative broad spectrum antibiotics are used to prevent bacteremia and surgical site infection (SSI).

Cefotaxime (CTX), a third generation broad spectrum cephalosporin is commonly used as peri-operative antimicrobial prophylaxis in OLT. Cefotaxime is partly metabolised in the liver to three metabolites of which one, desacetylcefotaxime (DCTX) has a bactericidal activity of a tenth of the effect of CTX against the common Enterobacteriaceae [4]. Although controversial, antimicrobial prophylaxis is often continued postoperatively for 48 hours to adequately cover the perioperative vulnerable period in OLT. Administration of systemic antibiotics during major surgery may require adjustment because of extensive perioperative blood loss and fluid replacement, which may change distribution volumes and clearance of these drugs and reduce their prophylactic efficacy [5]. An impaired clearance of CTX after OLT has been reported [6, 7], but to our knowledge no data are available on biliary concentrations during the first 48 hours postoperatively.

Both from a pharmacodynamic and pharmacokinetic point of view, it seems more appropriate to administer CTX by continuous infusion. In vitro studies and studies in laboratory animals show that killing of micro-organisms by cephalosporins is time rather than concentration dependent and that time above the MIC is the most important pharmacodynamic parameter [8, 9]. Furthermore, cefotaxime does not show a post-antibiotic effect against Gram-negative bacilli. Intermittent administration produces high peak and low trough concentrations in serum which may fall below the MIC for the organisms during the dosing interval. Continuous infusion of CTX produces a relatively constant concentration that can be maintained above the MIC, thereby optimising the drug's pharmacodynamic properties [10].

We conducted a study to investigate whether continuous infusion of CTX would produce more favourable concentration versus time profile in relation to a target MIC in serum and bile compared to intermittent infusion in patients during the first 48 hours of OLT.

Materials and methods

The study protocol met the standards of the hospital's medical ethical committee. Written informed consent was obtained from the patient.

Patient population

Patients over 16 years of age who underwent an elective OLT between January 1997 and October 1998 were asked to participate in the study. Exclusion criteria were: 1) known allergy to CTX; 2) pre-operative severe renal impairment defined as a calculated creatinine clearance < 10 ml/min and/or urinary output < 10ml/h over the preceding 12 hours and/or hemofiltration or dialysis.

The following parameters were assessed peri-operatively: demography data including age, sex, weight and cause of liver disease. Peroperative blood loss, fluid replacement and duration of surgery were documented.

Serum creatinine, ALAT, ASAT, bilirubin and albumin were assessed daily. Creatinine clearance was estimated from the serum creatinine concentration by using the Cockroft-Gault equation [11].

Study design

Due to logistic reasons the study had a non-randomised block design. The indications for liver transplantation and operative procedure did not change during the study period.

The daily dose was 4000 mg per 24 hours. In the first block 8 elective patients received CTX 1000 mg iv by bolus infusion (BI) intermittently every 6 hours (q6). In the second block 7 elective patients received a CTX 1000 mg iv loading dose followed by a 4000 mg iv continuous infusion (CI) per 24 hours (q24). The maximum duration of prophylaxis and thus the maximum study period was 48 hours. The first dose was given 30 minutes prior to incision.

CTX administration

For the continuous infusion, 4000 mg of CTX (Claforan, Hoechst Marion Roussel, Hoevelaken, The Netherlands) was dissolved in 50 ml 0.9% NaCl prior to administration and infused with an electronic pump (Ivac Medical System, Hampshire, England). The loading dose and the intermittent bolus infusions were prepared according to the manufacturer's guidelines and were infused in 20 minutes using an electronic pump.

Only in case of severe renal impairment there is significant change in elimination rate of CTX and DCTX. When the calculated creatinine clearance dropped <10ml/min the total daily dose was halved.

Pharmacokinetics

Peroperative and postoperative serum sampling: to determine CTX and DCTX concentrations in serum, 2 ml blood samples were taken from an indwelling arterial catheter in the contra-lateral arm prior to infusion (t=0) and at 20min, 30min, 60min and once hourly throughout surgery for both CI and BI. Postoperatively, 4 samples were taken within 48 hours with a sample interval of at least 6 hours during continuous infusion. During intermittent infusion blood samples were taken just prior to the 5th or 6th dose and at 20 min, 30 min, 1h, 2h, 4h, and 6h following start infusion.

Postoperative bile sampling: in patients with a T-tube, a minimum of 500 microliter of bile was sampled at intervals to determine the CTX and DCTX concentrations. During continuous infusion 4 samples were taken within 48 hours with a sample interval of at least 6 hours. During intermittent infusion bile samples were taken just prior to the 5th or 6th dose (-30min-0min) and at 0-30min, 30min-1h, 1-1.5h, 1.5-2h, 3.5-4h, and 5.5-6h following the start of infusion [12, 13].

Postoperative urine sampling: urine was collected over 6 hours. The volume was measured and a sample was taken for analysis of CTX concentrations.

Pharmacokinetic analysis: after sampling, blood was allowed to clot on ice for 20min and centrifuged. Serum, bile and urine samples were stored at -70°C until analysis. CTX and DCTX concentrations were determined by using high performance liquid chromatography (HPLC) [14]. The lower limit of detection was 0.1 mg/L in serum and bile and 0.5 mg/L in urine and the method was linear up to 250 mg/L. The interday coefficient of variation was less than 5%.

The primary descriptive parameters after BI were area under the concentration curve (AUC0-6h), the serum elimination half-life (T½b), the volume of distribution (Vd), the total body clearance (CLtotal) and concentrations in serum and bile reached perioperatively. Time above the target minimal inhibitory concentration (T>MIC) was estimated from the individual curves. Perioperatively, a target CTX concentration of at least 4 mg/L was chosen (e.g. 4 times a MIC of 1 mg/L), as CTX provides inhibition against most gram-negative pathogens isolated on the ICU at concentrations < 1 mg/L [15].
In the CI group, the AUC0-6h in serum and bile was calculated by multiplying the mean concentration in serum and bile over 24h times 6. The CLtotal was calculated by dividing the infusion rate through the mean concentration over 24h. In the intermittent therapy group, the AUC0-6h, T½b and Vd in serum were estimated with the MWpharm program (Mediware, Groningen, The Netherlands) using a two compartment model based on the Akaike criteria [16]. The AUC was calculated using the trapezoidal rule (AUC0-24h). The CLtotal was calculated using a non-compartmental equation (Clearance = Dose / AUC (mL/min)). The AUC0-6h in bile was estimated by multiplying the mean concentration over 6h times 6. The AUCbile/AUCserum ratio was calculated in patients with both sample ports available.
The renal clearance of CTX or DCTX (CLrenal) was defined as fe x CL, where fe is the percentage unchanged CTX or DCTX eliminated in urine in 6 h. The biliary clearance (CLbile) was calculated by CLbile = Q0-6/AUC0-6, where Q0-6 is the total amount of CTX or DCTX recovered in bile during 6 h. The total metabolic clearance (CLtm) was estimated as follows: CLtm = CLtotal – (CLrenal+CLbile); this metabolic clearance represents the biotransformation of CTX in all metabolites. The partial metabolic clearance (CLpm), which is the clearance by biotransformation of CTX into DCTX was calculated as follows: CLpm = (fe x CL)+(CLbile of DCTX), where fe is the percentage DCTX eliminated in urine in 6 h.
Statistical analysis
For description of plasma level profiles (i.e. plots, tables) after administration of CTX and DCTX, means and standard deviations were used. Mann-Whitney tests were used to determine differences between groups; a p-value <0.05 (two-tailed) was considered statistically significant. Correlation of CTX clearance with peroperative blood loss was determined by using the Spearman correlation statistic. Patients were eligible for analysis if they had completed the peroperative phase.

Results
Fifteen patients were enrolled, of whom seven received continuous and eight received intermittent CTX as perioperative antibiotic prophylaxis. Postoperatively, all patients were concomitantly given a selective decontamination regimen consisting of tobramycin, colistine and amphotericin B orally [17]. All patients received the standard regimen. Dose adjustments due to an impaired renal function were not necessary. One patient in the intermittent group died after 1 day due to arteria hepatica thrombosis; one patient in CI group died at the end of surgery due to a myocardial infarction.
Demographics: The demographic characteristics of the study patients are summarised in table 1. The groups were comparable as regards to age, body mass index, transaminases,

bilirubin and creatinine clearance. The duration of operation varied between 4.3 and 9 h. The peroperative blood loss varied between 4 and 36 L and peroperative infused volume varied between 11 and 41 L.

Table 1. Demographics (n=15)

	Intermittent (n=8)	**Continuous (n=7)**	**P**
Age (yr)	52 (10)	52 (9)	0.9
Body Mass Index (kg/m^2)	43 (7)	44 (7)	0.8
Male / female	6 / 2	3 / 4	
Cause of liver failure			
- Hepatitis	n=3	n=2	
- Primary biliary sclerosis	n=1	n=1	
- Alcohol	n=3	n=2	
- Other	n=1	n=2	
ALAT (U/L)	44 (29)	36 (12)	0.6
ASAT (U/L)	72 (46)	62 (22)	0.6
Bilirubin (µmol/L)	96 (93)	60 (33)	0.4
CL_{CR} before surgery (ml/min)	112 (22)	109 (48) 0.8	
Duration of operation (h)	6.6 (1.0)	6.8 (1.5)	0.9
Volume of ascites (L)	3.3 (0.9)	3.3 (2.2)	1.0

If applicable, data are means (SD)

Pharmacokinetics in serum: Peroperatively, serum concentrations were measured in 7 patients after CI and in 8 patients after BI. Postoperatively, serum concentrations were measured in 6 patients after CI and in 7 patients after BI. Table 2 illustrates the peroperative pharmacokinetic parameters in serum of both dosing regimens.

CTX

The curves for mean (SD) serum concentrations of CTX versus time of both regimens are shown in figure 1. The total body clearance did not significantly differ between the two dosing regimens. The mean concentration in serum after CI was 18.2 mg/L (concentrations from the loading dose were not included). The lowest serum concentration was 5 mg/L in the CI group and undetectable in the intermittent group. Serum concentrations of ≥ 4 mg/L were reached for 100% of the dosing interval during CI and approximately 60% during intermittent administration. Seven out of eight patients in the intermittent group had trough concentrations lower than 4mg/L, two patients had undetectable concentrations. Compared to healthy volunteers [18, 19] (T1/2=1.2 h; CL=200 mL/min and Vd=240 mL/kg), the mean serum half-life was increased, the mean total body clearance was comparable and the mean volume of distribution was increased approaching total body water. There was no correlation between the amount of blood loss and the rate of total body clearance (R2=0.1).

Postoperatively, the mean AUC0-6h in serum was comparable for both regimens. The mean concentration in serum after CI was 26.4 mg/L (inter individual variance =12%). The lowest serum concentration was 7.8 mg/L in the CI group. One patient in the intermittent group had trough concentrations <0.1 mg/L, 2 of 7 patients had trough concentrations <

4mg/L. Compared to healthy volunteers (T1/2=1.2 h; CL=200 mL/min and Vd=240 mL/kg), the mean serum half-life

Fig 1. Serum concentratins of cefotaxime in liver transplantation patients after intermittent (□; n=8) and continuous (●; n=7) infusion

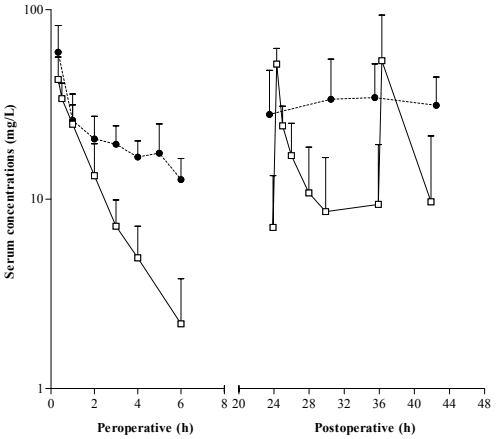
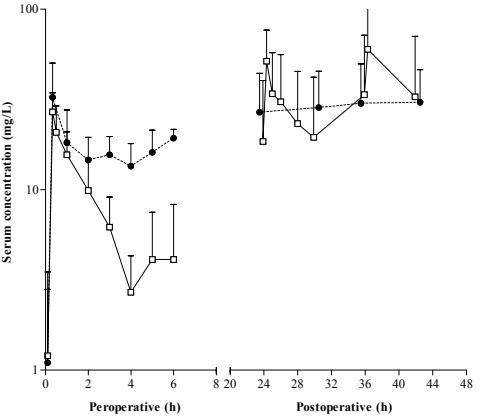


Fig 2. Serum concentration of desacetylcefotaxime in liver transplantation patients after intermittent (□; n=8) and continuous (●; n=7) infusion



was increased, the mean total body clearance was decreased and the mean volume of distribution was increased. Overall, the mean (SD) amount of unchanged CTX found in urine was 51 (23)% of the administered dose, corresponding with a mean (SD) renal clearance of 91 (69) mL/min. The overall total metabolic clearance was 54 (43) mL/min and the partial metabolic clearance was 32 (31) mL/min.

DCTX

The curves for mean (SD) serum concentrations of DCTX versus time of both regimens are shown in figure 2. Metabolism was hampered, but still AUCdctx/AUCctx ratios varying between 0.7-0.9 were reached peroperatively. The mean concentration in serum after CI was 15.0 mg/L. The lowest serum concentration was 7.3 mg/L in the CI group and undetectable in the intermittent group.

Postoperatively, AUCdctx/AUCctx ratios were higher than peroperatively (1.1-1.4). The mean concentration in serum after CI was 29.3 mg/L. The lowest serum concentration was 5.5 mg/L in the CI group; the lowest trough concentration in the BI group was 1.8 mg/L. Overall, the mean (SD) amount of DCTX found in urine was 24 (13)% of the administered dose.

Pharmacokinetics in bile: CTX and DCTX concentrations reached in bile were measured in 6 patients after CI and in 6 patients after BI. In one patient in the BI group no T-tube was present.

CTX

Table 3 illustrates that, the mean $AUC_{0\text{-}6h}$ in bile after intermittent administration did not significantly differ from the $AUC_{0\text{-}6h}$ during CI. In bile, an AUC of approximately 80-90% of the concomitant serum AUC was attained. The mean concentration in bile after CI was 22.6 mg/L (inter individual variance =19%). The lowest concentration in bile was 4.6 mg/L

in the CI group and 4.0 mg/L in the BI group. With both regimens, concentrations exceeded 4 mg/L throughout the dosing interval. The total amount of unchanged CTX found in bile was approximately 0.1% of the administered dose, which corresponds with a clearance of CTX in bile of approximately 0.1 ml/min.

DCTX

The total amount of DCTX found in bile was approximately 0.1% of the administered dose. Noteworthy is the observation that the AUCbile/AUCserum ratio was significantly higher after CI.

Table 2. Peroperative pharmacokinetic parameters of CTX and DCTX in serum in liver transplant patients

PK parameter	Intermittent administration (1000mg q6)		Continuous infusion (4000mg /24h)		P-value
	CTX	DCTX	CTX	DCTX	
	n=8		*n=7*		
$AUC_{0\rightarrow 6h}$ (mg.h/L)	72 (21)	53.4 (23.2)	109 (27)	90 (24)	0.01 / 0.05
AUC_{DCTX}/AUC_{CTX} (serum)	0.7 (0.2)		0.9 (0.3)		0.7
C_{max} (mg/L)	42.9 (13.4)	27.0 (7.4)			
C_{trough} (mg/L)	2.2 (1.6)	4.1 (4.6)			
C_{mean} (mg/L)			18.2 (4.5)	15.0 (4.5)	
$C_{trough} \leq 4$ mg/L	7/8		0		
Vd (L/kg)	0.53 (0.22)				
T½β (h)	2.0 (0.7)	6.0 (3.3)			
CL (mL/min)	238 (77)		194 (63)		0.2
Calculated CL_{CR} (mL/min)	112 (22)		109 (48)		0.9
Blood loss (L)	13 (7)		14 (10)		0.7
Substituted fluid (L)*	23 (8)		22 (9)		0.9

Data are means (SD)

* Packed cells, fresh frozen plasma, colloids, saline and donor platelets

Table 3. Postoperative pharmacokinetic parameters of CTX en DCTX in serum and bile in liver transplant patients after intermittent and continuous administration

Pharmacokinetic parameter	Intermittent administration (1000mg q6)		Continuous infusion (4000mg/24h)		P-value
	CTX	DCTX	CTX	DCTX	
Serum	*n=7*		*n=6*		
$AUC_{0\rightarrow 6h}$ (mg.h/L)	105 (41)	165 (133)	159 (60)	176 (100)	0.1 / 1.0
AUC_{DCTX}/AUC_{CTX} (serum)	1.4 (0.6)		1.1 (0.5)		0.2
C_{max} (mg/L)	51.7 (10.9)	51.6 (24.9)			
C_{trough} (mg/L)	8.6 (8.0)	19.5 (22.6)			
C_{mean} (mg/L)			26.4 (9.9)	29.3 (16.6)	
$C_{trough} \leq 4$ mg/L	2/7		0		
Vd (L/kg)	0.396 (0.166)				
T½β (h)	3.6 (2.8)	6.0 (4.5)			
CL (mL/min)	147 (88)		126 (72)		0.7
CL renal (mL/min)	96 (88)		99 (84)		1.0
CL metabolic (mL/min)	33 (41)		24 (19)		0.6
Calculated CL_{CR} (mL/min)	95 (41)		84 (37)		1.0
Bile	*n=6*		*n=6*		
$AUC_{0\rightarrow 6h}$ (mg.h/L)	75 (41)	158 (109)	109 (78)	546 (340)	0.3 / 0.01
AUCbile/AUCserum	0.8 (0.5)	1.6 (1.0)	0.9 (0.4)	3.2 (1.9)	0.6 / 0.01
C_{mean} (mg/L)			22.6 (10.0)	91 (57)	
C_{max} (mg/L)	20.8 (8.3)	34.4 (25)			
C_{trough} (mg/L)	9.2 (6.3)	23.4 (20.7)			
$C_{trough} \leq 4$ mg/L	0		0		
V_{BILE} (mL/6h)	35 (14)		44 (19)		0.3
Bile clearance (mL/min)	0.09 (0.03)	0.1 (0.04)	0.12 (0.05)	0.1 (0.1)	0.3 / 0.4

Data are means (SD)

Discussion

This study showed that from a pharmacodynamic point of view continuous infusion of CTX in patients undergoing a liver transplantation, resulted in favourable concentrations in serum compared to intermittent infusion especially during surgery. The peri-operative pharmacokinetics of CTX were deranged and variable in this patient group. This was mainly caused by an increased volume of distribution and a decreased hepatic clearance. The formation of DCTX was decreased, but concentrations remained high through accumulation. Biliary clearance was low, but sufficient concentrations of CTX and its metabolite were reached.

Patients undergoing an OLT suffer several assaults on their physiology which can influence their pharmacokinetic profile. In short, the technique of OLT consists of three phases: 1) The hepatectomy phase; 2) the anhepatic phase and 3) the reperfusion phase.
During the hepatectomy phase in which the own diseased liver is resected, the blood loss can be substantial due to the presence of portal hypertension and severe coagulopathy. Large amounts of fluid, packed red blood cells, fresh frozen plasma and donor platelets are needed to compensate the loss. A cell saver is used to wash the patients own blood lost during surgery and to return it as packed cells. Furthermore, when crossclamping of the portal vein and the abdominal vena cava inferior leads to hemodynamic instability due to a decreased venous return to the heart, a veno-venous bypass is used. With this bypass, the venous return of the splanchnic and lower extremity vascular beds is transferred to the axillary vein.
The anhepatic phase in which the graft is anastomosed takes about 60-90 minutes, a period in which no liver metabolism takes place.
During the reperfusion phase in which the transplant is recirculated again and the bilio-digestive anastomosis is made, profound hemodynamic disturbances and clotting disorders occur due to circulating cytokines and enhanced fibrinolysis. Furthermore, the graft has to regain its function. This deranged physiology can have an effect on the pharmacokinetics of drugs.

CTX demonstrates concentration independent killing therefore the time above the MIC determines the microbiological outcome. Maximal efficacy of CTX is achieved when concentrations in serum are maintained above 4 x MIC at least 60-70% of the dosing interval [9, 20]. However, in case of surgical prophylaxis the onset of the infection is unknown. Sufficiënt concentrations have to be present in the tissues during the entire procedure as exogenous contamination can occur at any time until the wound is closed and endogenous contamination can occur late in the course of the procedure. Therefore, the target concentration must be maintained throughout the dosing interval, especially during the reperfusion phase (5-6h after start of surgery) when translocated pathogens re-circulate. In this study, the continuous regimen of 4000mg/24h after a loading dose of 1000mg resulted in a mean steady state concentration in serum of 18 mg/L during surgery. The intermittent bolus regimen of 4 times 1000mg per 24h resulted in a sufficient maximum concentrations in serum during surgery, but the trough concentration in serum fell below the intended concentration of 4 mg/L in 7 out of 8 patients. Twenty-five percent of the

patients in the intermittent group had undetectable trough concentrations in serum during surgery. During the anhepatic phase (2-3 h after start of surgery) serum concentrations were sufficient for both regimens. However, during the reperfusion phase, intermittent administration resulted in insufficient concentrations.

The extent of blood loss and the total body clearance did not correlate, and the latter was not increased compared to healthy volunteers [18, 19]. Most likely, there was an increased clearance, but the impaired hepatic clearance during the an-hepatic phase did compensate for antibiotic loss caused by bleeding, resulting in a normal total body clearance. The sub-optimal concentrations in serum after intermittent administration during surgery however, can be explained by the large increase in volume of distribution. Blood loss exerts an influence on serum concentrations of drugs, which are mainly distributed intravascularly. CTX is distributed extracellularly. Therefore, the increase in the volume of distribution during surgery, caused by large amounts of fluid replacement and the extra volume of the cell saver and the veno-venous bypass machine is important. From this increased extravascular pool CTX steadily re-enters the circulation causing lower, and sometimes sub-optimal concentrations in serum during intermittent administration. Arnow et al. found normal serum concentrations of intermittently administered CTX in 15 OLT patients, with a high dosing schedule (e.g. 8g/24h). However, intra-operative blood loss was much lower (3.3 L) than in our population [21]. They reported an increase in volume of distribution (300mL/kg), but not as large as in our population. Furthermore, total body clearance was lowered by impaired hepatic and renal function in their population.
Despite a compromised hepatic function (due to pre-existent liver failure and during the anhepatic phase), the DCTX AUC was approximately 70-90% of the CTX AUC in serum. This is high compared to data derived from healthy volunteers [22, 23] and patients with chronic hepatic disease [24]. Apparently, the remaining hepatic function was sufficient, reflected in the mean transaminases of 36-72 U/L. A possible explanation is that the distribution of CTX is different from DCTX in this patient group. In other words, the Vd of CTX is larger than the Vd of DCTX during surgery.

Postoperatively, the pharmacokinetic profile of the patient can be influenced by decreased graft function, hemodynamic instability (rejection, sepsis, bleeding), an enlarged Vd (peroperative positive fluid balance) and renal dysfunction (reperfusion damage). We found postoperatively that the CI regimen provided serum CTX concentrations of ≥ 4 mg/L for 100% of the dosing interval, while during intermittent administration 2 of 7 patients dropped below this target concentration. The volume of distribution was still approximately 60% higher than in healthy volunteers, most likely caused by the positive fluid balance. The total body clearance was impaired beyond predictions based on renal function. While the renal clearance was comparable to values found in healthy volunteers (105 mL/min), the metabolic clearance (normal values: 93-103 mL/min) was decreased [12, 18]. Hepatic function in transplantated livers is sub-optimal early after the operation, and consequently, the clearance of CTX by metabolising it is lower. Both the increased volume of distribution and the decreased clearance caused a two-fold increase in elimination half-life. Burckart et al. reported an impaired clearance of CTX after OLT as well [7].

The DCTX AUC was approximately 110-150% of the CTX AUC in serum. CTX is actively excreted by the kidneys and therefore relatively insensitive to renal impairment. Only in case of a creatinine clearance <10mL/min, there is accumulation. However, DCTX starts to accumulate in mild renal insufficiency already (CLcreat 30-89 mL/min) [25]. In the postoperative phase there was a drop in creatinine clearance in both groups, explaining the accumulation of DCTX.

The biliary tract anastomosis is the site at risk after OLT surgery when bile flow is minimal. Biliary anastomotic leakage and cholangitis due to biliary obstruction are frequently encountered complications after OLT [1, 26]. Therefore, adequate biliary concentrations are desirable to suppress bacterial proliferation in the (relatively) stagnant bile. In this study, the CTX AUCs in bile were approximately 90% of the concomitant serum AUCs for both regimens. The continuous regimen resulted in a mean concentration in bile of >20mg/L; the intermittent bolus regimen resulted in sufficient concentrations in bile as well. This resulted in the time above the target concentration of 4mg/L in bile of 100% of the dosing interval for both regimens. By using an indwelling T-drain an unknown part of produced bile flows into the duodenum, therefore we underestimated the biliary clearance of CTX. Jehl et al. measured biliary clearance of CTX in cholecystectomised patients with a T-drain in which the distal end of the intracholedochal branch of the T-drain was locked by a inflated balloon of a Fogarty catheter. They found a mean bile production of 108 mL in 8h and a biliary clearance approximately twice as high as our estimated biliary clearance [12]. Strikingly, the DCTX concentration and subsequently the AUC in bile were significantly higher after continuous infusion. The biliary transport of drugs is, similar to active secretion in the kidney, confined to a maximum rate of transport [27]. A possible explanation for the difference therefore is, that during intermittent infusion the transport rate is maximal with DCTX serum peak concentrations and less than maximal during trough concentrations (Michaelis-Menten kinetics). During CI, the transport rate is maximal throughout the dosing interval causing higher concentrations of DCTX in bile.

We conclude that an intermittent bolus infusion of CTX of 1000 mg q6 produces insufficient serum concentrations during surgery in patients undergoing a liver transplantation. This can be avoided with continuous infusion. Postoperatively, the clearance of CTX is impaired by a decreased metabolic clearance and there is substantial accumulation of DCTX. In bile, sufficient concentrations of CTX and its active metabolite are reached with both regimens.

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CHAPTER 10

FUTURE DIRECTIONS IN THE MANAGEMENT OF TERTIARY PERITONITIS

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Introduction

Over the past few decades the mortality of severe secondary peritonitis has markedly reduced as a result of increased knowledge of the underlying pathophysiology, aggressive surgical techniques, broad spectrum antimicrobial agents and advanced life support facilities. However, not uncommonly, the surgeon encounters a clinical situation in which the abdominal infection persists and multiple organ failure develops despite optimal treatment. Typically, radiodiagnostic imaging or re-laparotomy reveal no evident focus; indeed, only sero-sanguinous fluid is found in which selected microorganisms can be cultured. This syndrome, so-called therapy-resistant or tertiary peritonitis is associated with a mortality rate of more than 60% and presently represents the limit of surgical treatment of severe secondary peritonitis [1, 2]. This review provides an overview of the different pathophysiological processes and their treatment options that are thought to be involved in this complex nosocomial infection.

Surgical aspects

Secondary peritonitis is defined as an infection of the peritoneal cavity caused by perforation or anastomotic disruption of the digestive tract. Therapy is primarily surgical, i.e. an operation to control the infectious source and to reduce the bacterial load and debris. In the majority of cases (>80%) the infection can be eliminated with a single operation. However, when there is extensive contamination of the peritoneal cavity, the infection often persists or may recur. In these severe cases, often with profound systemic toxicity, repeated surgical interventions are necessary to clear the infectious source(s). Two aggressive operative strategies to manage severe secondary peritonitis are either planned re-laparotomies or open management [3].

Planned relaparotomies refer to repeated operations at fixed intervals (24-72h) *irrespective* of the patient's condition. Its purpose is to anticipate the formation of infectious collections and to preclude their systemic effects. Re-laparotomies are discontinued when the peritoneal cavity has become macroscopically clean. Adverse effects include damage to the often fragile viscera, necrosis of the abdominal fascia and complications related to general anaesthesia [4].

Open management of the abdomen (laparostomy) involves leaving the abdominal wall open and covering it with meshes or foil in combination with a continuous drainage system. Advantages include continuous exposure for inspection and maximal drainage, and easy access to the peritoneal cavity without additional damage to the abdominal wall. Furthermore, by enlarging the peritoneal cavity, the abdominal compartment is decompressed, visceral perfusion is maintained and pulmonary ventilation is optimised. Early complications of open management include evisceration, losses of fluid, electrolytes and proteins, and enteric fistulae [5]. Eventually, a ventral hernia will remain for which operative correction is often necessary.

These therapeutic modalities have been evaluated over the last two decades in retrospective and/or prospective non-randomised studies [3]. Randomisation can be difficult as open management is sometimes inevitable. A clear advantage of either treatment over the other has yet to be demonstrated; the overall mortality rate is approximately 30% [5]. As the

incidence of complications is higher with the open management approach, the current consensus is to use this only in patients who need three or more laparotomies, or in those whose abdomen cannot be closed due to an abdominal compartment syndrome [3].
When the combination of aggressive surgical treatment and appropriate anti-microbial therapy are unable to contain the infection, therapy-resistant or 'tertiary' peritonitis develops. In tertiary peritonitis, the surgical strategy does not appear to be the pivotal factor [6]. Relaparotomy reveals no evident infectious foci, in fact only sero-sanguinous fluid is found in which selected micro-organisms are cultured [7].
Mechano-surgical solutions are likely to have reached their limit once tertiary peritonitis has develped. Indeed, repeated interventions may play a fundamental role in causing a further deterioration of the local immune response. Intra-operative peritoneal lavage is used in an attempt to reduce bacterial contamination and debris. Its efficacy, however, has never been proved. With every abdominal irrigation using crystalloid solutions, inflammatory cells and cytokines are dispersed throughout the peritoneal cavity. While their target is largely removed, their programmed mission remains. It can be hypothesised that this can lead locally to a chaotic and inferior immune apparatus with deteriorating systemic effects [8, 9]. Furthermore, manipulation of the viscera may endanger the integrity of the intestine and thereby promote translocation. Some authors therefore advocate limiting the peritoneal toilet to vacuum drainage of purulent exudate and faecal debris, plus debridement of abscesses [10].

Local and systemic immune paralysis
In response to infection or surgical trauma, the peritoneal environment produces cytokines. Pro-inflammatory cytokines recruit inflammatory cells to combat pathogens, clear damaged tissue and stimulate wound repair. To protect the host from damage by this inflammatory response, anti-inflammatory cytokines are also produced. They diminish the ability of monocytes to produce inflammatory mediators as well as their antigen-presenting capacity (HLA-DR expression). Homeostasis is restored when the infection is controlled by a balanced immune response. When the peritoneal defence mechanism is unable to control the infection, a systemic immune response develops. Initially, a predominant pro-inflammatory reaction causes septic shock with organ dysfunction. If peritonitis persists and tertiary peritonitis develops after a series of interventions, the anti-inflammatory cascade prevails, causing suppression of the immune system. Due to inhibition of the synthesis of pro-inflammatory agents, peritoneal inflammation is lacking and there is no tendency towards healing of wounds or organ recovery [11]. The immune system can be considered as one failing organ in the syndrome of multiple organ failure. Predisposing factors for immune paralysis include patient-related factors (e.g. genetic immune deficiencies, age and poor nutritional status), iatrogenic factors (e.g. surgery, blood transfusions and immunosuppressive drugs), and underlying diseases (e.g malignancy and neutropenia) [12-14].
Immune paralysis can be defined by the critical level of deactivated monocytes with less than 30% HLA-DR expression [15]. This decreased cellular immunity has been demonstrated in trauma, burn-injured and transplantation patients, and is associated with high infection rates and mortality [12, 16, 17]. Immune stimulation by removal of

inhibitory factors (plasmapheresis) or by administration of haemopoietic growth factors such as G-CSF, GM-CSF and interferon-gamma (IFN-□) may be useful during this period [18].
Granulocyte colony-stimulating factor (G-CSF) regulates neutrophil differentiation and function. Furthermore, G-CSF potentates the killing capacity of antimicrobial agents. Considerable experimental evidence in animals suggests that treatment with G-CSF may have a beneficial effect in the management of infections in non-neutropenic hosts [19]. Clinical experience remains scarce. Gross-Weege et al measured G-CSF in 59 surgical intensive care patients and found transiently raised levels in patients without infectious complications and in those who survived [20]. Agnes et al studied the effect of G-CSF substitution in 10 septic patients with immune paralysis (HLA-DR+ monocytes < 30%) and found a persistently higher level of HLA-DR+ monocytes in the six survivors [21]. Docke et al administered IFN-□ to septic patients with low monocytic HLA-DR expression. The deficient HLA-DR expression and in vitro LPS-induced TNF-alpha secretion was restored. Recovery of monocyte function resulted in clearance of sepsis in eight of nine patients [22]. Whether immune monitoring [23] with selective immuno-stimulatory therapy is beneficial in patients with tertiary peritonitis is worth pursuing.

Microbiology and antimicrobial therapy
Pathogens frequently cultured from the peritoneal cavity in tertiary peritonitis include multi-resistant Gram-negative organisms, endogenous organisms of low intrinsic pathogenicity (e.g. *Staphylococcus epidermidis, Candida* species and enterococci) [7, 24]. The main source of these pathogens is thought to be the patient's own digestive tract. In critical illness intestinal hypoperfusion, intestinal starvation and elimination of normal gut flora by antimicrobial agents cause mucosal atrophy with subsequent loss of gut barrier function and microbial translocation [25, 26]. Additionally, frequent manipulation during surgery may damage the bowel promoting translocation of pathogens. Toxins and microbes escaping from the gut lumen into the bloodstream and the peritoneal cavity activate the host's immune inflammatory defence mechanisms. However, as the target is undefined, the immune response will be both uncontrolled and unbalanced, leading to tissue destruction and multiple organ failure. Adequate perfusion and enteral feeding are important for preservation and restoration of the gastro-intestinal tract and maintenance of barrier function [27]. Furthermore, mucosal immunity, originating in small intestine gut-associated lymphoid tissue (GALT) appears to be preserved by enteral feeding [28]. Clinical trials have shown that early enteral feeding is not beneficial in all patient groups [29], however there is substantial evidence in both critically ill and high risk surgical patients that enteral feeding leads to significantly fewer infectious complications [30, 31].
Antimicrobial treatment in tertiary peritonitis remains a matter of debate. Contamination with the above-mentioned pathogens correlates with the severity of organ dysfunction and mortality, however no cause-effect relationship can be necessarily inferred. It appears to be more a manifestation than a cause of morbidity and mortality [32]. On the other hand, in some cases with secondary sepsis (defined as positive blood cultures) the attributable mortality of these pathogens can be as high as 35% [33]. As long as a clear distinction cannot be made between contamination and infection, and our knowledge in this area

remains insufficient, antimicrobial therapy is warranted. In our institution, antimicrobial therapy is reserved for deep infection (e.g. positive cultures from tissue or deep peritoneal aspirate) or secondary sepsis. Present insights justify a short course of antibiotics, using as limited a regimen as possible, until normalisation of the systemic inflammatory response occurs [34].

Another option would be to eliminate all potentially pathogenic Gram-negative bacteria and fungi in the digestive tract by selective decontamination (SD) [35, 36]. Luiten et al showed a reduced mortality in patients with necrotizing pancreatitis when infection of the pancreatic tissue was prevented by SD [37]. A recent meta-analysis [38] did show a notably reduced mortality in critically ill surgical patients through reduction of the nosocomial infection rate. However, patients with severe secondary or tertiary peritonitis form a specific population with a high *a priori* mortality rate in whom the contribution of (super-) infection to an adverse outcome is not established. We speculate that prevention of such infections by SD is not likely to be beneficial.

The outcome of antimicrobial treatment depends on multiple variables. Beside the adequacy of the empirical and streamlined therapy given, [39] and the state of the host defences, dosing schedules play an important role in the efficacy and safety of the antimicrobial agents used [40]. Some antimicrobial agents, such as the aminoglycosides, show concentration-dependent killing in which the rate and extent of bactericidal activity correlates with the magnitude of the concentration. In contrast, other antimicrobials, such as the beta-lactams, show time dependent killing in which concentrations above 4-5 times the minimal inhibitory concentration (MIC) do not kill the organism any faster; in this instance, bactericidal activity largely depends on the time of exposure. Greater attention paid to the pharmacodynamic properties of these different groups of antibiotics has resulted in higher efficacy and less antimicrobial resistance in both *in vivo* and *in vitro* models [41]. Efficacy studies with once daily aminoglycoside regimens in patients show equal efficacy compared to multiple dosing, but a reduction in toxicity. Studies in peritonitis patients are not yet available, but there are some indications of clinical benefit. For example, a delay in attaining therapeutic levels of aminoglycosides has been associated with persistence of infection and treatment failure in patients with intra-abdominal infection [42].

Effective and safe dosing schedules thus require understanding of the drug's pharmacokinetics. Critically ill patients show aberrant and variable pharmacokinetics which are not easy to predict [43]. Factors such as a hyperdynamic circulation, peripheral oedema, organ dysfunction, an altered metabolic condition and altered gastro-intestinal absorption influence the pharmacokinetic profile of the critically ill. Therefore, therapeutic drug monitoring and individualised, goal-oriented dosing could potentially enhance antibiotic efficacy [44].

Endocrine dysfunction

Endocrine pathways play an important role in the body's physiological response to peritonitis. In response to an infectious insult the hypothalamic-pituitary-adrenal (HPA) axis is activated, resulting in increased serum cortisol concentrations. The role of corticosteroids in metabolism, maintenance of vasomotor tone and immune modulation is essential to restore homeostasis [45]. In persistent stress, such as in complicated peritonitis,

this adrenocortical response can become deranged. When glucocorticoid production no longer meets the body's increased needs, a phenomenon called relative adrenal insufficiency (RAI) develops. The aetiology of RAI is not fully understood, but is thought to be caused by depletion of the adrenal cortex and glucocorticoid receptor resistance. Substitution of corticosteroids in patients with RAI can reverse the septic shock state dramatically [46].
Prolonged critical illness is characterised by catabolism of whole-body protein stores resulting in muscle wasting and a negative nitrogen balance [47]. This catabolic state is associated with increased morbidity and mortality. This has prompted research into the combined use of anabolic steroids such as growth hormone (GH) and insulin-like growth factor (IGF-1) to enhance protein metabolism in the critically ill [48, 49]. Furthermore, anabolic agents play a modulating role in the immune response. They stimulate proliferation and differentiation of T-lymphocytes and NK-cells and augment proliferation, chemotaxis and phagocytosis of granulocytes [49, 50]. Several experimental and clinical studies in critically ill patients with burns, trauma and sepsis have shown positive effects of GH on metabolic parameters, wound healing and immune competence, but a recent study by Takala et al has called clinical impact and safety into question [51]. They showed an increased mortality in a heterogeneous group of critically ill patients with (mainly) prolonged respiratory failure after surgery or trauma. Possible explanations postulated included a harmful modulation of the immune response, insulin resistance and interference with adrenocortical and thyroid function. Timing of administration of growth hormone seems to be important. Growth hormone increases the pro-inflammatory response and hypermetabolic state in non inflamed tissue, but causes no further increase of these reponses in patients with an ongoing systemic inflammatory response like in burns, trauma or sepsis. It might be possible that the patients studied by Takala et al have been negatively affected by the pro-inflammatory and hypermetabolic effects of GH because they did not already have a systemic inflammation as a component of their disease process [52]. After all, patients with burns and septic shock were excluded. No data exist concerning the effect of these agents in patients with tertiary peritonitis with multiple organ failure. The anti-catabolic and immunostimulatory actions of GH could be beneficial in this patient group because they already suffered a systemic inflammatory response.

Summary

Tertiary peritonitis represents the current limit of the surgical approach to severe intra-abdominal infection. Specific pathogens are cultured from the peritoneal cavity, though these appear to be more a symptom than the cause of critical illness. Therefore, the role of antimicrobial agents is debatable and currently reserved for infection with systemic toxicity and secondary sepsis. Short, narrow-spectrum courses are recommended with attention being paid to the individual pharmacokinetic profile of the patient and the pharmacodynamic activity of the drugs used.
Lack of peritoneal inflammation with systemic anergy suggests immune paralysis. This anti-inflammatory state can have endogenous (primary massive insult, gut-associated sepsis, immune deficiency) or exogenous (repeated surgery, blood transfusions, immune suppressive drugs, malnutrition) origins. By development of immune monitoring assays,

selective use of immune-modulating therapies could be beneficial. Pilot trials with immune stimulation show promising results.
Finally, the endocrine stress response is essential for metabolic, cardiovascular and immunological homeostasis. Derangement of this response is likely in patients with prolonged stress such as tertiary peritonitis. Monitoring of endocrine function with substitution of cortisol when necessary could be beneficial in patients with tertiary peritonitis. The role of anabolic steroids like growth hormone is yet unclear.

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CHAPTER 11

SUMMARY AND CONCLUSIONS

Summary

Chapter 1: The rationale and the outline of this thesis are presented in this chapter. Despite all advances in intensive care medicine the past decades, mortality due to severe infections remains high in the surgical ICU today. Furthermore, there is an increasing prevalence of resistant pathogens. Therefore, attempts are made to optimise antimicrobial therapy, the cornerstone in the treatment of severe infections. In the outcome of antimicrobial treatment, dosing schedules seem to play an important role. It is thought that antimicrobial efficacy can be increased and the emergence of resistant mutants during therapy can be prevented when modern insights in pharmacodynamics are complied. However, the critically ill patient shows a deranged pharmacokinetic profile, which makes optimal dosing schedules difficult to design. Therefore, insight in the pharmacokinetics of these drugs in critically ill patients is necessary.

Chapter 2: In this chapter the clinical pharmacokinetics of antimicrobial agents in critically ill patients are described and the pharmacodynamic principles of different groups of antimicrobials are reviewed.
Despite the fact that enteral absorption in ICU patients is compromised by motility disturbance, mucosal atrophy and chemical interactions, the bioavailability of several antimicrobials is adequate. Caution is necessary in case of less susceptible pathogens in which higher dosage or combination therapy may be needed. The volume of distribution is increased and variable during critically illness. This is caused by third spacing and a decrease in serum protein for the highly protein bound antimicrobials. These factors can lead to suboptimal serum and tissue concentrations. During stress hepatic metabolism can be increased up to 50%. However, during critically illness, hepatic metabolism is more often impaired by pre-existent causes or acute causes including infection or shock induced failure. The pharmacokinetics of several antimicrobials are influenced by a variable liver function, but the extent of liver function is difficult to quantify in the clinical setting. Furthermore, in a multiple drug setting like an ICU, several drug-drug interactions involving antimicrobial agents are possible. Approximately one third of all critically ill patients develop renal failure. As most antimicrobials are eliminated from the body through the kidneys, this has a serious impact on the pharmacokinetics of these drugs.
To determine the optimal antimicrobial regimen the different parameters of antimicrobial activity are important. The in vitro activity tests (MIC, MBC) are predictors of the potency of the drug, but do not give information on the antimicrobial effect of the concentration-time profile in serum and at the site of infection. Antimicrobial agents either show concentration dependent activity, in which the rate and extent of bactericidal activity correlates with the magnitude of the concentration. In contrast, others show time dependent killing, in which activity largely depends on the time of exposure, not the magnitude. Knowledge of the pharmacodynamic efficacy parameters of antimicrobial agents (T>MIC, T/MIC, AUC/MIC) can help to determine the optimal dosing schedules. Individual therapeutic drug monitoring (TDM) combines, the serum concentrations of a certain drug with the pharmacokinetic profile of a patient in order to optimize dosage regimens according to modern pharmacodynamic insights. A positive impact of TDM has been documented on clinical outcome, reduction of hospital stay and toxicity. In critically ill

patients with a deranged pharmacokinetic profile with wide inter- and intra patient variability, TDM can be of particular benefit in guiding the physician to the optimal dosing schedule. The different methods available for TDM in critically ill patients including a nomogram, the Sawchuk and Zaske method and Bayesian monitoring are reviewed.

Chapter 3: This chapter deals with the epidemiology and clinical outcome of infections in surgical intensive care patients and describes the antimicrobial use and susceptibility patterns of the pathogens on the SICU of the University Hospital Rotterdam in The Netherlands anno 1999.
One hundred and four episodes of infection and 155 infection sites (90% CDC defined) were documented. Overall, the incidence density of infection was 61 episodes per 1000 patient days. The majority of primary infections were localised in the abdominal cavity (40%), whereas ICU-acquired infections were more often pulmonary (43%). In primary infections three-quarters of the gram-negative pathogens reflected normal predominant endogenous flora (*E. coli*, Klebsiella spp, Proteus spp), whereas in ICU-acquired infections the majority of gram-negative pathogens were selected Enterobacteriaceae or Pseudomonas spp. Among gram-positive pathogens, staphylococci rather than streptococci were present in ICU-acquired infections. Eight percent of the *P.aeruginosa* strains were multiple resistant. No multiple resistant Acinetobacter spp or Enterobacter spp were identified in our population. The incidence of MRSA and VRE was low. The total use of antibacterial agents on our SICU in 1999 was three times as high as the overall use in our hospital and five times greater than the use in Dutch hospitals in 1996. Patients with an episode of infection, either primary or ICU-acquired, had a significant higher in-unit mortality rate. Eighty-one out of 104 episodes (78%) were successfully treated. Inadequate antimicrobial therapy was associated with a significant increase in treatment failure and infection related death.
Concluding, in long-stay SICU patient the incidence of infection is high. Insights in susceptibility patterns of pathogens, antimicrobial utilization and treatment outcome on a local level are necessary to periodical evaluate the quality of care.

Chapter 4: This chapter describes a case of *S.pyogenes* soft tissue infection resulting in a streptococcal toxic shock syndrome, multi-organ failure and death. It illustrates the overwhelming character of severe infection and the current limits of treating it.

Chapter 5: Ceftazidime is an antibiotic frequently used in patients with severe intra-abdominal infection (IAI). It shows time-dependent killing, which means that time>MIC determines the efficacy. The objectives of this chapter were to determine the pharmacokinetics of ceftazidime in serum during continuous and intermittent infusion in patients with abdominal sepsis and to determine the concentrations of ceftazidime reached in the peritoneal exudate.
Continuous infusion resulted in a mean concentration in serum above 40 mg/L and a time above 4 x MIC of most pathogens encountered in severe IAI for >90% of the course of therapy in serum and peritoneal exsudate. Eight-hourly administration resulted in time above 4 x MIC of most pathogens encountered in severe IAI for >90% of the dosing interval, but in peritoneal exudate only for 44% of the dosing interval. In case of *P.*

aeruginosa infections the intermittent regimen preformed less in serum and peritoneal exudate. During continuous infusion, AUCs in the peritoneal exudate were approximately 60% of the concomitant serum AUCs.
Thus, in critically ill surgical patients with severe intra-abdominal infections, continuous infusion of ceftazidime resulted in more favourable concentrations in serum and peritoneal exudate than eight-hourly bolus infusion.

Chapter 6: In surgical intensive care patients, the incidence of Candida infections is increasing and is associated with a high mortality. Especially patients with complicated intra-abdominal infections are at risk. Fluconazole has fungi-static activity against most species of Candida encountered in surgical intensive care patients. Fluconazole has excellent enteral bioavailability in healthy volunteers, but no data are available on the bioavailability of fluconazole in ICU patients with peritonitis and/or recent gastro-intestinal surgery. No data are available on the concentrations of fluconazole at the site of infection in this specific patient group.
The objective of this chapter was to determine the pharmacokinetics of sequential intravenous and enteral fluconazole in serum of surgical ICU patients with deep mycoses and to determine the concentrations of fluconazole reached at the site of infection.
The mean AUC0-24h in serum after enteral administration did not significantly differ from the AUC0-24h during intravenous treatment. The elimination half-life was lengthened compared to healthy volunteers. The mean (95% CI) estimated bioavailability was 124 (90-158)%. The mean (95% CI) area under the concentration time curves (AUCs) achieved in the exudate from the site of infection were 67 (55-79)% of the AUCs reached in serum for both regimens.
We concluded that in critically ill patients with recent gastro-intestinal surgery and/or peritonitis the bioavailability of enteral fluconazole was adequate. Concentrations of fluconazole reached in exudate were lower than in serum for both regimens, but adequate to treat most cases of deep mycoses in this specific patient group.

Chapter 7: Aminoglycosides show concentration dependent killing and therefore once-daily aminoglycoside (ODA) regimens have been instituted. Data on experience with ODA regimens in critically ill patients are limited. In this chapter we describe our experience with an ODA-program in critically ill patients. The pharmacokinetics of aminoglycosides (gentamicin and tobramycin) and the incidence of nephrotoxicity associated with an ODA regimen in this specific patient group are assessed.
One hundred and nine pharmacokinetic profiles were gathered. A first dose of 7 mg/kg/24h of gentamicin or tobramycin was given to every patient independent of renal function. Subsequent doses were chosen on the basis of the pharmacokinetic results of the first dose.
The volume of distribution of aminoglycosides was significantly higher in critical ill patients with septic shock than in those without. Consequently, the maximum concentration reached was significantly lower in patients with septic shock. In *P. aeruginosa* infections the mean (SD) estimated Cmax/MIC ratio was 10.3 (3.3). In n= 17 (49%) of the patients treated >24h (n=35), a dose adjustment or lengthening of interval was necessary. The recommended dosing interval based on the Hartford Hospital nomogram and one serum

concentration at 6 hours was correct in only 62% of all cases. Signs of renal impairment occurred in n=12 (14%) of the patients; in all survivors renal function recovered completely, no haemofiltration was needed.
An ODA-regimen of 7mg/kg produced Cmax/MIC ratios >10 in the majority of critically ill patients. Septic shock and renal dysfunction caused an aberrant pharmacokinetic profile of aminoglycosides in these patients, which was not suitable for the Hartford Hospital nomogram. Therefore, individual therapeutic drug monitoring is warranted. Signs of renal impairment were common in the presence of shock, but appeared to be reversible.

Chapter 8: Oral formulations of ciprofloxacin have been used successfully in the treatment of severe Gram-negative infections but no data are available on the pharmacokinetics of multiple enteral dosing of ciprofloxacin in ICU patients with severe intra-abdominal infections. In this chapter the comparative steady state pharmacokinetics of intravenous versus enteral ciprofloxacin was studied in 5 tubefed ICU patients with severe intra-abdominal infections in a randomised crossover study.
The mean bioavailability of enteral dosing was 53.1 (95% CI 43.5-62.8) %. In 7 additional ICU patients with intra-abdominal infections receiving enteral ciprofloxacin, the mean serum steady state concentration at 2 hrs after administration was 3.9 (95% CI: 1.9-5.9) mg/L, not significantly different from that found in the crossover study (p=0.4).
We concluded that in tube-fed ICU patients with severe intra-abdominal infections the bioavailability of enteral ciprofloxacin is adequate. In case of *P. aeruginosa* infections higher doses or combination therapy is needed.

Chapter 9: Liver transplantations (LTX) are frequently complicated by bacterial infections of the abdomen, the lower respiratory tract and the bloodstream. Peri-operative translocation of Gram-negative bacteria is believed to be an important factor in the pathophysiology of infectious complications after LTX and therefore perioperative broad spectrum antibiotics are used to prevent bacteremia and surgical site infection. In this chapter we studied the pharmacokinetics of cefotaxime and its active metabolite after continuous and intermittent infusion in serum and bile in fifteen patients undergoing a liver transplantation.
This study showed that continuous infusion of cefotaxime in patients undergoing a liver transplantation, results in favourable concentrations in serum compared to intermittent infusion especially during surgery. The peri-operative pharmacokinetics of cefotaxime are deranged and variable in this patient group, mainly caused by an increased volume of distribution and a decreased hepatic clearance. The formation of desacetylcefotaxime was decreased, but concentrations remain high through accumulation. Biliary clearance is low, but sufficient concentrations of cefotaxime and its metabolite are reached.
We conclude that an intermittent bolus infusion of cefotaxime of 1000 mg q6 produces insufficient serum concentrations during surgery in patients undergoing a liver transplantation. This can be avoided with continuous infusion. Postoperatively, a decreased metabolic clearance in freshly transplantated livers and a drop in renal function cause an impaired clearance of cefotaxime and accumulation of its metabolite. Because of this, both regimen produce adequate concentration in serum and bile.

Chapter 10: Tertiary peritonitis represents the current limit of the surgical approach to severe intra-abdominal infection. Specific pathogens are cultured from the peritoneal cavity, though these appear to be more a symptom than the cause of critical illness. Therefore, the role of antimicrobial agents is debatable and currently reserved for infection with systemic toxicity and secondary sepsis. Short, narrow-spectrum courses are recommended with attention being paid to the individual pharmacokinetic profile of the patient and the pharmacodynamic activity of the drugs used.
Lack of peritoneal inflammation with systemic anergy suggests immune paralysis. This anti-inflammatory state can have endogenous (primary massive insult, gut-associated sepsis, immune deficiency) or exogenous (repeated surgery, blood transfusions, immune suppressive drugs, malnutrition) origins. By development of immune monitoring assays, selective use of immune-modulating therapies could be beneficial. Pilot trials with immune stimulation show promising results.
Finally, the endocrine stress response is essential for metabolic, cardiovascular and immunological homeostasis. Derangement of this response is likely in patients with prolonged stress such as tertiary peritonitis. Monitoring of endocrine function with substitution of cortisol when necessary could be beneficial in patients with tertiary peritonitis. The role of anabolic steroids like growth hormone is yet unclear.

Conclusions

1. Approximately 60% of the long-stay (>48 hours) surgical ICU admissions are diagnosed with an infection at some time during their SICU stay and 60% of all deaths are infection related.
2. Inadequate antimicrobial therapy is associated with a significant increase in treatment failure and infection related death in intensive care patients.
3. In critically ill patients with peritonitis, continuous infusion of ceftazidime results in more favourable concentrations in serum and peritoneal exudate than eight-hourly bolus infusion.
4. The bioavailability of fluconazole and ciprofloxacine in critically ill patients with peritonitis is adequate.
5. Critically ill patients show an aberrant and variable pharmacokinetic profile of aminoglycosides. Therefore, this patient group is not suitable for the Hartford Hospital nomogram and individual monitoring is warranted.
6. An intermittent bolus infusion of cefotaxime of 1000 mg q6 produces insufficient serum concentrations during surgery in patients undergoing a liver transplantation. This can be avoided with continuous infusion.
7. In the treatment tertiary peritonitis, the current limit of the surgical approach to severe intra-abdominal infection, the role of antimicrobial agents is yet unclear.

Samenvatting

Hoofdstuk 1: Ondanks de vooruitgang in de intensive care geneeskunde de laatste 20 jaar, blijft de mortaliteit door ernstige infecties op de chirurgische IC hoog. Bovendien is er een toename in voorkomen van pathogenen resistent voor antimicrobiële middelen. Daarom worden er pogingen ondernomen om de antimicrobiële therapie – de hoeksteen in de behandeling van (ernstige) infecties - te optimaliseren.
Het resultaat van een antimicrobiële therapie blijkt sterk afhankelijk van het gebruikte doseringsschema. Wanneer de moderne pharmacodynamische inzichten worden nageleefd kan de effectiviteit van de antimicrobiële therapie worden verhoogd en kan het ontstaan van resistente pathogenen worden tegengegaan. Echter, intensive care patiënten vertonen een afwijkend en variable pharmacokinetisch profiel, waardoor het moeilijk is de goede doseringschema's op te stellen. Daarom is het noodzakelijk om inzicht te verkrijgen in het pharmacokinetische profiel van antimicrobiële middelen in deze patiënten groep.

Hoofdstuk 2: Dit hoofdstuk bevat een overzichtsartikel over de farmacokinetiek van antimicrobiële middelen in chirurgische intensive care patiënten. Daarnaast worden de pharmacodynamische principes van de verschillende soorten antimicrobiële middelen beschreven.
Een ernstige sepsis veroorzaakt een fysiologische respons die gevolgen heeft voor de farmacokinetiek van medicatie. Een bedreigde enterale absorptie, een toename van het verdelingsvolume, lever- en nierfunctiestoornissen, zorgen voor een afwijkend, maar vooral ook variabel farmacokinetisch profiel.
De effectiviteit van antimicrobiële middelen is mede afhankelijk van het concentratie verloop in serum en ter plaatse van de infectie. Sommige middelen vertonen concentratie afhankelijke activiteit, waarbij de de bacterie dodende of remmende werking toeneemt met de hoogte van de concentratie. Andere middelen vertonen tijdsafhankelijke activiteit, waarbij met name de tijd van expositie van belang is. Het in acht nemen van deze farmacodynamische principes kan leiden tot betere behandelingsresultaten en een vermindering van ligduur en toxiciteit.
Omdat IC patiënten een afwijkend en variable farmacokinetisch profile hebben is monitoring van het concentratie verloop van belang om het optimale dosringsschema op te stellen.

Hoofdstuk 3: In dit hoofdstuk worden de epidemiologie en behandelingsresultaten van infecties beschreven op de chirurgische IC van een tertiair medisch centrum in Nederland anno 1999. Ook is er gekeken naar het gebruik van antimicrobiële middelen en resistentie patronen van pathogenen.
De incidentie van infectie was 61 per 1000 patiënt-dagen. De meerderheid van de primaire infecties ware van abdominale oorsprong (40%), tewijl de IC-verkregen infecties vaker pulmonaal waren (43%). Drie-kwart van de gram-negatieve pathogenen die gekweekt werden uit primaire infecties waren afkomstig van de endogene flora (*E. coli*, Klebsiella spp, Proteus spp), terwijl uit IC-verkregen infecties vaker geselecteerde Enterobacteriaceae or Pseudomonas spp werden gekweekt. In het gram-positieve spectrum domineerde staphylococci. Acht procent van alle *P.aeruginosa* stamen waren multipel resistent. Er

werden geen multipel resistente Acinetobacter spp of Enterobacter spp gezien in deze populatie. De incidentie van MRSA en VRE was laag.
Het totale gebruik van antimicrobiële middelen op onze IC in 1999 was drie maal hoger dan het totale gebruik in het ziekenhuis en vijf maal hoger dan het gemiddelde gebruik in Nederlands ziekenhuizen in 1996. Bij patiënten met een infectie, primair of IC-verkregen, werd een significant hogere mortaliteit gezien. Eén-en-tachtig van de 104 infectie-episodes (78%) werden met succes behandeld. Inadequate antimicrobiële therapie was geassocieerd met een significante toename van therapie falen en mortaliteit.

Hoofdstuk 4: In dit hoofdstuk wordt een casus besproken van een patiënt met een *S.pyogenes* weke delen infectie met daarbij toxisch shock syndroom en multi-orgaan falen. Het illustreert het overweldigende karakter van ernstige sepsis en de huidige grenzen van de behandelingsmethoden.

Hoofdstuk 5: Ceftazidime is een antibioticum wat frequent gebruikt wordt voor de behandeling van patiënten met abdominale sepsis. Het vertoont een tijds-afhankelijke activiteit, dus de tijd > MIC bepaalt de effectiviteit. Het doel van het onderzoek beschreven in dit hoofdstuk was het bepalen van de farmacokinetiek van ceftazidime in serum tijdens continue en intermitterende toediening bij patiënten met abdominale sepsis. Daarnaast werden er concentraties in het buikvocht bepaald.
Continue infusie resulteerde in een gemiddelde concentratie in serum van > 40 mg/L. Bovendien was de tijd > 4 x MIC van de meest frequent gekweekte pathogenen in abdominale sepsis voor >90% van het doseringsinterval in serum en buikvocht.
Intermitterende toediening resulteerde ook in een tijd > 4 x MIC >90% van het doseringsinterval in serum, maar slechts voor 44% van het doseringsinterval in buikvocht. In het geval van *P. aeruginosa* infecties was de intermitterende toediening inferieur in serum en buikvocht. Tijdens continue infusie waren de AUCs in het buikvocht ongeveer 60% van de bijbehorende serum AUC.
Concluderend, in chirurgische intensive care patiënten met abdominale sepsis leidt continue infusie van ceftazidime tot betere concentraties in serum en buikvocht dan tijdens intermitterende infusie.

Hoofdstuk 6: De incidentie van Candida infecties neemt toe onder chirurgische intensive care patiënten en is geassocieerd met een hoge mortaliteit. Zeker patiënten met een gecompliceerde abdominale sepsis hebben een verhoogd risico op Candida infecties. Fluconazole heeft fungostatische activiteit tegen de meeste Candida soorten gekweekt op de IC. Fluconazole heeft een uitstekende biologische beschikbaarheid in gezonde vrijwilligers, maar data over biologische beschikbaarheid in IC patiënten met peritonitis of recente gastro-intestinale chirurgie ontbreken. Verder zijn er geen data over de concentraties ter plaatse van de infectie in deze patiënten groep.
Het doel van de studie was om de farmacokinetiek te bestuderen van intraveneus, gevolgd door enteraal fluconazole in serum van chirurgische IC-patiënten met diepe Candida infecties (peritonitis of mediastinitis). Bovendien werd er gekeken naar de concentraties fluconazole ter plaatse van de infectie.

De gemiddelde AUC0-24h in serum na enterale toediening verschilde niet van de AUC0-24h na intraveneuze toediening. De halfwaarde tijd was significant langer dan bij gezonde vrijwilligers. De gemiddelde biologische beschikbaarheid was 124%. De gemiddelde AUC in exsudaat was 67% van de bijbehorende AUC in serum voor beide toedieningsvormen.
Concluderend, in IC-patiënten met peritonitis en/of recente gastro-intestinale chirurgie is de biologische beschikbaarheid adequaat. Concentraties in exsudaat zijn lager dan in serum, maar hoog genoeg voor de behandeling van de meeste Candida infecties in deze patiënten groep.

Hoofdstuk 7: Aminoglycosiden vertonen een concentratie afhankelijke activiteit en daarom worden zij bij voorkeur gegeven volgens een éénmaal daags schema. Gegevens over de ervaringen met een dergelijk schema in intensive care patiënten zijn schaars. In dit hoofdstuk bescrijven wij onze ervaringen met een éénmaal daags gentamicine of tobramycine schema in intensive care patiënten. De farmacokinetiek van de aminoglycosiden gentamicin en tobramycin werd bestudeerd en de incidentie van nefrotoxiciteit geassocieerd met dit éénmaal daags schema in deze specifieke patiënten groep.
Honderd en negen giften werden gemeten. Iedere patiënt kreeg als eerste gift 7 mg/kg/24uur gentamicine of tobramycine onafhankelijk van de nierfunctie. De hoogte van de volgende dosis werd gekozen op basis van farmacokinetische resultaten van de eerste dosis.
Het distributie volume van aminoglycosiden was significant hoger in patiënten met septische shock dan in patiënten zonder. Daardoor was ook de maximale concentratie in serum lager in patiënten met septische shock. In patiënten met een *P. aeruginosa* infectie was de gemiddelde geschatte Cmax/MIC ratio 10.3. In n= 17 (49%) van de patiënten die langer dan 24 uur werden behandeld (n=35), was een dosis aanpassing of een verlenging van het doseringsinterval noodzakelijk. Het aanbevolen doseringsinterval gebaseerd of het Hartford Hospital nomogram en één serum concentratie na 6 uur, was slechts correct in 62%. Tekenen van nefrotoxiciteit deden zich bij n=12 (14%) patiënten voor. Dit was reversibel in alle overlevende patiënten; er was geen niervervangende therapie noodzakelijk.
Concluderend, een éénmaal daags aminoglycoside schema van 7mg/kg leidde tot een Cmax/MIC ratio >10 in de meerderheid van de intensive care patiënten. Septische shock en nierfalen veroorzaken een afwijkend farmacokinetisch profile van aminoglycosiden in deze patiënten groep, waardoor zij niet geschikt zijn voor het Hartford Hospital nomogram. Daarom is individuele therapeutische monitoring noodzakelijk. Tekenen van nierfunctie verval komen, zeker in geval van shock, frequent voor, maar blijken reversibel.

Hoofdstuk 8: De enterale toedieningsvorm van ciprofloxacine wordt frequent gebruikt voor de behandeling van ernstige gram-negative infecties. Echter, data over de farmacokinetiek van enteraal ciprofloxacine in IC patiënten met abdominale sepsis ontbreken. In dit hoofdstuk werd in een gerandomiseerde cross-over studie, de steady state farmacokintiek van intravenous en enteraal ciprofloxacine bestudeerd in 5 IC patiënten met abdominale sepsis.

De gemiddeld biologische beschikbaarheid na enterale toediening was 53.1%. In 7 IC-patiënten met abdominale sepsis werden additioneel metingen gedaan., De gemiddelde steady state serum concentratie 2 uur na enterale toediening, was niet significant anders dan gevonden werd in de cross-over studie (p=0.4).
We concluderen dat de biologische beschikbaarheid van enteral ciprofloxacine adequaat is in IC-patiënten met abdominale sepsis. In het geval van *P. aeruginosa* infections is een hogere dosering of combinatie therapie geïndiceerd.

Hoofdstuk 9: Lever transplantaties worden frequent gecompliceerd door bacteriële infecties van het abdomen, de luchtwegen of de bloedbaan. Perioperatieve translocatie van gram-negative bacteriën wordt gezien als belangrijke factor in de pathofysiologie van infectieuze complicaties na levertransplantatie. Daarom worden er perioperatief breed spectrum antibiotica gegeven om bacteremiën en (diepe) wond infecties te voorkomen. In dit hoofdstuk werd de farmacokinetiek van cefotaxime en de actieve metaboliet bestudeerd na continue en intermitterende toediening in serum en gal in vijftien lever transplantatie patiënten.
Deze studie toonde aan dat continue infusie van cefotaxime in lever transplantatie patiënten, resulteerde in betere concentraties in serum tijdens de operatie vergeleken met intermitterrende toediening. De perioperatieve farmacokinetiek van cefotaxime is afwijkend en variable in deze patiënten groep, hoofdzakelijk door een toename in het verdelingsvolume en een verminderde hepatische klaring. De vorming van desacetylcefotaxime was verminderd, maar de concentraties bleven hoog door accumulatie. De klaring in gal was laag, maar de bereikte concentraties van cefotaxime en de metaboliet waren voldoende.
Concluderend, intermitterende toediening van 1000 mg q6 cefotaxime leidt tot onvoldoende serum concentraties tijdens lever transplantatie. Dit kan worden vermeden met continue infusie. Postoperatief is er sprake van een verminderde metabole klaring in de vers getransplanteerde levers. Deze verminderde metabole klaring en een verminderde renale klaring zorgen voor een verminderde klaring van cefotaxime en accumulatie van de metaboliet. Hierdoor worden postoperatief met beide toedieningsschema's adequate concentrations bereikt in serum en gal.

Hoofdstuk 10: De tertiaire peritonitis vertegenwoordigt de huidige grens van de chirurgische behandeling van ernstige intra-abdominale infectie. Specifieke pathogenen worden uit de peritoneaal holte gekweekt, al lijken deze pathogenen meer een symptoom dan de oorzaak van het ziek zijn. Daarom staat de role van antimicrobiële therapie ter discussie en wordt deze gereserveerd voor die infecties met systemische toxiciteit en secundaire sepsis. Korte, gestroomlijnde kuren worden aanbevolen, met speciale aandacht voor het individuele farmacokinetische profiel van de patiënt en de farmacodynamische eigenschappen van met gebruikte middel.
Het ontbreken van peritoneale ontstekingsverschijnselen bij tertiaire peritonitis met systemische anergie suggereert dat er sprake van paralyse van het immuunsysteem. Deze anti-inflammatoire status kan een endogene (de oorspronkelijke secundaire peritonitis, translocatie van pathogenen, immuun-deficientie) of exogene (relaparotomiën, bloed

transfusies, immuun suppressiva, ondervoeding) origine hebben. Er zijn assays ontwikkeld om het immuunsysteem te monitoren, waardoor selectieve gebruik van immuun-modulerende therapiën mogelijk worden. Pilot studies met immuun stimulatie vertonen veel belovende resultaten.
De endocriene stress response speelt een essentiële rol in de metabole, cardiovasculaire en immunologische homeostase. Een verstoring van deze respons ligt voor de hand in patiënten onder langdurige stress zoals patiënten met tertiaire peritonitis. Het monitoren van de endocriene functie met selectieve substitutie van cortisol zou patiënten met tertiaire peritonitis ten goede kunnen komen. De rol van anabole steroïden als het groeihormoon is nog niet duidelijk.

Conclusies

1. Zestig procent van de "langliggers" (> 48 uur) op chirurgische IC ontwikkelt een infectie tijdens hun verblijf aldaar en 60% van alle gevallen van overlijden zijn aan een infectie gerelateerd.
2. Inadequate antimicrobiële therapie is bij intensive care patiënten geassocieerd met een significante toename van therapie falen en overlijden.
3. Bij intensive care patiënten met peritonitis, resulteert continue infusie van ceftazidime in betere concentraties in serum en buikvocht dan na bolus toediening driemaal daags.
4. De biologische beschikbaarheid van enteraal fluconazole en ciprofloxacine is adequaat bij intensive care patiënten met peritonitis.
5. Intensive care patiënten vertonen een afwijkend en variabel farmacokinetisch profiel van aminoglycosiden. Daarom is deze patiënten groep niet geschikt voor het Hartford Hospital nomogram en is individuele monitoring noodzakelijk.
6. Intermitterende toediening van 1000 mg cefotaxime à 6 uur leidt tot te lage serum concentraties tijdens lever transplantatie. Dit kan worden vermeden met continue infusie.
7. De rol van antimicrobiële middelen in de behandeling van tertiaire peritonitis, -de huidige grens van de chirurgische behandeling van peritonitis-, is onduidelijk.

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Curriculum vitae

Steven Buijk werd geboren op 11 november 1970 in Roosendaal. Hij doorliep het atheneum B op het Gertrudis Lyceum aldaar. Hij studeerde Geneeskunde aan de Erasmus Universiteit in Rotterdam en behaalde in juni 1996 zijn artsexamen. Aansluitend werkte hij op de Chirurgische Intensive Care van het toenmalige Dijkzigt ziekenhuis, thans Erasmus MC Rotterdam (hoofd: prof.dr. H.A. Bruining). Hij deed er onderzoek naar de bijnierschorsfunctie van patiënten met shock en bestudeerde de farmacokinetiek van antimicrobiële middelen bij intensive care patiënten. De resultaten van de laatstgenoemde studies zijn beschreven in dit proefschrift.
In maart 1999 startte hij met de opleiding tot chirurg in het Reinier de Graaf Gasthuis in Delft (opleiders: dr. P.W. de Graaf en dr. L.P.S. Stassen). Thans doet hij zijn academische jaren in het Erasmus MC in Rotterdam (opleider: prof.dr. H.J. Bonjer).
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