VU Research Portal

Infectious complications in critically ill patients: focus on clinical, pharmacological and economic aspects

van Zanten, A.R.H.

2008

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)
van Zanten, A. R. H. (2008). *Infectious complications in critically ill patients: focus on clinical, pharmacological and economic aspects.*

Introduction

Infectious complications are frequently encountered among critically ill patients treated in the Intensive Care Unit (ICU). Patients admitted to the ICU may present with infections on admission, or develop infections in the course of their ICU stay.

Sepsis can be defined as the body's response to an infection. Although this reaction is a necessary part in helping the body fight the infection, an excessive response may lead to organ dysfunction. Many patients are admitted to ICUs throughout the world because of sepsis-induced organ dysfunction; surveys have estimated that severe sepsis accounts for 2–11% of all admissions to hospital intensive care units (ICUs) [1,2]. In addition, an even greater number of patients may develop sepsis or sepsis-like syndromes in the course of their ICU stay.

Sepsis is a complex syndrome that basically represents an inflammatory response to an infection or another triggering event (see below). It is characterised by the release of vast amounts of pro-inflammatory cytokines leading to systemic inflammation, diffuse endovascular injury, and a pro-coagulant host response, which can lead to multi-organ dysfunction. An infection is caused by micro-organisms (usually bacteria) that invade the body; this can be limited to a particular organ or region of the body, or spread throughout the body via the bloodstream (septicaemia). Sepsis can arise from virtually any part of the body, although some regions (the lungs, abdomen, urinary tract, skin, bones and central nervous system) are the most common sources. In around 20% of the cases the source of sepsis is never found.

A septic response is usually triggered by infectious agents; however, cytokine release can be induced by numerous other causes, and a sepsis-like response may occur without active infection. For this and other reasons, it has proved difficult to agree on the definition of sepsis and its sequelae. This lack of consensus on on the correct defini-

tion of sepsis has hampered efforts to study severe sepsis and to determine the scope of the clinical problem. In 1991, the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) convened a 'Consensus Conference', to develop working definitions of sepsis and multi-organ failure. In 1992 this led to the introduction of the term 'systemic inflammatory response syndrome' (SIRS) [3]. In 2001 these definitions for sepsis and related conditions were revised [4]; the present definitions are stated in table 1.

Table 1: SIRS-criteria en sepsis definitions [4]	
SIRS	More than one of the following clinical findings:
	* body temperature ‹36°C or ›38°C
	* heart rate ›90 beats/min
	* hyperventilation, evidenced by respiratory rate > 20/min or $PaCO_2$ < 32 mmHg
	* white blood cell count > 12,000 cells/ml or < 4,000 cells/ml.
Sepsis	SIRS with an infectious cause.
Severe sepsis	Sepsis associated with acute organ dysfunction, hypoperfusion or hypotension.
Septic shock	Sepsis with hypotension despite 'adequate' fluid resuscitation.

Infection induces a SIRS-reponse that can be self-limiting, or can progress to severe sepsis and on to septic shock [5]. Sepsis remains one of the leading causes of morbidity and mortality worldwide. The number of severe sepsis cases is set to grow at a rate of 1,5% per year [2], mainly owing to the aging population, increasing number of high-risk individuals (immunocompromised, cancer, haematological and HIV patients), broadening awareness of this condition among physicians, more complex surgical interventions, and greater use of invasive procedures. As the incidence and mortality of sepsis increases with age, this makes sepsis to a substantial degree a disease of the elderly (Figure 1) [2].

It is estimated that over 18 million cases of severe sepsis occur worldwide each year. The number of cases in Europe is approximately 88 per 100,000 [6]; in the United States around 750,000 cases arise per year [6]. However, the interpretation of these numbers is complicated by a low diagnostic rate and difficulties in tracking sepsis in many countries.

Sepsis remains one of the leading causes of morbidity and mortality worldwide. Despite aggressive treatment mortality ranges from 16% with sepsis to ›50% with septic shock [4]. Mortality increases along the sepsis continuum, from approximately 10%–36% in sepsis, to 18%–52% in severe sepsis and 46%–82% in septic shock [5].
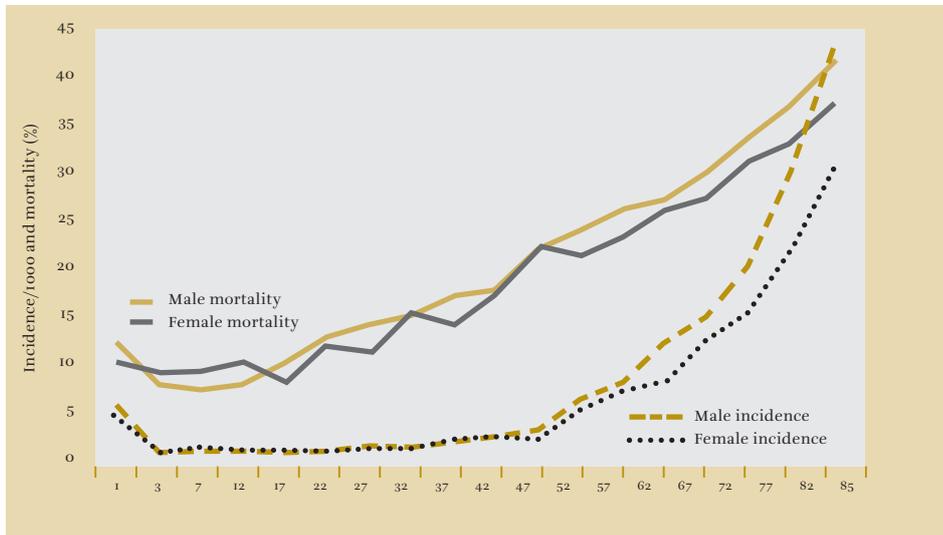
Figure 1: Age and mortality of sepsis in the USA [2]. Permission for use granted by Lippincott, Williams & Wilkins

Around 30% of patients from all sepsis categories die within the first month, and 50% within 6 months [7]. However, there are signs that the death rate in some subgroups of patients may have decreased – owing to better detection of the underlying infection, improved supportive care, and some specific treatments that have shown benefits in large well-designed trials [8]. Effective treatment of organ failure is essential, because it is the cumulative burden of organ failure that leads to death. The average risk of death increases by 10%–20% with the failure of each additional organ [2].

As mentioned above, although many patients are admitted to the ICU with infectious complications and resulting organ dysfunction there is a substantial number that develops an infectious episode in the course of their stay in the ICU, as a result of their acute pathology, underlying morbidity, or due to invasive procedures or other medical treatments administered in the ICU. This risk of acquired ("nosocomial") infections in ICU patients is directly linked to the duration of their stay in the ICU [9].

Critically ill and mechanically ventilated patients are at particularly high risk for noso-comial infections. Ventilator-associated pneumonia and central venous catheter infec-tions are well recognized complications of invasive procedures. Alteration of physical defences, bacterial flora, and immune response contribute to the susceptibility of the critically ill ventilated patient. Nosocomial sinusitis is another complication of endotra-cheal intubation and mechanical ventilation in critically ill patients. Its incidence is

often underestimated because of the lack of clinical signs, partly due to the fact that most ICU patients are unconcious and cannot express symptoms or complaints.

Infectious complications are related to worse outcome (increased morbidity and mortality) and the incurrence of major additional costs. Various surveys have estimated that the annual costs of sepsis are € 7.6 billion in Europe and € 17.4 billion in the United States [2]. The cost of treating an ICU patient with sepsis is six times greater than the cost of treating a patient without sepsis [10].

In order to decrease mortality and morbidity of ICU patients while simultaneously reducing the overall costs of ICU care, all aspects of the diagnostic process and subsequent therapeutic interventions (including their timing) need to be as close to optimal as possible. Therefore, high-quality treatment of severe infections in the critical care setting should comprise establishing an early and accurate diagnosis, initiating prompt therapeutic interventions, and meticulous monitoring and documentation of success, failure and side effects.

Although much information on the pathophysiology and treatment of sepsis has emerged in recent years, there are still many areas where much remains to be elucidated. This includes the usage of antimicrobial medications. Much of the currently available information concerning antimicrobial therapy is based on studies performed in patient populations with a much lower severity of disease than ICU patients. It is questionable whether the results of these studies can be directly extrapolated to the ICU setting.

Bacterial infections are the most frequent cause of severe sepsis and septic shock. Antibiotic therapy and optimal source control can be considered the cornerstones of treatment of bacterial infections. Therefore, strategies to optimise antimicrobial therapy in critically ill patients can be regarded as key elements in the treatment of severe sepsis.

GENERAL PRINCIPLES OF ANTIMICROBIAL THERAPY

Antibiotics are a *conditio sine qua non* for the effective treatment of bacterial infections. The treatment of bacterial infections is founded on principles of appropriate drug selection for both empiric and targeted (final) therapy, based on suspected susceptibility patterns for the causative pathogen. The goal of antimicrobial prescription is to achieve drug concentrations that are sufficiently effective to combat the infection. Achieving optimum drug levels is of particular importance in the case of antibiotics, to exert the maximum killing effect for the causative pathogen and to prevent the emergence of antimicrobial resistance.

An optimal antibiotic strategy should include the proper application of pharmacokinetic and pharmacodynamic principles to antimicrobial therapy [11,12].

The science of pharmacokinetics (PK) studies the time course of absorption, distribution, metabolism, and excretion of drugs in the body; *i.e.*, how the body handles drugs.

In general, the absorption of drugs in critically ill patients may be reduced due to the acute illness. For this reason many medications, including antibiotics, are usually administered intravenously in critically ill patients; in theory this leads to a maximum bioavailability. However, numerous other factors may affect the pharmacokinetics of antibiotics in this setting. For example, many critically ill patients have an increased volume of extracellular fluid, enhancing the likelihood of increased volumes of distribution for the antibiotic used [13]. Furthermore, organ dysfunction in ICU patients may affect the clearance of drugs [14].

The science of pharmacodynamics (PD) addresses the biochemical and physiologic effects of drugs and their mechanism of action; *i.e.* how drugs exert their effects in the body. In the case of antibiotics, previous research has shown that the mechanism of action for different antibiotic classes may vary. Some antibiotics produce time-dependent killing of pathogens; in these circumstances antibiotic drug levels should exceed the minimal inhibitory concentrations of the pathogen for as long as possible during the dosing interval. Then continuous infusion or frequent multiple dosing regimens may be considered. In contrast, other antibiotics have a more concentration-dependent killing mechanism, depending either on the maximum concentration achieved (*e.g.* aminoglycosides such as gentamicin) or on the total dose (*e.g.* fluoroquinolones such as ciprofloxacin) of the drug related to the MIC of the causative pathogen. When administering antibiotics with this type of pharmacodynamic profile, a once-daily dosing regimen would be used in the first example (aminoglycosides, effect depending on peak concentration) and a high total daily dose in the second example (fluoroquinolones, effect depending on overall total dose).

Standard antimicrobial dosing regimens are often based on research performed many decades ago, in studies that for the most part were performed in patients who were not critically ill. Severely ill patients may develop changes in drug pharmacokinetics, such as limited renal clearance due to renal dysfunction or a larger volume of distribution. In addition, multiple medications may cause various drug interactions. Due to the potentially large variations in PK/PD values in severely ill patients a more individualised approach may be necessary. This suggests that therapeutic drug monitoring may be required in situations where the metabolism of antibiotics may be altered, such as can be the case in critically ill patients.

Antimicrobial resistance in the ICU is characterized by an increase in overall resistance rates among both gram-negative and gram-positive pathogens, and by increased

incidence of multidrug-resistant organisms. Development of antimicrobial resistance has been associated with a liberal use of antibiotics, but also with underdosing leading to sub-therapeutic drug levels [15].

RESEARCH FOCUS

These observations led us to focus on and study specific aspects of infectious complications in critically ill patients.

To test whether dosing regimens based on limited information from studies performed in healthy subjects or in patients who were not severely ill could be reliably applied in critically ill patients, we developed techniques enabling us to measure serum drug levels for therapeutic drug monitoring with relative ease. We used this method, for example, to effectively study the pharmacokinetics of a commonly used fluoroquinolone antibiotic, ciprofloxacin, with a generally accepted dosing regimen in critically ill patients.

THERAPEUTIC DRUG MONITORING OF CIPROFLOXACIN

Ciprofloxacin is a broad-spectrum antibacterial drug which is used to treat a wide range of infections in the ICU. Therapeutic drug monitoring of ciprofloxacin has been described previously; however, relatively complex methods were used in these studies, including the use of a gradient mobile phase or the addition of an internal standard after sample extraction. In order to more easily study the ICU population we developed a convenient rapid high-performance liquid chromatography (HPLC)-ultraviolet (UV) method to quantify the total (unbound + protein-bound) ciprofloxacin concentrations in human serum. In addition, we addressed the influence of storage on the sample stability in various conditions.

PHARMACOKINETICS OF CIPROFLOXACIN IN ICU PATIENTS

Fluoroquinolones have acquired a prominent position in the management of moderate-to-severe infections in critically ill patients. This class of synthetic antibiotics has an antimicrobial activity ranging from *Enterobacteriaceae* and opportunists to some gram-positive pathogens. Based on their excellent tissue penetration and favourable therapeutic ratio's fluoroquinolone antibiotics such as ciprofloxacin can be used in the management of a wide range of infections including infections of the genitourinary-, respiratory- and gastrointestinal tracts, as well in the treatment of skin-, joint- and soft tissue infections. In the case of quinolones the killing of bacteria is determined by the "area-under-the-curve" (AUC), which can be obtained by mathematical integration of the serum concentration-time curve (surface area) and the peak concentration (C_{max}). The ratio of the AUC to the MIC of the causative micro-organism (AUC/MIC) is a good predictor of treatment efficacy.

For ciprofloxacin, one of the oldest and most well-studied fluoroquinolones, various studies have suggested that an AUC/MIC-ratio of at least 125 is required for optimum clinical effects [17]. However, as outlined above the currently available clinical studies dealing with this issue have been performed mainly in healthy volunteers and in general populations of hospitalised patients. Few data are available regarding the use of fluoroquinolones in critically ill patients, although these drugs are widely used in this population because they are well tolerated, *i.e.* have few side effects and have a broad microbiological spectrum.

These considerations led us to prospectively study the pharmacokinetics of ciprofloxacin in critically ill patients in the ICU. The measured drug levels were correlated to MIC values of pathogens commonly found in our ICU population.

The next step was to study another class of antibiotics, cephalosporins, with a different mechanism of action, i.e. time-dependent killing [18]. This issue was addressed in two study populations: in critically ill patients with various illnesses and causes of infection, and in a more homogeneous population of COPD patients with (suspected) respiratory infections. In both studies a "traditional" intermittent dosing regimen was compared to continuous infusion; our hypothesis, based on theoretical pharmacodynamic considerations, was that continuous infusion would be superior. A new development in these studies was that the total daily dose required for continuous infusion was lower than that used in patients receiving intermittent administration, thereby reducing total antibiotic load and costs.

PHARMACOKINETICS AND PHARMACODYNAMICS OF BETA-LACTAM ANTIBIOTICS

Based on current knowledge of the pharmacokinetics and pharmacodynamics of beta-lactam antibiotics, continuous infusion of these drugs is usually recommended as the most effective form of treatment. The reason for this is that various studies have shown a close relationship between treatment efficacy and the duration of time that serum concentrations of the antibiotic exceed the MIC for the causative microorganism. In contrast to other categories of antibiotics such as aminoglycosides and quinolones, beta-lactam antibiotics do not have a significant "post-antibiotic effect" [18]. This implies that, in theory, the fluctuations in antibiotic serum concentrations associated with intermittent administration could lead to serum and tissue concentrations below MIC between scheduled doses. This could reduce the efficacy of the antibiotic strategy and increase the risk for development of antibiotic resistance.

According to the literature, bacterial killing rates by beta-lactam antibiotics are largely determined by the percentage of time – at least 60-70% of the dosing interval – that antibiotic concentrations are at least 4-5 x MIC, while bacterial resistance is related to the time during which antibiotic concentrations are below MIC [18].

PHARMACOKINETICS OF CEFOTAXIME IN THE CRITICALLY ILL

Although these hypotheses have been extensively studied in *in vitro* studies and animals experiments, they have not been thoroughly validated in the clinical setting.

Very few studies have been performed to assess the pharmacokinetics of continuous versus intermittent administration of cephalosporins in ICU patients. Various factors may combine in this category of patients that could significantly alter pharmacokinetics; these include impaired renal- and liver function, altered volume of distribution, use of numerous co-medications, etc. On the other hand the effectiveness of antibiotic treatment and the prevention of antibiotic resistance may be even more important in the critical care setting than elsewhere, making effective dosing an issue of paramount importance. Therefore, we designed a prospective randomised study to compare the pharmacokinetics of cefotaxime during either continuous or intermittent administration in ICU patients.

PHARMACOKINETICS AND PHARMACODYNAMICS OF CEFOTAXIME IN COPD PATIENTS

In addition to the ICU patient group we wanted to gain more insight in the effects of different administration methods in other patient categories, focussing not just on pharmacokinetics but also with respect to the clinical efficacy and bacterial susceptibility. We felt that these endpoints could be better studied in a more homogeneous patient population, and decided to perform a prospective randomised trial to compare the pharmacokinetics and pharmacodynamics of continuous versus intermittent administration of the beta-lactam antibiotic cefotaxime in patients with chronic obstructive pulmonary disease (COPD). Apart from the pharmacokinetic aspects we also assessed the clinical course of the infections in our study patients, as well as bacteriological aspects including antibiotic resistance.

In our next study we wanted to address some of the economic aspects of antibiotic treatment in hospitalised patients

COSTS ASSOCIATED WITH INTRAVENOUS ANTIBIOTICS ADMINISTRATION IN ICU PATIENTS

The overall quality of care, outcome, and patient and family satisfaction in intensive care units is closely linked to (excessive) workload and staffing levels of physicians and nurses. Budgetary restrictions may play an important role in the organisation of the ICU, and cost reduction is an important issue in intensive care medicine today since ICU costs account for up to 10% of overall hospital expenditure [20].

Antibiotics are among the most frequently used drugs in intensive care patients, and thus account for a substantial proportion of drug expenditure in ICUs. When performing pharmacoeconomic evaluations of ICU expenditure, it is customary to consider only the direct price of purchasing these medications [21]. However, to assess

the total costs of intravenous (IV) drug therapy in the ICU setting it is necessary to take other costs into account, such as the effect on the workload of nurses and the medical staff as well as other health care workers, and to evaluate costs associated with preparation, administration and monitoring of IV antibiotic therapy. Gaining insight into all the factors that contribute to the actual total overall costs of drug therapy may help increase awareness into what actually drives the costs of hospital services, and to identify opportunities for cost savings.

To assess the costs associated with drug preparation and administration we performed an observational time and motion study in two ICUs. For comparison, we also performed this analysis in a general internal medicine ward. The basis of a time and motion study is the measurement, through direct observation by the investigators and the research nurses involved in the study, of staff members performing specific tasks in a process that is subdivided into various components.

RATIONAL USE OF INTRAVENOUS ANTIBIOTICS ADMINISTRATION IN THE ICU

Critically ill patients treated in the ICU for severe infections need to be treated quickly and effectively to improve the chances of a favourable outcome. Early recognition and diagnosis of infections and prompt initiation of antimicrobial treatment have long been recognized as fundamental principles of therapy [22]. The probability of success in treating bacterial infections depends on factors such as the condition of the patient, the aetiology of the infection and the appropriateness of antimicrobial therapy. Selection of antimicrobial drugs is often based on *in vitro* susceptibility of causative pathogens to specific antibiotics, although usually initial treatment is started empirically, based on knowledge of pathogens commonly involved in infections of particular organs and drug resistance patterns in a specific location [23]. The interactions between antibiotics, causative pathogens and host defences in immunocompetent or immunocompromised patients is highly complex; many ICU patients should be regarded as having (temporarily) diminished immune functions, due to factors such as downregulation of immune function following severe infections, administration of drugs such as corticosteroids, underlying (chronic) diseases, impairment or interruption of local defence systems (e.g. endotracheal intubation and mechanical ventilation), and various other factors [24].

In Chapter 8 information is provided on strategies for antibiotic treatment that take pharmacokinetics and pharmacodynamics for the applied antibiotic into consideration and increase efficacy and reduce the risk of antimicrobial resistance. In addition, economic aspects of drug therapies are also be taken into account. The question whether an optimal antibiotic strategy necessarily means a more expensive strategy and therapy is addressed in this chapter.

Finally, to enable targeted treatment of specific infections or empiric treatment for suspected infection requires establishing a reliable diagnosis of the source of the infection. This can be far more difficult in ICU patients, as many signs and symptoms may be absent or suppressed, or may be difficult to measure. Diagnostic challenges for infections in the ICU were addressed in a separate study, designed to develop a practical approach to diagnose nosocomial sinusitis in critically ill patients with fever of unknown origin.

FEVER, A CLINICAL SIGN OF INFECTION?

We studied PK/PD aspects of antibiotics administered for suspected or diagnosed infections in both ICU and COPD patients. However, in clinical practice in many patients clinical signs and symptoms of infection such as elevated body temperature and fever may precede the confirmation of infection. In some patients the cause of fever remains unknown after initial evaluation (fever of unknown origin). Fever is a common problem in ICU patients. The presence of fever frequently results in the performance of diagnostic tests and procedures that significantly increase medical costs and expose the patient to unnecessary invasive diagnostic procedures and the inappropriate use of antibiotics. ICU patients frequently have multiple infectious and non-infectious causes of fever, necessitating a systematic and comprehensive diagnostic approach [19].

This aspect of diagnostic challenge of infections in the ICU setting was addressed in a study designed to develop a practical approach to diagnose nosocomial sinusitis in critically ill patients with fever of unknown origin.

FEVER OF UNKNOWN ORIGIN AND THE ROLE OF SINUSITIS IN ICU PATIENTS

Many patients admitted to the ICU are likely to develop fever of unknown origin at some point of their stay. In many cases, well-recognised hospital-acquired infections such as ventilator-associated pneumonia and central venous catheter infections are found to be the cause of these febrile episodes [19]. However, if the cause of fever is not immediately apparent other causes should be taken into consideration.

The potential role of sinusitis as a source of hospital-acquired infections has not been well studied. It is well recognised that sinusitis can occur as a complication of nasotracheal intubation; however, the incidence of sinusitis in patients after orotracheal intubation is unclear, and the data from the literature have been conflicting. We therefore assessed the role of sinusitis as a hospital-acquired infection in mechanically ventilated and orotracheally intubated patients admitted to the ICU, in a prospective study using a rigorous protocol with predefined criteria for suspecting sinusitis.

CRITICAL CARE ORGANISATIONAL ASPECTS IN THE NETHERLANDS

In an addendum to this thesis, organisational aspects of critical care are summarized, in order to give the reader contextual information on the setting in which many patients in the Netherlands are treated for infectious complications during their stay in the ICU.

REFERENCES

1   Balk RA. Severe sepsis and septic shock. Definitions, epidemiology, and clinical manifestations. Crit Care Clin 2000; 16(2):179-92.

2   Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29(7):1303-10.

3   American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20: 864-874.

4   Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; International Sepsis Definitions Conference 2001 SCCM/ESICM/ACCP/ATS/SIS. Crit Care Med 2003; 31(4):1250-6.

5   Salvo I, de Cian W, Musicco M, Langer M, Piadena R, Wolfler A, Montani C, Magni E. The Italian SEPSIS study: preliminary results on the incidence and evolution of SIRS, sepsis, severe sepsis and septic shock. Intensive Care Med 1995; 21 Suppl 2:S244-9.

6   Davies A, Green C, Hutton J, Chinn C. Severe sepsis: A European estimate of the burden of disease in ICU. Intensive Care Med 2001; 27:S 284, Abstract 581.

7   Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM; Surviving Sepsis Campaign Management Guidelines Committee. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004; 32(3):858-73.

8   Natanson C, Esposito CJ, Banks SM. The sirens' songs of confirmatory sepsis trials: selection bias and sampling error. Crit Care Med 1998; 26(12):1927-31

9   Trilla A. Epidemiology of nosocomial infections in adult intensive care units. Intensive Care Med 1994; 20 Suppl 3:S1-4.

10 Edbrooke DL, Hibbert CL, Kingsley JM, Smith S, Bright NM, Quinn JM. The patient-related costs of care for sepsis patients in a United Kingdom adult general intensive care unit. Crit Care Med 1999;27(9):1760-7.

11 Maglio D, Nicolau DP. The integration of pharmacokinetics and pathogen susceptibility data in the design of rational dosing regimens. Methods Find Exp Clin Pharmacol 2004;26(10):781-8.

12 Jacobs MR. How can we predict bacterial eradication? Int J Infect Dis 2003;7 Suppl 1:S13-20.

13 Roberts JA, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. Clin Pharmacokinet 2006; 45(8):755-73.

14 Pinder M, Bellomo R, Lipman J. Pharmacological principles of antibiotic prescription in the critically ill. Anaesth Intensive Care 2002; 30(2):134-44.

15 Rybak MJ. Pharmacodynamics: relation to antimicrobial resistance. Am J Infect Control 2006; 34 5 Suppl 1: S38-45.

16 Von Rosenstiel N, Adam D. Quinolone antibacterials. An update of their pharmacology and therapeutic use. Drugs 1994; 47(6):872-901.

17 Forrest A, Nix DE, Ballow CH, et al: Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993; 37:1073-1081.

18 Craig WA. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. Diagn Microbiol Infect Dis 1995; 22(1-2):89-96.

19 Marik PE. Fever in the ICU. Chest 2000; 117(3):855-69.

20 Halpern NA, Pastores SM, Greenstein RJ. Critical care medicine in the United States 1985-2000: an analysis of bed numbers, use, and costs. Crit Care Med 2004; 32(6):1254-9.

21 Birmingham MC, Hassett JM, Schentag JJ, Paladino JA. Assessing antibacterial pharmacoeconomics in the intensive care unit. Pharmacoeconomics 1997; 12(6):637-47.

22 Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. Am J Med 2003; 115(7):529-35.

23 Eliopoulos GM, Moellering RC Jr. Principles of antibiotic therapy. Med Clin North Am 1982; 66(1):3-15.

24 Oberholzer A, Oberholzer C, Moldawer LL. Sepsis syndromes: understanding the role of innate and acquired immunity. Shock 2001; 16(2):83-96.