Jordi Rello · Marcos I. Restrepo *Editors*

Sepsis

New Strategies for Management

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Preface

Infectious-related mortality has remained an important problem around the world, and the majority of these deaths are related to pneumonia and sepsis. Although new interventions have emerged over the last decade, the mortality rates for these illnesses have remained significantly high and represent an important health care problem. This book is intended to address new concepts in medical care for a wide variety of clinicians who are involved in the care of patients with pneumonia and sepsis. This material is a compendium that goes from basic science research regarding genetics in sepsis and the impact of inflammation and aging in pneumococcal disease to new and future interventions translating basic information into clinical practice. Other topics covered in this book include issues regarding antibiotic therapy, such as other roles for macrolides, and appropriate dose adjustment and pharmacodynamic considerations. Finally, a wide variety of novel and innovative therapies are reviewed, including corticosteroids, statins, and nonspecific removal of sepsis mediators that are being used in patients with pneumonia and sepsis.

An outstanding panel of international experts has focused on recent developments. It has been an honor working with them, and thanks to their efforts the bulk of the references are less than five years old. Ms. Rosi Luque, with the sponsorship of the CIBERes, helped us in the coordination of the editorial work, and we are indebted to her for this. The authors hope that their experiences as summarized in these pages are of value to the reader and, ultimately, improve the care of patients with pneumonia and sepsis.

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Chapter 1
Macrolides in Severe Community-Acquired Pneumonia and Sepsis

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1.1 Introduction

More than 750,000 cases of severe sepsis occur annually (Angus et al. 2001), making the incidence of severe sepsis higher than that of breast cancer, AIDS, or first myocardial infarction. The incidence of sepsis is increasing because of the aging population, the growing number of immunocompromised patients, and the increasing use of invasive procedures, and to a lesser extent, because of antibiotic resistance among pathogens. In the United States alone, almost $17 billion is spent each year treating patients with sepsis (Angus et al. 2001).

Despite advances in care, more than 210,000 patients with severe sepsis die annually (Angus et al. 2001). The mortality rate associated with severe sepsis remains between 20% and 80% (Zeni et al. 1997). Even dysfunction of a single organ places patients at a significant risk for dying (about 20%), with mortality rates increasing approximately 15–20% for each additional dysfunctional organ (Vincent et al. 1998). Mortality rates are highest (ranging from 50 to 80%) for patients with cardiovascular compromise (septic shock) (Rangel-Frausto et al. 1995). Respiratory infections, whether community- or hospital-acquired account for the most sepsis cases (Angus et al. 2001; Bernard et al. 2001; Martin et al. 2003). Community-acquired pneumonia (CAP) is one the most common reasons for sepsis and is itself, independent of sepsis, the seventh leading cause of death and the leading cause of infectious death in the United States (Hoyert et al. 2005).

The pathogenesis of sepsis is complex and, despite significant advances, still not well understood (Annane et al. 2005). Essentially, sepsis is the result of the interaction between microorganisms and/or their products and the host factors released in response (cytokines and other mediators). An important component of the host response is the initial innate mechanisms developed to protect the organism from harm. However, in sepsis, the immune response itself initiates a cascade of secondary responses that may lead to organ dysfunction and even death, despite eradication of the invading microorganism. Initial concepts of sepsis as an uncontrolled proinflammatory response have been replaced by more complex models, which also incorporate dysregulation of anti-inflammatory, coagulation, and tissue healing/repair pathways (Annane et al. 2005). However, the proinflammatory response,

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particularly release of tumor necrosis factor (TNFα), is clearly critical in the early phase of sepsis (Van Amersfoort et al. 2003; Annane et al. 2005; Carlson et al. 2005; van Leeuwen et al. 2005).

Normally, a potent complex immunologic cascade ensures a prompt protective response to microbial invasion in humans. A deficient immunologic defense may allow infection to become established; however, an excessive or poorly regulated response may harm the host through a maladaptive release of endogenously generated inflammatory compounds. The complexity of immunologic defenses makes the development of pharmacologic interventions difficult (Parrillo et al. 1990). A key element associated with early biochemical events in sepsis is cytokines, which are host-produced, pleomorphic immunoregulatory peptides. The most widely investigated cytokines are tumor necrosis factor (TNFα), interleukin-1 (IL-1), IL-6, IL-8, which are generally proinflammatory, and IL-1Ra and IL-10, which tend to be anti-inflammatory. A trigger, such as microbial toxin, stimulates the production of TNFα and IL-1, which in turn promote endothelial cell-leukocyte adhesion, release of proteases and arachidonate metabolites, and activation of clotting. IL-1 and TNFα are synergistic and share some biologic effects, and their inhibition improves organ function and survival in animal models of sepsis. IL-8, a neutrophil chemotaxin, may have an especially important role in perpetuating tissue inflammation. IL-1Ra and IL-10, which are perhaps counterregulatory, inhibit the generation of TNFα, augment the action of acute-phase reactants and immunoglobulins, and inhibit T-lymphocyte and macrophage production. TNFα is a cytokine that, for a number of reasons, is thought to play a central role in the pathogenesis of sepsis and septic shock: (1) TNFα concentrations are increased during clinical and experimental sepsis (Debets et al. 1989; Dofferhoff et al. 1992; Casey et al. 1993); (2) increasing concentrations and especially persistence of high concentrations of TNFα during sepsis are associated with decreased survival (Dofferhoff et al. 1992); (3) endotoxin and bacterial challenge in animals and low-grade endotoxinchallenge in humans lead to TNFα release (Michie et al. 1988); (4) TNFα challenge in animals (Eichenholz et al. 1992) and humans (Creaven et al. 1989; Lenk et al. 1989) leads to or simulates sepsis and organ failure; and (5) TNFα neutralization in experimental sepsis frequently leads to amelioration of sepsis symptoms and increases survival (Beutler et al. 1985; Tracey et al. 1987; Beutler 1993). These studies clearly underline the pivotal role that TNFα plays in the pathogenesis of sepsis.

Based on the findings of the studies outlined above, drugs against TNFα were produced and clinical trials were conducted to test whether inhibiting TNFα also improves survival in human sepsis. Early studies of anti-TNFα antibodies and TNFα-receptor fusion proteins did not lead to the results hoped for in phase III trials (Abraham et al. 1995, 1997, 1998; Cohen and Carlet 1996; Fisher et al. 1996; Reinhart et al. 1996). However, a meta-analysis of all randomized controlled clinical studies shows that anti-TNFα strategies with monoclonal antibodies are effective in increasing survival, with a mean improvement in survival of ~3% (Reinhart and Karzai 2001). It is striking that most trials showed a small, albeit nonsignificant, increase in survival in patients treated with anti-TNFα drugs, suggesting that TNFα

inhibition has led to beneficial effects in subgroups of patients. The recent positive results with afelimomab targeting patients with sepsis and elevated serum interleukin-6 levels (Panacek et al. 2004) further reinforces the fact that effective reduction in TNFα production or effect has therapeutic potential.

A variety of reasons have been suggested for why the effects of these anti-TNFα strategies have not produced the dramatic clinical benefit expected from the animal studies (Reinhart and Karzai 2001; Eichacker et al. 2002; Deans et al. 2005). In addition to other reasons, each of these strategies attempted to neutralize already-produced TNFα. A more effective strategy may be to suppress or modulate the ongoing production of TNFα and the other cytokines. In addition, each of these strategies affects the intravascular space predominantly, if not exclusively. Much of the organ dysfunction caused by sepsis may be occurring in spaces without direct intravascular involvement, such as the respiratory epithelium. In addition, the effect of anti-TNFα antibodies is only on extracellular or membrane-associated TNFα and not at intracellular levels (Fumeaux et al. 2004).

Early in the antibiotic era, the inability of appropriate antibiotic therapy to salvage all patients with severe infections was recognized. The classic example was and remains penicillin treatment of bacteremic pneumococcal pneumonia. However, Mortensen and colleagues showed that early appropriate guideline concordant therapy may improve survival in hospitalized patients with community-acquired pneumonia even in the first 48 h of admission (Mortensen et al. 2006b). More modern critical care has focused on organ support, such as early aggressive fluid resuscitation, lung-protective ventilatory strategies, and renal replacement therapy. Once again, while beneficial, a significant percent (20–30%) of severe sepsis patients die despite this state-of-the-art care.

1.2 Immunomodulation in Sepsis

Immunomodulation was thought to be an important mechanism to improve outcome of sepsis. While still logical and strongly supported by animal models, the results of these interventions have been disappointing. The early focus was on anti-TNFα strategies because of pivotal role in animal models of sepsis (Beutler et al. 1985; Tracey et al. 1987). However, these studies, despite encouraging preliminary studies or subgroup results, did not demonstrate an overall improvement in 28-day mortality (Abraham et al. 1995, 2001). Subsequent ones focusing on other mediators, such as IL-1 receptor antagonist, had similar results (Eichacker et al. 2002; Panacek et al. 2004). Whether low dose steroids have a benefit via replacement of relative adrenal insufficiency (Annane et al. 2002) or its immunomodulatory benefit is unclear.

The first immunomodulatory agent specifically approved by the Food and Drug Administration (FDA) for use in severe sepsis was drotrecogin-alfa activated, based on its overall 6.1% absolute risk reduction in a large Phase III trial (Bernard et al. 2001). Subsequent questions have arisen regarding the efficacy of drotrecogin-alfa activated for patients at low risk of dying (Abraham et al. 2005), with infections

other than pneumonia (Abraham et al. 2005; Laterre et al. 2005), and its overall risk/benefit (Eichacker et al. 2005). The cost (exceeded $7,000), the adverse effects (bleeding), and the limited efficacy to those severely ill with an acute physiologic and chronic health assessment (APACHE)-II score of ≥25 and several organ failures have limited the use in clinical practice.

The conclusion is that new immunomodulatory agents with either greater efficacy or lower toxicity are clearly needed. A variety of agents are presently in clinical trials. However, most are new molecular compounds which are likely to be similarly expensive to drotrecogin-alfa activated and may have significant or unknown side effects or toxicity. The potential to use a macrolide antibiotic, with its known side-effect profile and low cost, is particularly attractive.

1.3 Macrolides as Immunomodulators

The macrolides are a class of antibiotics that are characterized by a many-membered macrocyclic lactone ring. The original antibiotic was erythromycin, which was found to be a metabolic product of *Streptomyces erythreus*. Other common members of the class include roxithromycin, clarithromycin, and azithromycin. Azithromycin is derived from erythromycin by having a methyl-substituted nitrogen in its 15-member lactone ring. Macrolides with 15-member and 14-member lactone rings (roxithromycin, clarithromycin, and erythromycin) appear to have immunomodulatory properties that the larger macrolides do not have (Yamanaka et al. 2001). The macrolide antibiotics are structurally similar to the macrolide immunosuppressant agents' tacrolimus and rapamycin.

The antimicrobial mechanism of action of macrolide antibiotics is to inhibit bacterial protein synthesis by reversibly binding to the 50S ribosomal subunit, blocking transpeptidation and/or translocation in susceptible organisms. It is suggested that macrolides have immunomodulatory benefits that are independent of their bactericidal/bacteriostatic properties. The following data supporting these effects of macrolides derive from laboratory, animal, and clinical studies.

1.4 Laboratory Evidence

A considerable number of in vitro and in vivo studies have documented immunomodulatory properties of macrolides. The effect of macrolides on inflammatory molecules is confusing and somewhat variable. Macrolide antibiotics fairly consistently reduce production of inflammatory cytokines, including TNFα, IL-1β, IL-6, IL-8, and gamma interferon (IFN-γ) (Vazifeh et al. 2000) (summarized in Table 1.1).

The effect of macrolides may be somewhat dose dependent. Macrolides also appear to decrease intercellular adhesion molecule (ICAM)-1 (Khair et al. 1995; Kawasaki et al. 1998), although the effect of this on polymorphonuclear (PMNs) leukocytes recruitment into the lung is inconclusive. Macrolides are consistently

Table 1.1 Macrolide effect on cell lines

Cell line	Effect
Neutrophils	• Increase apoptosis
	• Decrease oxidants
Respiratory epithelial cells	• Increase IL-6 and IL-8 levels
T lymphocytes	• Decrease IL-1 and TNF levels
	• Increase IL-2, IL-4, and IFN-gamma
Monocytes	• Decrease IL-1, TNF, and GM-CSF
	• Increase IL-8 and IL-10 levels

GM-CSF granulocyte-macrophage colony-stimulating factor; *IFN* interferon; *IL* interleukin; *TNF* tumor necrosis factor

shown to suppress nitric oxide release, probably via inhibition of inducible nitric oxide synthetase (iNOS) gene expression (Tamaoki 2004). However, macrolides appear to increase neutrophil degranulation as measured by ex vivo release of bactericidal/permeability increasing protein (BPI), neutrophil elastase, and lactoferrin (Schultz et al. 2000). At the same time, they reduce IL-8 levels and other chemokines levels. In both human respiratory epithelial cells (Desaki et al. 2000) and monocytes (Kikuchi et al. 2002), macrolides appear to suppress nuclear factor kappa beta activation. A suggestion that the anti-inflammatory action of macrolides may be upstream of cytokine action (Vazifeh et al. 2000) remains highly speculative. The effect of macrolides may vary and could be cell-type specific. Immunomodulatory effects have been studied in neutrophils (Vazifeh et al. 2000), monocytes/macrophages (Khan et al. 1999; Kohri et al. 2000; Kikuchi et al. 2002), keratinocytes (Kobayashi et al. 2004), and respiratory epithelial cells (Desaki et al. 2000). Erythromycin inhibited IL-8 production in response to *Pseudomonas* stimulation in neutrophils but not alveolar macrophages (Oishi et al. 1994). Given the multitude of effects, macrolides likely act at multiple sites within the inflammatory cascade (Tamaoki 2004). Macrolides readily diffuse into intracellular sites and accumulate in cells at up to 50 times the serum concentration (Ishiguro et al. 1989; Rodvold 1999; Beringer et al. 2005), and interference with multiple target sites is quite feasible.

Macrolides have other important non-antibiotic properties relevant to sepsis. Firstly, macrolides inhibit neutrophil oxidative function, possibly by interference with the phospholipase D-phosphatidate phosphohydrolase transduction pathway (Abdelghaffar et al. 1997), or via protein kinase A inhibition (Mitsuyama et al. 1995). In addition, macrolides reduce respiratory secretions (Tamaoki 2004) by an undetermined mechanism. While potentially important, these effects do not explain macrolide inhibition of cytokine production and need further evaluation.

1.5 Experimental Evidence

Two recent publications have demonstrated a clear survival advantage of clarithromycin in a rabbit-pyelonephritis model of sepsis (Giamarellos-Bourboulis et al. 2005a,b). Although clarithromycin had no antimicrobial activity against the *Escherichia coli*

causing the sepsis, its addition to therapy resulted in a marked increase in survival. The survival benefit was almost equivalent to that of an active gram-negative bactericidal agent (amikacin). Furthermore, the increase in survival with administration of clarithromycin was accompanied by a marked decrease in monocyte activation and TNFα production compared to control (Giamarellos-Bourboulis et al. 2005a,b). Earlier work by the same group showed a similar benefit in a rabbit *Pseudomonas*-peritonitis sepsis model (Giamarellos-Bourboulis et al. 2004), demonstrating that the effect was dependent on neither site nor microorganism.

The strong association between TNFα and severe sepsis led to Phase II and III trials of anti-TNFα agents with different blocking strategies. One possible explanation for the lack of a beneficial effect of these agents was that a balance of positive and negative effects of blocking the TNFα response, rather than lack of efficacy alone, was responsible (Bone 1996; Reinhart and Karzai 2001). Macrolides have a significant anti-inflammatory action, reducing TNFα by up to fourfold but not completely ablating TNFα response (Khan et al. 1999; Kohri et al. 2000; Vazifeh et al. 2000; Kikuchi et al. 2002; Kobayashi et al. 2004). Modulation rather than complete ablation of TNFα may avoid many of the deleterious effects of anti-TNFα antibodies including increased risk of nosocomial infections. Furthermore, as TNFα response also involves autocrine signaling in some cell types (Kuno et al. 2005; Vila-del Sol and Fresno 2005), there are potential advantages of macrolides over anti-TNFα antibodies as the former have an intracellular (presecretory) mechanism of action. In addition, not all cytokines are affected equally by macrolides. Fluoroquinolones also have immunomodulatory effects (Dalhoff and Shalit 2003; Hall et al. 2004; Williams et al. 2005). When PMNs leukocytes from healthy volunteers were stimulated with phorbol myristate acetate, clarithromycin decreased IL-4 expression but did not affect the Th1 cytokine IFN-γ, whereas fluoroquinolones suppressed both IL-4 and IFN-γ (Williams et al. 2005). The net result was that the Th1/Th2 ratio increased with clarithromycin, potentially maintaining protection from a bacterial challenge (Ferguson et al. 1999).

Finally, it is clear that macrolides alter the production of a much wider range of inflammatory proteins than just TNFα, providing additional potential beneficial responses in patients with severe sepsis.

1.6 Clinical Evidence

Macrolide antibiotics have been used as antimicrobial agents for more than 50 years. More recently, clinicians have begun to use these agents not for their antimicrobial action but for their effect on immune function. The most dramatic example of the efficacy of macrolides as immune modulators is in diffuse panbronchiolitis. This noninfectious, autoimmune lung condition had a 70% 5-year mortality rate until long-term low-dose erythromycin was found to reduce the 5-year mortality rate to <20% (Yamamoto et al. 1990; Kudoh et al. 1998; Kadota et al. 2003).

Table 1.2 Macrolide effects on different respiratory conditions in human subjects

Conditions	Effects
Asthma	Increase FEV_1, change on the provocative dose of methacoline
Bronchiolitis obliterans	Increase FEV_1, decrease neutrophil and IL-8 levels
Cryptogenic pneumonia	Symptomatic improvement and radiographic resolution
Cystic fibrosis	Increase FEV_1, reduced risk of bacterial exacerbation and reduced need for antimicrobial therapy
Diffuse panbronchiolitis	Improve survival, decrease sputum production, increase FEV_1 and vital capacity
COPD	Decrease IL-8, TNFα, lactoferrin, and 2-microglobulin of neutrophils

COPD chronic obstructive pulmonary disease; *FEV_1* forced expiratory volume in the first second; *IL*, interleukin; *TNF* tumor necrosis factor

The exact mechanism is unknown but is clearly not solely antimicrobial (Amsden 2005). Macrolide antibiotics are now being used in a variety of predominantly respiratory diseases as immunomodulatory agents. Some are clearly infectious, such as cystic fibrosis (Equi et al. 2002; Hoiby 2002; Wolter et al. 2002a,b; Saiman et al. 2003; Schultz 2004; Southern and Barker 2004; Amsden 2005; Clement et al. 2006) and bronchiectasis (Koh et al. 1997; Yalcin et al. 2006) (Table 1.2). In these cases, other effects, such as inhibition of bacterial toxic or biofilm production, quorum sensing, and even intracellular killing despite resistance of the bacteria by usual sensitivity testing, may explain the beneficial effect. However, an immunomodulatory role has been suggested by an analysis of cytokine levels and a differential response with other antibiotics.

Other disorders where macrolides have been suggested to be of benefit are clearly not infectious (Table 1.2). In obliterative bronchiolitis post transplant (Gerhardt et al. 2003; Schultz 2004; Tamaoki et al. 2004; Stover and Mangino 2005; Verleden et al. 2006), they appear to have significant efficacy. Other disorders in which macrolides have been suggested to be effective include asthma (Miyatake et al. 1991a,b; Hendeles 1992; Amayasu et al. 2000; Kraft et al. 2002; Gotfried 2004; Hatipoglu and Rubinstein 2004; Kostadima et al. 2004; Amsden 2005; Johnston et al. 2006; Piacentini et al. 2007), chronic obstructive pulmonary disease (Culic et al. 2002; Basyigit et al. 2004; Parnham et al. 2005), pyometra (Mikamo et al. 1998), and even as a post operative anti-inflammatory analgesic (Chow et al. 2000).

However, the strongest data available is derived from clinical studies in patients with pneumococcal and community-acquired pneumonia (CAP). Interest in the role of macrolides as immunomodulatory agents for sepsis was first stimulated by the retrospective review of mortality in bacteremic pneumococcal community-acquired pneumonia done by Waterer and collaborators (Waterer et al. 2001). The use of a single effective antibiotic was associated with an increased mortality compared to the use of two effective agents. The two populations were well matched for severity, as suggested by APACHE II scores and pneumonia severity index score. Macrolide-containing combinations were the most common type of combination therapy and

had lower mortality than predicted by the APACHE II prediction model. The statistically significant mortality difference persisted in multivariate analysis. When only patients with PSI scores >90 (potential ICU patients (Mandell et al. 2003)) were analyzed, the predicted mortality-adjusted odds ratio for death with monotherapy was 5.5 (95% confidence interval (CI) 1.7–17.5). Mufson and Stanek (1999) had also documented a significant mortality benefit of adding specifically a macrolide to β-lactam therapy in a large prospective observational trial of bacteremic pneumococcal CAP. Stimulated by these results, two large prospective observational trials (Martinez et al. 2003; Baddour et al. 2004) and a retrospective single site study (Weiss et al. 2004) have all documented a survival advantage to adding a macrolide to a β-lactam for bacteremic pneumococcal infections (Table 1.3).

Table 1.3 Studies of macrolide therapy in patients with serious infections

Reference	Year	Design	Subjects	Infectious disease	Main results
Mufson	1999	Population-based, retrospective cohort	600	Bacteremic pneumococcal pneumonia	Mortality difference among macrolide combination therapy vs. nonmacrolide monotherapy (7.3% vs. 24.2%) Absolute risk reduction of 16.9
Waterer	2001	Multicenter, retrospective cohort	225	Bacteremic pneumococcal pneumonia	Mortality difference among macrolide combination therapy vs. nonmacrolide monotherapy (4.4% vs. 19.4%) Absolute risk reduction of 15.0
Martinez	2003	Multicenter, prospective cohort	409	Bacteremic pneumococcal pneumonia	In-hospital mortality was lower with macrolide therapy (OR 0.40; 95% CI 0.17–0.92; $p = 0.03$)
Baddour	2004	Multicenter, prospective cohort	844	Bacteremic pneumococcal pneumonia	14-day mortality was lower with combination therapy vs. monotherapy in critically ill patients (23.4% vs. 55.3%; $p = 0.0015$) and ICU-admitted patients (8.2% vs. 23.1%; $p = 0.03$) 14-day mortality was lower with macrolide therapy (14.6%; $p = 0.007$)

(continued)

Table 1.3 (continued)

Reference	Year	Design	Subjects	Infectious disease	Main results
Weiss	2004	Population based, retrospective cohort	95	Bacteremic pneumococcal infection	Mortality was lower with combination therapy vs. monotherapy (7.5% vs. 25.6%; $p = 0.002$) with an absolute risk reduction of 18.1
Garcia Vasquez	2005	Multicenter, prospective cohort	1,391	CAP	Mortality was lower with combination therapy vs. monotherapy in all CAP patients (6.9% vs. 13.3%; $p = 0.001$) and in PSI V patients (25.7% vs. 32.6%; $p = 0.02$) Mortality was higher if macrolide therapy was not used (OR 2.95; 95% CI 1.24–3.23)
Rodriguez	2007	Multicenter, prospective cohort	270	ICU CAP with septic shock	28-day ICU survival was higher with combination therapy in CAP patients with shock (HR 1.69; 95% CI 1.09–2.60, $p = 0.01$) and in patients that received macrolide therapy (HR 1.73; 95% CI 1.08–2.76, $p = 0.02$)
Metersky	2007	Population based, retrospective cohort	2,209	Bacteremic pneumonia	Macrolide therapy was associated with lower in-hospital mortality (OR 0.59; 95% CI 0.40–0.88, $p = 0.01$), 30-day mortality (OR 0.61; 95% CI 0.43–0.87, $p = 0.007$) and hospital re-admission within 30 days post discharge (OR 0.59; 95% CI 0.42–0.85, $p = 0.004$)

CAP community-acquired pneumonia; *CI* confidence interval; *HR* hazard ratio; *OR* odds ratio; *PSI* pneumonia severity index

Further support for the addition of macrolides has come from observational studies in more general CAP cohorts which have also documented outcome benefits of combination therapy over monotherapy, especially with β-lactam monotherapy (Dudas et al. 2000; Houck et al. 2001; Brown et al. 2003; Garcia Vazquez et al. 2005). The majority of combination therapy in these studies included a macrolide. These results suggest that the benefit of macrolides may not be limited to bacteremic pneumococcal disease or even to only pneumococcal CAP.

The mortality benefit from the addition of a macrolide appears to be quite striking, with odds ratios for death ranging from 0.22 to 0.45. The greatest difference appears to be in the critically ill with the highest adjusted odds ratios of death without macrolide therapy in the most critically ill as defined by Pittsburgh Bacteremia score (Baddour et al. 2004), PSI score (Waterer et al. 2001), or simply need for ICU care. The survival advantage of macrolides was only apparent when adjusted for severity of illness but was independent of septic shock (Martinez et al. 2003).

The survival curves in all the studies indicate that the mortality reduction consistently begins 48–72 h after the commencement of therapy, with most benefit being seen in the first 7–10 days. These survival curves are representative of all the other studies as well. The timing of the mortality benefit is important, as macrolides appear to be affecting outcome in the initial 2–7-day period when proinflammatory-driven secondary organ failure (such as acute respiratory distress syndrome, renal, and hepatic failure) is the predominant cause of death. The absence of a clearly discernable survival benefit in the first 24–48 h is not unexpected, given the historical data demonstrating that antibiotics have no impact on mortality compared to placebo (or even immune serum) during that period (Austrian and Gold 1964). Patients who die during the first 48 h typically present in refractory septic shock with multiorgan failure already present, markedly limiting the potential for any intervention to affect outcome. However, recent data suggested that empiric guideline concordant antibiotic therapy was associated with lower mortality even during the first 48 h of admission to the hospital in patients with CAP (Mortensen et al. 2006b).

Two principal explanations have been put forward for the observed beneficial effect of macrolides. The first is the already-discussed immunomodulatory properties of macrolides. The second possibility is unrecognized coinfection (in the case of pneumococcal pneumonia) with a second "atypical" pathogen such as *Mycoplasma, Legionella*, or *Chlamydia* (Waterer 2003). However, fluoroquinolones should have been equivalent to, if not better than, macrolides and yet in our study fluoroquinolone monotherapy had worse outcome compared to macrolide combination therapy (Waterer et al. 2001). Several studies only analyzed macrolides provided in the first 48 h (Waterer et al. 2001) and a short course is less likely to result in a mortality difference even if copathogens were present. In addition, the incidence of atypical copathogens is significantly less common in patients with severe CAP requiring ICU admission than in patients hospitalized on a general floor or treated as outpatients (Ruiz et al. 1999).

However, the most convincing data that coverage of atypical pathogens is not the explanation for the survival benefit of macrolides is recent data from Mortensen and colleagues. We have shown that the combination of a β-lactam and a fluoroquinolone is substantially inferior to that of a β-lactam and a macrolide in patients with severe CAP (Mortensen et al. 2006a). The actual mortality in patients receiving macrolide

combination therapy was 17.2%, an absolute risk reduction of 13.8% for the general population. Once again, the benefit of a nonquinolone (mainly macrolide) combination was most pronounced in the more severely ill patients (17.9% mortality vs. 29.7% for fluoroquinolone combinations in patients with PSI category IV or V patients). As fluoroquinolones have equivalent atypical pathogen cove-rage, the most likely explanation is the favorable immunomodulatory properties of macrolides.

These studies provide strong evidence that combination antibiotic therapy with a macrolide is associated with improved outcome from severe CAP. The same benefit is not achieved with fluoroquinolone-based combination therapy, suggesting that the benefit is not a result of coverage of atypical pathogen coinfection and more likely due to immunomodulatory effects of the macrolides. These immunomodulatory effects are also not reproduced by the fluoroquinolones, which may actually have an adverse effect on immune function (Williams et al. 2005). However, all of the studies demonstrating a benefit have been either retrospective or observational trials, leaving open the possibility that factors not included in the multivariate analyses may be the actual cause of the mortality difference. Several editorials have therefore called for a prospective randomized trial of combination macrolide therapy in severe CAP (Waterer 2003, 2005; Weiss et al. 2004). However, a recent randomized control trial in patients with sepsis due to ventilator associated pneumonia treated with clarithromycin did not show a survival benefit (Giamarellos-Bourboulis et al. 2008). On the other hand, clarithromycin accelerated the resolution of ventilator associated pneumonia, and weaning from mechanical ventilation in surviving patients and delayed death in those who died of sepsis.

An even greater issue is whether the benefit of macrolides extends to other infections. A few of the studies included primary or concomitant pneumococcal meningitis or primary bacteremia. However, the benefit in principally gram-negative infections, such as intra-abdominal or urinary tract, is more uncertain. The animal data (Giamarellos-Bourboulis et al. 2005a,b) and the clinical benefit in cystic fibrosis (Kraft et al. 2002; Wolter et al. 2002a,b; Saiman et al. 2003; Gotfried 2004; Kostadima et al. 2004; Schultz 2004; Amsden 2005; Johnston et al. 2006; Piacentini et al. 2007) and bronchiectasis (Koh et al. 1997; Yalcin et al. 2006) do support a clinical trial for gram-negative infections as well. CAP usually accounts for up to 40% of cases of severe sepsis or septic shock in large multicenter therapeutic trials (Bernard et al. 2001) and may even be the major subgroup driving results in the overall trial (Laterre et al. 2005). Concern for the differential benefit in non-CAP infections does warrant stratification of randomization to ensure a balance of CAP patients in each group.

1.7 Conclusion

This chapter summarizes the evidence that macrolide therapy may be useful in the treatment of severe sepsis and severe community-acquired pneumonia. Further randomized clinical trials are needed to clarify the mechanisms why macrolide therapy could modulate the immune response and the impact on clinical outcomes in patients with severe sepsis due to any origin.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

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Chapter 2
The Potential Role of Statins in Severe Sepsis

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2.1 Introduction

Sepsis is the tenth leading cause of death in the United States (Hoyert et al. 2001) and has a mortality rate of up to 70% (Angus et al. 2001; Annane et al. 2003). Inpatients with sepsis have a 26-fold increased risk of death compared to intensive care unit subjects without sepsis (Annane et al. 2003). New medications are urgently needed to prevent and treat sepsis since only a few new classes of antibiotics have been added to the armamentarium in the past ten years, and only one new class of medication specifically targeting sepsis (drotrecogin-alfa) has been added (Bernard et al. 2001).

In the United States, almost $17 billion is spent each year treating patients with sepsis (Angus et al. 2001). More than 750,000 cases of severe sepsis occur annually (Angus et al. 2001), with the incidence increasing due to the aging population, the growing number of immunocompromised patients, increasing use of invasive procedures, and increasing antibiotic resistance. Despite advances in care, the mortality rate due to severe sepsis remains up to 80% (Annane et al. 2003). Even single organ dysfunction is associated with a mortality rate of 20% with mortality increasing by up to 20% for each additional dysfunctional organ (Vincent et al. 1998).

Recently, several classes of medications including HMG-CoA reductase inhibitors (statins) have been found to attenuate the systemic inflammatory response (de Bont et al. 1998; Jialal et al. 2001; Musial et al. 2001; Ridker et al. 1998; Rosenson and Tangney 1998; Rosenson et al. 1999; Strandberg et al. 1999). In addition, statins have been demonstrated to have protective endothelial effects, influence inflammatory cell signaling, directly effect T-cell activity, and influence the nitric oxide balance to promote hemodynamic stability (Almog 2003; Hothersall et al. 2006; Terblanche et al. 2007). Several epidemiologic studies have demonstrated that subjects receiving statins hospitalized with bacteremia and community-acquired pneumonia have improved clinical outcomes, or decreased incidence of sepsis (Almog et al. 2004, 2007; Fernandez et al. 2006; Frost et al. 2007; Gupta et al. 2007; Hackam et al. 2006; Kruger et al. 2006; Liappis et al. 2001; Martin et al. 2007; Mortensen et al. 2005a,b; Schlienger et al. 2007; Thomsen et al. 2006; Yang et al. 2007).

The purpose of this article is to review the scientific literature regarding the potential role of statins in the prevention and/or treatment of severe sepsis.

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2.2 Statins

A growing body of evidence suggests that the magnitude of effect of statins on cardiovascular outcomes may be greater than their attributable effect on lowering cholesterol (Arntz 1999; Koenig 2000). This evidence suggests that a secondary mechanism of action may include increasing inflammatory responses that are either primary or secondary contributors to progression of atherosclerosis, which is similar to the pathogenesis of sepsis (Ross 1999). Inflammation is considered the first line of defense in host–pathogen interactions. The inflammatory process is necessary so that pathogens are contained and eliminated, and the ability of an organism to mount and successfully resolve inflammatory responses is imperative to the subsequent health of that organism (Cazzola et al. 2005). Inflammation is mediated by a number of cytokines including proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-a; and anti-inflammatory cytokines such as IL-10 and transforming growth factor (TGF)-b. These cytokines are necessary for proper function of the immune system, but the overexpression, or inappropriate expression of these proinflammatory cytokines can result in tissue destruction, sepsis, or death (Nathan 2002). At least four studies have documented short-term (7 week to 12 month) declines in one or more of the following cytokines/inflammatory markers after treatment with statins: C-reactive protein, TNF-α, or IL-6 in patients taking statins for hypercholesterolemia (Jialal et al. 2001; Musial et al. 2001; Rosenson et al. 1999; Weis et al. 2001).

In addition, there are several other potential pathways that statins may exert effects on the body (Table 2.1). These include effects on T-cell activity, coagulation and fibrinolysis, antioxidant effects, nitric oxide balance, leukocyte–endothelium interactions, and inflammatory cell signaling and gene expression (Hothersall et al.

Table 2.1 Physiologic actions of statins

Actions	References
Antioxidant effects	Aviram et al. 1998; Girona et al. 1999; Grosser et al. 2004; Landmesser et al. 2005; Rikitake et al. 2001; Shishehbor et al. 2003; Yamamoto et al. 1998
Coagulation	Bickel et al. 2002; Bourcier et al. 2000; Shi et al. 2003; Steiner et al. 2005
Cellular apoptosis	Hakamada-Taguchi et al. 2003; Newton et al. 2002; Rudich et al. 1998
Cytokine release	Ando et al. 2000; Diomede et al. 2001; Ikeda and Shimada 1999; Ikeda et al. 1999; Kleemann et al. 2004; Nath et al. 2004; Steiner et al. 2005; Wang et al. 2005
Inflammatory cell signaling	Dichtl et al. 2003; Grip et al. 2002; Jacobson et al. 2005; Kleemann et al. 2004
Leukocyte–endothelial cell adhesion	Diomede et al. 2001; Grip et al. 2002; Jacobson et al. 2005; Kallen et al. 1999; Kimura et al. 1997; Kothe et al. 2000; Lefer et al. 2001; Ni et al. 2001; Pruefer et al. 2002; Rice et al. 2003; Romano et al. 2000; Scalia et al. 2001; Yoshida et al. 2001
Nitric oxide balance	Grosser et al. 2004; Landmesser et al. 2005

2006; Terblanche et al. 2007). These so-called pleiotropic effects of statins have numerous potential sites of action, and it is unclear which potential mechanisms for the observational studies demonstrate a protective association between statin use and infectious diseases.

There are several potential adverse effects for statins in sepsis that should be acknowledged. Besides previously demonstrated adverse effects of statins such as rhabdomyolysis and hepatotoxocity, other studies had demonstrated that lipoproteins may be protective against endotoxins so that lowering the serum levels of lipoproteins may be detrimental (Almog 2003; Bonville et al. 2004; Harris et al. 2000). In addition, lower levels of serum cholesterol have been shown to be a predictor of higher hospital mortality and increased risk of various infections, including HIV (Claxton et al. 1998; Iribarren et al. 1998).

2.3 Observational Studies

Several published studies have examined the effect of statin use on infectious disease-related outcomes (Table 2.2). The first published paper by Liappis et al. (2001) studied 388 patients hospitalized with bacteremia, and found a protective effect of in-hospital statin use on in-hospital mortality (6% vs. 28%, $p < 0.002$). After adjusting for confounding factors (including comorbid conditions, age, concurrent medications, site of infection, vital signs, and laboratory data), not being on a statin (odds ratio (OR) 7.6, 95% confidence interval (CI) 1.01–57.5) was associated with increased mortality.

2.3.1 Studies of Sepsis

There have been four published studies that examine the association of statin use on the incidence of sepsis or survival after sepsis. Almog et al. described a prospective study of 361 patients hospitalized with cellulitis, CAP, or urinary tract infections which demonstrated a decreased rate of sepsis for patients who were taking statins versus those who were not (2.4% vs. 19%, $p < 0.001$) (Almog et al. 2004). However, no significant difference was seen in 28-day mortality. Another study recently published in the Lancet describes the results of a population-based cohort study ($n = 141{,}487$) that examined the impact of statin use to prevent sepsis using administrative databases from Ontario, Canada (Hackam et al. 2006). After adjusting for potential confounders, the incidence of sepsis was lower in patients receiving statins as compared to controls (hazard ratio 0.8, 95% CI 0.7–0.9). However, this paper did not examine the effect of statin use on patients already hospitalized with sepsis. Finally, another recent study was published in *JAMA* by Gupta et al. (2007) with the aim of examining whether statin use was associated with decreased incidence of hospitalization for sepsis. This prospective cohort study included

Table 2.2 Observational studies of statin use and infectious/pulmonary diseases

Reference	Year	Design	Subjects	Infectious disease	Results
Liappis (Liappis et al. 2001)	2001	Single center, retrospective cohort	388 total 35 on statins	Bacteremia	Increased mortality for those not on statins (OR 7.6, 95% CI 1.01–57)
Almog (Almog et al. 2004)	2004	Single center, prospective cohort	361 total 82 on statins	Severe sepsis incidence	Statins protective against sepsis 2.4% vs. 19%, $p < 0.001$
Mortensen (Mortensen et al. 2005a)	2005	Multicenter, retrospective cohort	787 total 110 on statins	Community-acquired pneumonia	Statins protective (OR 0.36, 95% CI 0.14–0.92)
Fernandez (Fernandez et al. 2006)	2005	Single center, retrospective cohort	438 total, 38 on statins	Mechanically ventilated >96 h, ICU-acquired infections	No difference in infections (29 vs. 38%) and higher mortality for statins (61% vs. 42%
Hackam (Hackam et al. 2006)	2006	Population-based, retrospective cohort	69,168 total 34,584 on statins	Incidence of sepsis per 10,000 person years	71.2 for statins vs. 88 for non-statins ($p = 0.0003$)
Kruger (Kruger et al. 2006)	2006	Single center, retrospective cohort	438 total, 66 on statins	Bacteremia	Mortality less for statins (10.6% vs. 23.1%, $p = 0.02$)
Thomsen (Thomsen et al. 2006)	2006	Population-based, retrospective cohort	5,353 total, 176 on statins	Bacteremia	No difference in 30-day mortality 31–180 mortality less for statins (8.4% vs. 17.5%, $p < 0.05$)
Majumdar (Majumdar et al. 2006)	2006	Multicenter prospective cohort	3,415 total 325 on statins	Community-acquired pneumonia	No difference for in-hospital mortality (8% for statins vs. 10%, $p = 0.2$)
Martin (Martin et al. 2007)	2007	Single center, retrospective cohort	53 total 16 on statins	Incidence of severe sepsis	56% for statins group vs. 86%, $p < 0.02$
Yang (Yang et al. 2007)	2007	Single center, retrospective cohort	454 total 104 statins	Sepsis	No difference in 30-day mortality with statin use (19.2% vs. 18.9%, $p = 0.95$)
Schlienger (Schlienger et al. 2007)	2007	Population-based, retrospective case control	1,253 pneumonia cases 4,838 controls	Incidence of pneumonia	Statin users had reduced risk of fatal pneumonia (OR 0.47, 95% CI 0.25–0.88)
Gupta (Gupta et al. 2007)	2007	Multicenter, prospective cohort study	1,041 total 143 statins	Incidence of sepsis	Statin use protective against sepsis (incident rate ratio 0.24, 95% CI 0.11–0.49)
Almog (Almog et al. 2007)	2007	Single center, prospective cohort	11,362 total 5,698 statins	Infection-related mortality	Statins users had significantly lower mortality (hazard ratio 0.37, 95% CI 0.27–0.52)
Frost (Frost et al. 2007)	2007	Population-based, retrospective cohort and case control	76,232 total 11,583 statins	Mortality due to influenza/pneumonia	Statin use associated with decreased mortality (OR 0.6, 95% CI 0.44– 0.81)

1,041 incident dialysis patients at 81 centers and followed them for a mean of 3.4 years. They found that, after adjustment for potential confounders using propensity matching, statin use was strongly protective against sepsis (OR 0.24, 95% CI 0.11–0.49).

The only study of statins and sepsis not to find a potentially protective association was recently published in the *American Journal of Emergency Medicine*. Yang et al. (2007) examined 454 Taiwanese subjects hospitalized with sepsis. After adjusting for potential confounders, they found no significant difference in 30-day mortality (risk ratio 0.95, 95% CI 0.53–1.68). There was a trend toward lower mortality in those with gram-negative sepsis (10.3% vs. 16.4%, $p = 0.25$). Unfortunately, since the final models were not presented in the paper, it is unclear, however, how complete the risk adjustment was.

2.3.2 Studies of Pneumonia

There have been several studies of statin use and pneumonia-related outcomes. The first by Mortensen et al. (2005a) was a retrospective cohort study of 787 subjects hospitalized with CAP at two academic tertiary care hospitals to assess the effects of current outpatient statin use on 30-day mortality. Of the 787 subjects, 110 subjects (14%) were on statins, and after adjusting for potential confounders, including severity of illness, the use of statins (OR 0.4, 95% CI 0.1–0.9) was significantly associated with decreased 30-day mortality. Another study by Majumdar et al. (2006) showed no significant difference in mortality for patients with pneumonia who were statin users after adjusting for potential confounders. Although this study had a prospectively derived cohort of 3,415 subjects, there were several problems with this study including an inappropriate composite outcome, unclear model building, and a cohort with significantly lower rates of statin use in key populations as compared to other published studies of statins association with sepsis and/or pneumonia (Mortensen et al. 2006). Another paper by Schlienger et al. described a case-control study of 1,254 pneumonia cases that were matched with 4,838 control patients from a population-based database of 134,262 patients more than 30 years of age (Schlienger et al. 2007). They found that current statin use, but not past use, was associated with reduction in fatal pneumonia (OR 0.47, 95% CI 0.25–0.88).

2.3.3 Studies of Other Infectious and Pulmonary Diseases

In addition to the study by Liappis et al. discussed above, there have been several other studies which examine statins impact on outcomes for other infectious and pulmonary diseases. A retrospective study of 438 patients hospitalized with bacteremia demonstrated a significant difference for in-hospital mortality: 1.8% for patients on statins versus 23.1% for non-statin users ($p = 0.0002$) (Kruger et al. 2006).

Unfortunately, this study had significant limitations including not controlling comorbid conditions or other medications in the multivariable analyses. Another recent prospective population-based study by Almog et al. (2007) of 11,490 patients with cardiovascular disease that were followed by up to 3 years demonstrated that statin use was associated with significantly lower mortality (0.9% vs. 4.1%). A paper by Frost et al. (2007), which presents several analyses including a cohort study and several case-control analyses, found that statin use was associated with decreased odds of influenza/pneumonia death (OR 0.60, 95% CI 0.44–0.81) and COPD death (OR 0.17, 95% CI 0.07–0.42).

In contrast, Fernandez et al. examined 438 ICU patients that were mechanically ventilated for >96 h and demonstrated increased mortality (61% vs. 42%, $p = 0.03$) for those patients who were taking a statin prior to admission (Fernandez et al. 2006). However, this study included only highly selected patients who received at least 4 days of mechanical ventilation prior to inclusion. Therefore this study excluded patients who may have had improved outcomes due to statin use and did not need this duration of mechanical ventilation.

2.4 Conclusion

This chapter summarizes the evidence that statins may be useful in the prevention and/or treatment of severe sepsis. These results add an additional potential benefit of statins to their demonstrated benefits for subjects with vascular and renal disease. Additional research, especially randomized clinical trials, is needed to elucidate whether statins may have a role in prevention of sepsis or treatment of patients hospitalized with severe sepsis.

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Chapter 3
The Genetics of Sepsis: The Promise, the Progress and the Pitfalls

Grant W. Waterer

3.1 Introduction

Physicians are used to taking a family history of cardiovascular disease because of the known significant hereditary risk; yet the familial risk of dying from infection is even greater than that for atherosclerotic disease (Sorensen et al. 1988). There is certainly no doubt that genetic differences impact on the risk of developing or dying from infection. Obvious but rare examples include selective immunoglobulin deficiencies, complement deficiencies, and neutrophil function abnormalities. Genetic factors may also be protective, such as with sickle cell trait and malaria or mutations conferring resistance to human immunodeficiency virus infection.

Much more subtle differences in immune responses are now being described, usually as the result of one or more single nucleotide polymorphisms (SNP) in a gene. Rather than causing the failure of production of a protein or the production of a nonfunctional protein, SNPs are usually associated with changes in the rate of transcription, producing a much less severe phenotype than the classical examples of genetic defects mentioned above. It is now being appreciated that for many complex diseases, such as sepsis, the ultimate phenotype is the result of the interaction of genetic differences across many loci, not the dominant effect of a few key mutations.

As seen in Fig. 3.1, since the mid 1990s, an increasing body of literature has focused on the role that gene polymorphisms in key inflammatory genes play in sepsis. Indeed, with advances in knowledge of the human genome, greater understanding of the inflammatory response, and the development of high throughput genotyping technologies, so many genetic associations have been described that discussion of each one is well beyond the scope of this chapter. I will however summarize those findings that have been reported by multiple groups, as well as give an overview of the major groups of genes that have been implicated in genetic predisposition to sepsis and its adverse outcomes.

Despite all this apparent growth in knowledge over the past decade however, to date not one new intervention has been developed as a result of all the genetic studies. As I will discuss, significant limitations in research methodology in published studies combined with the fact that sepsis is not a single disease make it unlikely that we

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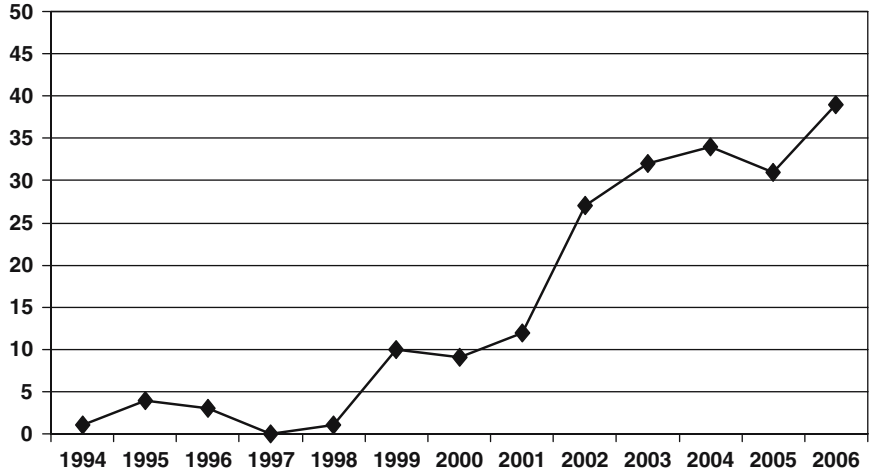

Fig. 3.1 Publications on the genetics of sepsis by year

will see any hope for new interventions in the near future. If we are to truly advance our understanding of sepsis and develop new therapeutic strategies, a substantial change in our current thinking will be required.

3.2 Basic Genetic Terminology

Some basic knowledge of genetic terminology is essential to decipher the sepsis-genetics literature and indeed many apparent contradictions have arisen due to terminology errors. A variety of mutations can occur in DNA, some of which leading to the change in function or production of a gene product. The simplest change is the substitution of one nucleotide for another, a SNP. A number of other mutations occur including the deletion or insertion of one or more nucleotides, including the insertion of multiple repeating sequences, sometimes called a microsatellite.

A region of DNA coding for a protein product is called an exon. Introns are the noncoding regions of DNA separating exons. Most genes consist of several exons and introns. The rate at which genes are transcribed is controlled by a variety of nuclear proteins that bind to different areas of DNA in the 5′ (upstream) region from the first exon. The segment of DNA controlling the regulation of transcription of a gene is also known as the promoter region.

When mutations occur in an exon they may lead to a change in the protein structure of the gene product (nonsynonymous mutation) or they may leave the protein product unchanged (synonymous mutation). When the change occurs in a promoter region, this may alter the binding of a transcription-activating or -suppressing factor, altering the rate of transcription of the gene. Although introns have been considered to be “junk DNA” and therefore mutations are likely to be of little biological importance, it is now appreciated that polymorphisms within introns can affect

gene regulation, particularly when they are at the intron–exon boundary (Rohrer and Conely 1998; Meloni et al. 1998; Webb et al. 2003; Lenasi et al. 2006).

Most of the confusion in genetic studies is around the labeling of SNPs. Initially SNPs were assayed by amplifying up the region of DNA with the mutation by polymerase chain reaction and then using an enzyme that cut the DNA based on whether the polymorphism was present or not. Early in the genetic literature it is therefore common to see SNPs referred to by the gene and the enzyme used, for example, the tumor necrosis factor (TNF) NcoI polymorphism (subsequently known as TNF-308).

As it rapidly became apparent that there were often multiple sites within a gene that could be cleaved by the same enzyme, this nomenclature was abandoned in favor of using the nucleotide position relative to the start of the transcription site for the gene (e.g., TNF-308, TNF-238, TNF+1850, etc). This nomenclature dominated the literature for nearly a decade as it is intuitively easy to understand and the number system gives an idea of what the functional significance of the polymorphism is likely to be (e.g., a negative value places it most likely in the promoter region, a positive value in an intron or an exon). When a mutation resulted in an amino acid change in the protein, an alternative nomenclature was often substituted to reflect this (e.g., Toll-like receptor 4 (TLR4) Thr399Ile indicates that an isoleucine is substituted for a threonine at amino acid position 399).

Unfortunately, differences in calculation of the transcription start site for genes led to increasing confusion – for example, the lymphotoxin alpha (LTA, formally known as tumor necrosis factor beta) polymorphism, reported by Stuber and colleagues (1996) as a risk factor for sepsis, was variably reported as LTA+249, LTA+250, LTA+251, and LTA+252. With hundreds of thousands if not millions of polymorphisms now described, the accepted practice for indicating the exact polymorphism being described is currently the reference sequence number (rs#) on the National Institutes of Health database (e.g., the TNF NcoI or -308 polymorphism is officially rs1800629). While all publications should reference the rs#, it is likely that older terminology will continue to be used for sometime until it is more familiar.

A final problem with nomenclature that needs to be discussed is the labeling of individual alleles. There was a convention commonly seen in early genetics literature that the most common allele in the population studies was referred to as allele 1 (or A), the second most common allele 2 (or B), and so on (i.e., TNF-308 allele 1). As allele frequencies can vary significantly between populations, this has the potential to lead to considerable confusion and they should instead be referred to by the nucleotide carriage (e.g., TNF-308 A or TNF-308 G) or the number of nucleotide repeats.

3.3 Studies of Genetic Influence on the Inflammatory Response

Genetic polymorphisms with potential influences on the inflammatory response have been identified in a variety of antigen recognition, pro- and anti-inflammatory cytokines. All of these polymorphisms are candidates for studies in genetic influences on sepsis and its outcomes, and Table 3.1 summarizes studies that have been published.

Table 3.1 An enormous number of genes have been identified as having potentially important polymorphic sites

Antigen recognition	Pro-inflammatory	Anti-inflammatory	Coagulation and tissue repair pathways
CD14 (Baier et al 2006; Barber et al 2006; Gibot et al 2002; Heesen et al 2002; Nakada et al 2005; Skinner et al 2005; Temple et al 2003)	TNF (Barber et al 2006; Calvano et al 2003; Gong et al 2005; Gordon et al 2004; Hedberg et al 2004; Majetschak et al 1999; Mira et al 1999; Nakada et al 2005; Nuntayanuwat et al 1999; O'Keefe et al 2002; Stuber et al 1995; Waterer et al 2001; Westendorp et al 1997)	IL-10 (Baier et al 2006; Balding et al 2003; Gallagher et al 2003; Gong et al 2006; Lowe et al 2003; Nakada et al 2005; Schaaf et al 2003; Shu et al 2003; Stanilova et al 2006; Sutherland et al 2005; Wattanathum et al 2005; Westendorp et al 1997)	Fibrinogen-beta (Manocha et al 2007)
TLR4 (Barber et al 2006; Lorenz et al 2002; Nakada et al 2005; Skinner et al 2005), TLR2 (Skinner et al 2005), TLR5 (Hawn et al 2003)	IL-1β (Watanabe et al 2005), IL-6 (Baier et al 2006; Balding et al 2003; Barber et al 2006; Schluter et al 2002; Sutherland et al 2005), IL-18 (Stassen et al 2003)	IL-1 receptor antagonist (Arnalich et al 2002; Balding et al 2003; Fang et al 1999)	Protein-C (Walley & Russell 2007)
Lippopolysaccharide binding protein (Barber & O'Keefe 2003; Hubacek et al 2001)	CXCL2 (Flores et al 2006)	Heat shock protein 70 complex (Schroder et al 2003; Waterer et al 2003)	Vascular endothelial growth factor (Zhai et al 2007)
IgG2 receptor (also the C-reactive protein receptor) (Yuan et al 2003)	Lymphotoxin alpha (Calvano et al 2003; Majetschak et al 1999; Rauchschwalbe et al 2004; Stuber et al 1996; Waterer et al 2001)		Factor V (Weiler etal 2004; Yan & Nelson 2004)
Myeloid differentiation protein-2 (MD-2) (Gu et al 2007)	Macrophage migration inhibition factor (MIF) (Gao et al 2007)		Apolipoprotein-E (Moretti et al 2005)
C-reactive protein (Eklund et al 2006)	Pre-B cell colony stimulating factor (PBEF) (Bajwa et al 2007; Ye et al 2005)		Plasminogen activator inhibitor-1 (Binder et al 2007a; Binder et al 2007b; Geishofer et al 2005a; Geishofer et al 2005b; Hermans et al 1999)
Mannose-binding lectin (Garred et al 2003; Gong et al 2007; Gordon et al 2006; Kronborg et al 2002; Roy et al 2002)	IRAK-1 (Arcaroli et al 2006)		
Surfactant-proteins (Gong et al 2004; Quasney et al 2004)			

As there is substantial overlap between the functions of many cytokines, and frequently multiple antagonists for any given agonist, there is a significant ability to compensate for a certain amount of divergence in production of individual cytokines. Therefore, for a single mutation to influence the outcome of an inflammatory response, it must markedly alter the production or function of a critical inflammatory protein. While possible, the more likely scenario already discussed is the inheritance of multiple mutations in multiple proteins, each leading to small changes in production or function, interacting to lead to a net serious deleterious effect.

While a complete review of all polymorphisms described within the immune response genes is well beyond the scope of this chapter, the following section will discuss some of the key findings in various components of the immune response.

3.3.1 Pattern Recognition Molecules

Once the microorganism reaches the lower respiratory tract, organization of the innate immune system allows recognition of molecular patterns that are not found in humans. These so-called pattern recognition molecules (PRMs) can then initiate opsonization and lysis of microorganisms, enhance clearance by alveolar macrophages and neutrophils, as well as initiate an antibody response.

3.3.1.1 Collectins

Collectins are a family of PRMs that include surfactant proteins A and D and mannose-binding lectin (MBL), with a large degree of sequence homology present between the three compounds. MBL is the plasma form and has independent ability to activate the complement system. Conservation of MBL in various species suggests that it plays an important role in innate immunity. Several mutations in the gene itself or in the promoter region can lead to little or no serum MBL. MBL polymorphisms were found to be a risk factor for severe sepsis in adults (Garred et al. 2003), and the incidence of homozygous variant alleles in the introns was twice as common in patients with invasive pneumococcal disease in one study (Roy et al. 2002) but not in other studies (Kronborg et al. 2002). Some of the conflicting reports may be due to looking at only a limited number of polymorphisms instead of all variants or because of the significant variability in frequency of the variant alleles in different racial/ethnic groups.

3.3.1.2 Toll-Like Receptors (TLRs)

Another class of PRMs is the toll-like receptors (TLRs), human transmembrane signaling proteins equivalent to the Drosophila toll molecule found to be important in immunity against bacteria and fungi. Ten TLRs have been identified in humans,

each with different affinities for antigens of different microorganisms (Beutler 2002). Most of the initial clinical research has focused on genetic variants of TLR4 essential for recognition of LPS. Variants in the TLR4 gene appear to increase the risk of serious gram-negative infections and sepsis (Lorenz et al. 2002). TLR4 is however unlikely to play an important role in gram-positive sepsis as TLR2 is more specific for recognition of peptidoglycans from gram-positive bacteria. Rare TLR2 polymorphisms have been described as increasing the risk of gram-positive infections (Sutherland et al. 2005b) and a TLR5 mutation has been associated with an increased risk of legionella infection (Hawn et al. 2003).

3.3.1.3 Other Endotoxin Recognition Molecules

Other key components of endotoxin recognition and signaling that have been studied as potential genetic risk factors for sepsis other than TLR4 include CD14, Myeloid differentiation protein-2 (MD-2), and lippopollysaccharide binding protein (LBP). The results for LBP gene mutations have been far from conclusive with conflicting reports (Hubacek et al. 2001; Barber and O'Keefe 2003). In contrast, studies of CD14 polymorphism have produced more consistent findings. A relatively common CD14 mutation is associated with higher soluble CD14 levels and an increased risk of septic shock (71% vs. 48%, $p = 0.008$) (Gibot et al. 2002). The same polymorphism is also associated with greater TNF production after endotoxin stimulation of peripheral blood mononuclear cells in healthy adults (Temple et al. 2003a). Mutations in MD2 have also been linked with an increased risk of sepsis (Gu et al. 2007).

3.3.1.4 Immunoglobulin Receptors

Genetic variation in adaptive immunity may also play a role in sepsis. A variant in the CD32 (FcγRII) subclass is associated with decreased binding of the IgG2 subclass (Yuan et al. 2003). Patients homozygous for the FcγRIIa-R131 allele were more common in patients with bacteremic pneumococcal pneumonia, nonbacteremic pneumonia, or healthy controls (Yee et al. 1997). This association has been confirmed in a separate case–control study (Yuan et al. 2003). Patients with the FcγRIIa-R131 allele also appear to be more susceptible to meningococcal meningitis, as well as more susceptible to severe complications such as septic shock (van der Pol et al. 2001).

3.3.2 Inflammatory/Anti-inflammatory Response

3.3.2.1 Tumor Necrosis Factor (TNF)

Tumor necrosis factor (TNF) is critical to the immune response to infection (Beutler and Grau 1993), and a key driver to the development of septic shock (Bochud and

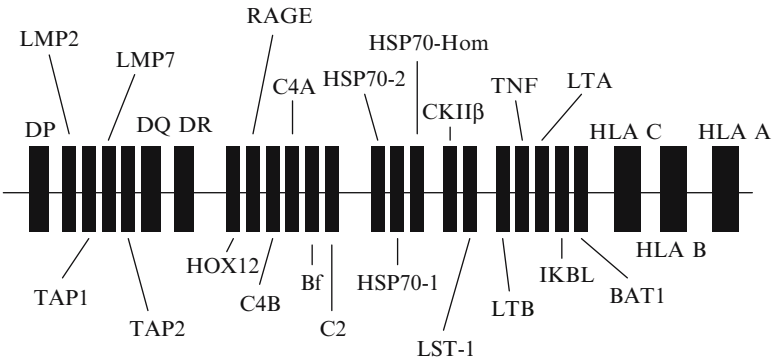

Fig. 3.2 The immunologically rich MHC region containing TNF

Calandra 2003). The TNF gene is also highly polymorphic, leading to a large array of association studies in literally hundreds of different diseases. Complicating matters further, TNF is in the immunology-gene rich area of chromosome 6 (Fig. 3.2).

The TNF-308 polymorphism is by far the most comprehensively studied genetic variation in immune response that has been reported. Carriers of the A allele (G is the more common nucleotide in all populations studied) has been associated with an increased risk of death from a variety of infectious diseases, including septic shock (Azim et al. 2007; Calvano et al. 2003; Cirpriano et al. 2005; Nakada et al. 2005; Schueller et al. 2006; Mira et al. 1999; O'Keefe et al. 2002). However, other investigators have not found a significant association between the TNF-308 A allele and death from or risk of sepsis (Stuber et al. 1995; Waterer et al. 2001). The TNF-308 polymorphism is in significant linkage disequilibrium with multiple other polymorphic sites within TNF itself and in the wider MHC region. This extensive linkage disequilibrium may not only explain the disparate findings between studies, but also why after over a decade of research, there is no agreement on whether or not the different TNF-308 alleles result in differential production of TNF (Bayley et al. 2004).

3.3.2.2 Lymphotoxin Alpha (LTA)

Adenine homozygosity of LTA+252, a G to A transition in the first intron of LTA, has been associated with increased TNF production and was one of the first genetic factors identified as a potential risk factor for death from septic shock (Stuber et al. 1996; Majetschak et al. 1999). The same genotype has also been associated with an increased risk of septic shock in patients with pneumonia (Waterer et al. 2001). In the latter study, it was interesting that respiratory failure correlated with the GG genotype (Waterer et al. 2001), the opposite of the association for shock. However, given LTA+252 is located in an intron, the association with variable TNF production is most likely due to linkage disequilibrium with other variant alleles in the TNF, LTA, or other nearby genes.

3.3.2.3 Interleukin – 1 (IL-1) Family

The IL-1 gene family includes the potent inflammatory agonists IL-1α and IL-1β, and the IL-1 receptor antagonist (IL-1RN), adjacent to each other on the same chromosome and therefore there is marked linkage disequilibrium between polymorphisms within the three genes. Two SNPs, the IL-1β+3953 and −511, which have both been suggested to influence levels of IL-1β (Pociot et al. 1992), were associated with increased risk of death from meningococcal infection in one cohort study (Read et al. 2000) but not with susceptibility to or outcome from septic shock (Fang et al. 1999). In contrast, variants of the IL-1RN gene have been demonstrated to have an excess mortality in septic patients in three sepsis studies in different ethnic groups (Fang et al. 1999; Arnalich et al. 2002; Ma et al. 2002; Turner et al. 1997), although these studies did not assess potential coinherited polymorphisms in IL-1α and IL-1β making it difficult to be sure the associations observed were attributable to the IL-1-RN variants.

3.3.2.4 Interleukin 10 (IL-10)

IL-10 is another highly polymorphic gene. Three promoter polymorphisms (-1082/-819/-592) have been extensively studied and different -819/-592 haplotypes associated with variable IL-10 production (Turner et al. 1997). The effect of the IL-10 haplotype however appears to be pathogen-dependent, with a significantly different genotype–phenotype relationship observed depending on whether the stimulus is gram-positive or gram-negative (Temple et al. 2003b).

Several case–control studies have suggested that carriage of the IL-10 -1082G allele is a significant risk factor for adverse outcome in patients with pneumonia (Gallagher et al. 2003; Schaaf et al. 2003). Case–control studies also suggest that the IL-10-1082G allele is a risk factor for death from septic shock (Stanilolva et al. 2006), and a risk factor for multiorgan dysfunction after major trauma (Schroder et al. 2004).

3.3.2.5 Heat Shock Protein

While intracellular heat shock proteins (HSPs) principally play a cytoprotective role, extracellular HSP70 can induce a proinflammatory response through TLR2 and TLR4 via a CD14-dependent mechanism. As shown in Fig. 3.2, the HSP-70 locus is also close to the TNF and LTA loci. A significant association between the A allele of HSPA1B+1267 and septic shock has been demonstrated in an extension of the pneumonia study mentioned above (Waterer et al. 2003), which was even stronger than that of the LTA+252. This stronger association, combined with functional studies showing that the HSP-A1B polymorphism was associated with variable HSP-70 production and TNF production (Temple et al. 2004) strongly suggests that this is the "real" cause of the associations described with LTA+252.

3.3.3 Coagulation Pathway Proteins

An extremely large number of polymorphisms have now been described within the pro- and anticoagulant hemostatic pathways, many of which being suggested to influence coagulation. With the increase in interest in the role of coagulation in the outcome of severe sepsis due to the success of activated protein-C (Bernard et al. 2001), it is not surprising that there has been an increase in interest in genetic differences in coagulation pathways and the risk of sepsis.

An insertion/deletion polymorphism in plasminogen activation inhibitor (PAI)-1 is associated with variation in serum PAI-1 levels (Ye et al. 1995) and has been suggested as a significant risk factor for mortality in children with meningococcal disease (Binder et al. 2007; Geishofer et al. 2005; Haralambous et al. 2003). One study in adults also suggests that the same polymorphism is a risk factor for death from septic shock in caucasians (Garcia-Segarra et al. 2007; Hermans et al. 1999).

3.4 Problems with Genetic Studies in Sepsis

What explains the diversity of findings in studies of genetic influence on sepsis? There is no doubt that simple genotyping error, particularly before the advent of highly automated platforms, is a significant source of error in polymorphism studies (Clark and Baudouin 2006; Sutherland and Russell 2005; Peters et al. 2003). As early studies typically contained less than 100 subjects, even a few genotyping errors, particularly with rare genotypes, can have a dramatic impact on statistical significance. It is important that all genetic studies perform and report adequate quality control measures to ensure genotyping is accurate.

The problems of linkage disequilibrium have been mentioned several times. As the human genome is so highly polymorphic, the likelihood that any studied polymorphism is the "real" site of significance is low. Newer genetic methods, particularly genotyping multiple nearby SNPs to determine the "length" of DNA associated with the clinical outcome (known as haplotype mapping) are a significant aid in trying to determine the key genetic area.

As already discussed with TNF-308, actually proving that a polymorphism is functionally significant is a very difficult task unless the polymorphism results in a change in the protein structure. There are numerous examples of different groups claiming that a polymorphism is (or is not) functionally important based on different stimuli, cell types, and sample timing.

Compounding the difficulty in finding associations is that even if a polymorphism results in a functional change in the production of a key protein, this could have both detrimental and beneficial effects depending on the outcome concerned. For example, a propensity to greater TNF may be protective in reducing the risk of developing infection; however, if pneumonia becomes established, it may predispose to a greater risk of acute respiratory distress syndrome or septic shock.

Another problem limiting the development of new therapeutic strategies arising from genetic studies is the timing of the influence of the polymorphism. For example, TNF polymorphisms may be important in the risk of septic shock; however, as the failed randomized controlled trials of anti-TNF antibodies demonstrated, once septic shock is established, modifying TNF production has no benefit. Many genetic factors predisposing to an initial event are likely to suffer from the same problem given that patients typically present well after infection has been established.

Finally, the number of polymorphisms already reported as being "important" is significant. Studies that address only one or two polymorphisms without studying previously reported polymorphisms so that the new findings can be put into a relative context do little to advance our knowledge (Waterer 2007). Unfortunately, given the issues with multiple testing, the sample size to sort out the relative contributions of all these polymorphisms is in tens of thousands.

3.5 Summary

There is an increasing array of polymorphisms in diverse inflammatory genes that have been identified as candidates to explain genetic variability in susceptibility to septic shock and its adverse outcomes. Unfortunately, to date, the ever-expanding volume of publications has not led to any new therapeutic insights. The failure to advance to the "next step" is due in part to failings of published studies, but mostly because of the fact that sepsis is almost certainly the result of hundreds, if not thousands, of mutations that each contribute in a small way to a very complex phenotype. Future studies will hopefully learn from the mistakes of the past and realize the enormous promise of genetic studies.

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Chapter 4
Corticoids in Severe Pneumonia

Carlos Agustí, Oriol Sibila, and Antoni Torres

4.1 Introduction

Pneumonia is the most prevalent infectious respiratory disease. It entails high morbidity and mortality and large health system expenses.

Community-acquired pneumonia (CAP) is one of the five leading causes of death in the world. Approximately 20% of CAP patients require hospitalisation, 25% of which require intensive care unit (ICU) admission, and their mortality rate is of 40–50% (Alvarez-Lerma and Torres 2004).

Furthermore, 20–30% of patients under mechanical ventilation for at least 48 h in the ICU develop mechanical ventilation-associated pneumonia (VAP). Mortality attributable to VAP is also higher than 30%, being the leading cause of morbidity and mortality in patients with ICU-acquired nosocomial infections (ATS 2005).

Despite the progress in life support measures and in antimicrobial therapy, with the use of new antibiotics more efficient every time and with a broader spectrum, mortality of severe pneumonia has not varied during the last years (Lepper and Torres 1995; Heyland et al. 1999), suggesting that other factors are of crucial importance in the evolution of this respiratory infection.

One of the key factors determining the evolution of pneumonia is the host inflammatory response, increased excessively both in non-responding severe CAP and in VAP (Menéndez et al. 2004; Ioanas et al. 2004).

4.2 Inflammatory Response Associated with Pneumonia

It is well known that the arrival of pathogens to the alveolar space creates a complex inflammatory response with the action of several defence mechanisms and the production of several inflammatory mediators and acute-phase proteins (Sibille and Reynolds 1990).

This inflammatory response aims to control the progression of the infection and to destroy microorganisms, and consists of several pro-inflammatory (TNF-alpha, IL-1beta, IL-6 and IL-8) and anti-inflammatory (IL-10, IL-1RA, sTNFrp55 or sTNFrp75)

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cytokines. Cytokines promote migration of defence cells – such as neutrophils, lymphocytes and platelets – through the circulatory system to inflammatory sites.

All this process will be beneficial as long as it is limited to the control of local infection. If this reaction is over-proportioned, several systemic consequences influence negatively the clinical evolution of the infection (Nelson et al. 1989).

Several studies have demonstrated that the inflammatory response can be reliably evaluated and that the determination of inflammatory mediators in serum and bronchoalveolar lavage (BAL) has diagnostic and prognostic value.

Studies have demonstrated an association between the increase of pro-inflammatory cytokines, such as IL-6 and TNF-alpha, and poor prognosis in sepsis (Martin et al. 1994). Studies concerning severe pneumonia showed that despite the local inflammatory response being initially compartmentalised (Dehoux et al. 1994), an increase of pro-inflammatory cytokines (IL-6, IL-8 and TNF-alpha) and anti-inflammatory cytokines (IL-10) in serum and in BAL was detected. These findings have also been related to poor prognosis of pneumonia (Montón et al. 1999a; Fernandez-Serrano et al. 2003).

In addition, a recent study of Yende et al. (2005) has demonstrated that patients with high levels of circulating cytokines in clinical stability (previous to infection) have a higher risk of suffering from community-acquired pneumonia, suggesting a crucial role of the inflammatory response in all the pathogenesis of this infection.

4.3 Glucocorticoids and Inflammatory Response

Due to the crucial importance of inflammatory response in the evolution of pneumonia, several anti-inflammatory treatments, with glucocorticoids (GC) being one of these, have been used in sepsis and in severe pneumonia.

GCs develop their action through their union to a specific intra-cytoplasmic receptor, the GC receptor (GR). After binding its ligand, the GR is activated and is translocated to the cell nucleus, where it binds DNA, producing an anti-inflammatory and immunosuppressive effect by two molecular mechanisms of action (see Table 4.1) (Rhen and Cidlowsly 2005): transrepression (or decrease in gene transcription of molecules with pro-inflammatory effect) and transactivation (or increase in gene transcription of molecules with anti-inflammatory effect.

GCs also provoke an anti-inflammatory effect by a third non-genomic mechanism of action: the activation of the endothelial nitric oxide synthetase (eNOS) which has a powerful effect on decrease in vascular inflammation.

In clinical practice, its usefulness seems demonstrated in several infections such as bacterial meningitis and pneumonia by *P. jiroveci* (Briel et al. 2005). In the field of sepsis, recent works by Keh et al. (2003) demonstrated that low dosages of hydrocortisone achieved quick haemodynamic stabilisation in patients with septic shock. This study verified that hydrocortisone attenuates the inflammatory and anti-inflammatory response, but does not have a negative effect on the phagocyte function of macrophages and monocytes.

Table 4.1 Effect of glucocorticoids in gene transcription

Decrease of gene transcription (transrepression)
• Cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-11, IL-13, tumoral necrosis factor alpha, granulocytes and macrophages colonies stimulating factors)
• Chemokines (RANTES, eotoxin, macrophage inflammatory protein 1 alpha (MIP-1α), monocytes 1 and 3 chemotactic proteins)
• Enzymes (inducible nitric oxide synthetase, cyclooxygenase 2, cytoplasmic phospholipase A2)
• Adhesion molecules (intracellular adhesion molecule 1, vascular cells adhesion molecule 1)
• Receptors (IL-2 receptor, tachikinin 1 (NK-1))
Increase of gene transcription (transactivation)
• Lipocortin 1
• Receptors β2
• SLPI (serum leukoprotease inhibitor)
• Clear cells protein (CC10, phospholipase A2 inhibitor)
• Antagonist of the IL-1 receptor
• Inhibitor of the nuclear factor kappa B
• IL-10

IL interleukin

4.4 Role of Glucocorticoids in Severe Pneumonia

The first studies conducted in patients with sepsis and pneumonia suggested a rapid improvement of symptoms in patients receiving GC, although effects in mortality were not evidenced, and some cases were associated with a higher number of side effects and to a poorer prognosis once the steroid treatment was suspended (Lefering and Neugbauer 1995). These contradictory findings were mostly due to the lack of knowledge on the role of the inflammatory response in the prognosis of this disease and its possible therapeutic modulation by GC.

A pilot work by Montón et al. in patients with severe pneumonia requiring mechanical ventilation (Montón et al. 1999) detected the possible immunosuppressive effect of GC in pneumonia, since the authors observed a decrease in pro-inflammatory cytokines, such as IL-6 and TNF-alpha, both in serum and in bronchoalveolar lavage of patients who received GC as co-adjuvant treatment (in most cases as a bronchodilator treatment associated with the antibiotic treatment). Furthermore, in the group of patients receiving GC treatment, a tendency to lower mortality was observed, although the population of the study was represented by only 20 patients.

The relationship between the intensity of the inflammatory response in severe pneumonia, GC dosage and the prognosis of this disease was subsequently studied by Agustí et al. (2003). In this study, the authors assessed the inflammatory response in bronchoalveolar lavage and in serum of patients with severe pneumonia who received GC treatment for long periods (>30 days). Results were compared to those from a group of patients with severe pneumonia without GC treatment and another group of patients with pneumonia and GC treatment, in most of the cases as a bronchodilator treatment, for a short period of time (9 ± 7 days).

These authors observed that the local inflammatory response (in BAL) and systemic inflammatory response (in serum), measured by such relevant cytokines as IL-6 or TNF-alpha, was markedly diminished in patients who received GC for long periods of time compared to patients who had not received such treatment. Furthermore, acute administration of GC had an intermediate effect in the suppression of the inflammatory response.

Mortality in the group of patients with severe pneumonia and prolonged corticoid treatment was similar to mortality of patients who did not receive GC treatment. Interestingly, patients who received GC treatment for short periods of time and showing an attenuated inflammatory response had, on the contrary, a tendency to lower mortality.

These results suggested that deep attenuation of the inflammatory response by prolonged corticoid treatment can be as harmful as an exaggerated inflammatory response, but its "moderated" attenuation by a short corticoid treatment can be beneficial for the modulation of the inflammatory response and for the prognosis of the disease.

In another work by Ioanas et al. (2004), in a series of patients with ICU-acquired pneumonia requiring mechanical ventilation, the authors found that high levels of IL-6 and IL-8 at the time of diagnosis and IL-6 levels on day 3 were the only factors related to the lack of response to empiric antibiotic treatment, suggesting again that the potential inflammatory response modulation could be beneficial also in this subgroup of patients. Furthermore, in the multivariate analysis of the several factors that could be related to the lack of response to treatment, the authors found that the concomitant administration of GC was a protective factor (OR 0.21).

In a recent work by Sibila and collaborators (2006) in an experimental model of severe pneumonia in ventilated pigs, in which the effect of GCs was studied by comparing three groups of animals with severe pneumonia induced by *Pseudomonas aeruginosa* (without treatment, with antibiotic treatment and with antibiotic treatment + GC), the authors evidenced that pigs treated with antibiotics + GC experimented, after 96 h of pneumonia onset, a decrease in the local inflammatory response compared to other groups.

Furthermore, animals treated with antibiotics and steroids presented lower bacterial count both in bronchoalveolar lavage and in pulmonary tissue obtained in the end of the 96-h study, a finding that was related to a clear tendency to suffer from less severe lesions, as revealed by the histopathological study.

Finally, animals treated with steroids also showed an improvement in pulmonary mechanics (measured by means of static compliance) compared with the rest of the group.

Although all these findings seem to point to the beneficial effect of the steroid treatment in severe pneumonia, a confirmation of these potential benefits is needed in randomised and controlled clinical trials.

According to these premises, Confalonieri and collaborators (Confalonieri et al. 2005) assessed the efficiency and safety of the administration of a continuous infusion of hydrocortisone in a double-blind, randomised, placebo-controlled trial including 46 patients with severe CAP requiring ICU admission.

An intravenous bolus of hydrocortisone, in a dose of 200 mg followed by a perfusion of 10 mg/h during 7 days, was given to 23 patients. These authors demonstrated a mortality reduction in the group treated with hydrocortisone (0% vs. 30%), a better modulation of systemic inflammatory response (determined by serum C-reactive protein) and a significant improvement in the main clinical endpoints, such as thorax X-ray, MODS severity scale, PaO2/FiO2 coefficient and ICU and hospital stay.

These results show that the modulation of systemic inflammation with early administration of GC can improve the evolution of community-acquired pneumonia and prevent possible complications from a secondary sepsis, thus improving mortality.

4.5 Pending Questions

Before being able to generalise the use of GC in patients afflicted with severe pneumonia, some questions must be specified.

Firstly, the spectacular results of the study by Confalonieri et al. (2005) must be confirmed by studies including a higher number of patients, with no differences between the two groups of the study. In the aforementioned work, the group receiving GC presented at the beginning of the study a significantly higher systemic inflammation level (measured by the blood C-reactive protein) than the group that did not receive corticoid treatment.

Another important aspect is the moment of suppression of the steroid treatment. An early suspension of GC can be potentially dangerous if pro-inflammatory cytokines increase again and their receptors continue being suppressed. Studies conducted in patients with septic shock have demonstrated that hydrocortisone infusion produces significant decrease in the circulating levels of proteins depending on the nuclear factor kappa B transcription (NF-κB), such as phospholipase A2, IL-6, IL-8 and soluble E-selectin. On the one hand, the suppression of the treatment provokes a rebound effect in most of these mediators, which highlights the short anti-inflammatory action of hydrocortisone and the need for administering a prolonged treatment to achieve a durable anti-inflammatory effect (Briegel et al. 1994). On the other hand, the prolonged use of corticoids can entail a suppression of the innate immune function since it alters the phagocyte action of macrophages and alveolar granulocytes, which can facilitate the acquisition of very severe bacterial infections and of opportunist microbes (Meersseman et al. 2004). Consequently, studies are needed to determine the duration of treatment with a special emphasis of the initial dosage, the maintenance time and the type of suspension.

Finally, other questions without an answer are related to the appropriate type of glucocorticoid for this treatment (hydrocortisone, methylprednisolone), and to a better study of the suprarenal function in patients with severe pneumonia and its potential modulation by GC (Annane et al. 2002).

4.6 Conclusions

Current information suggests that treatment with low dosages of GC in severe pneumonia is able to modulate (or diminish) the inflammatory response associated with pneumonia and improve the prognosis of this disease, mainly in cases where an increased host inflammatory response is demonstrated.

Scientific evidence is still scarce, and ample randomised and controlled clinical trials are needed to claim the aforementioned affirmation. Furthermore, it is of uppermost importance to design studies not only to get a better understanding of the effect of GC in severe pneumonia, but also to determine the type of GC, the dosage to administer and the duration of the treatment.

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Chapter 5
Aging, Inflammation, and Pneumococcal Disease

Angela J. Rodriguez and Carlos J. Orihuela

5.1 Introduction

Streptococcus pneumoniae (the pneumococcus) is the leading cause of community-acquired pneumonia (CAP) and otitis media, and a primary cause of bacteremia and meningitis (Pneumococcal vaccines 1999). As with most infectious diseases, the poorest nations experience the greatest burden of disease. This can be attributed to reduced vaccine use, decreased standards of living, and limited access to supportive critical care (Dopazo et al. 2001; Robinson et al. 2001). Worldwide, the incidence of invasive pneumococcal disease (IPD) is greatest in children. However, death, as a result of infection, primarily occurs in the elderly (>65 years of age) (Atkinson et al. 2007; Lexau et al. 2005). The World Health Organization (WHO) estimates that pneumococcal disease is responsible for 1.6 million deaths annually (Pneumococcal vaccines 1999).

Pneumococcal disease in the elderly is characterized by its rapid onset, severity, and high case-fatality rate; in the United States, the mortality rate for the elderly with pneumococcal pneumonia is 13–23%, compared to 5–7% in the general population. Likewise, case-fatality rates for the elderly with pneumococcal bacteremia and meningitis are 60% and 80%, respectively; in contrast, they are 20% and 30% for the general population (Atkinson et al. 2007). Risk factors for IPD include advanced age, alcoholism, bronchial asthma, immunosuppression, lung disease, heart disease, asplenia, diabetes, and institutionalization (Loeb 2004; Mufson 1999). It is of note that the majority of the elderly have one or more underlying medical conditions that puts them at increased risk for IPD (Robinson et al. 2001). Moreover, the elderly experience age-related changes in immune function that increase their susceptibility to infection.

5.1.1 Clinical Presentation

Clinical presentation of pneumonia in healthy adults includes fatigue, fever, chills, anorexia, sweats, myalgia, pleuritic chest pain, and cough with purulent sputum production (Johnson 2000; Koivula 1994). In the elderly, there are often fewer

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symptoms including a lack of fever or cough (Granton and Grossman 1993). Notably, absence of fever has been associated with a poor prognosis. Elderly patients with pneumonia often present with neurological symptoms, in particular an altered mental state. By and large it is dependent on the physician to recognize that the lack of overt clinical signs does not rule out the possibility of pneumonia in the elderly and that diagnosis of pneumonia is dependent on a thorough pulmonary lung exam and most importantly, visualization by chest X-ray of lobar involvement.

It is beyond the scope of this review to detail clinical management of pneumococcal pneumonia, bacteremia, or sepsis. However, several studies have documented that antibiotic therapy within the first 8 h of hospitalization was associated with decreased 30-day mortality rates (Loeb 2004; Niederman et al. 2001). Currently, the American Thoracic Society guidelines for treatment of pneumonia include administration of a second-generation cephalosporin with a macrolide, sulfamethoxazole-trimethoprim, or β-lactam with a macrolide if a susceptible strain is found (Niederman et al. 2001).

5.1.2 Vaccines

Immunity against pneumococcal disease is mediated by antibodies against the capsular serotype involved. At this time, only one vaccine, Pneumovax® 23 (Merck & Co. Inc.), is licensed by the United States Food and Drug Administration for use in adults against *S. pneumoniae*. Pneumovax® 23 is composed of capsular polysaccharide (CPS) from the 23 most common serotypes and has an overall protective efficacy of 55–70% against bacteremia and meningitis (Pneumococcal vaccines 1999; Shapiro et al. 1991). Unfortunately, Pneumovax® 23 does not protect against nonbacteremic disease (i.e., pneumonia without bloodstream infection) (French et al. 2000; Whitney et al. 2003). This is a major concern, as *S. pneumoniae* is the most frequent cause of CAP, and CAP is most severe in the elderly (Lexau et al. 2005; Gutierrez et al. 2006; Janssens 2005). In addition, the elderly do not produce a robust response to the vaccine as evidenced by a lack of protective antibody to the polysaccharide capsule (Bruyn and Van Furth 1991; Regev-Yochay et al. 2004). Currently, the United States Centers for Disease Control and Prevention recommends vaccination of all high-risk groups, and revaccination of the elderly every 5 years.

Children in the United States are vaccinated with a conjugate vaccine composed of CPS linked to the diphtheria toxoid (Prevnar®; Wyeth Inc.). Use of Prevnar® has not only led to a decrease in the incidence of IPD among children, but also to decreased nasopharyngeal colonization of the serotypes included in the vaccine (Whitney et al. 2003; McBean et al. 2006). Decreased carriage rates have in turn led to improved "herd immunity" and a reduction in incidence of IPD in the elderly. From 1998 to 2003, the incidence of invasive disease among the elderly has decreased by 18% (McBean et al. 2006).

Vaccination is the only proven method shown to reduce IPD. Unfortunately, protein conjugation is costly and imposes steric hindrances that limit the numbers

of capsule types that can be included in a vaccine formulation. Prevnar® is composed of CPS from seven of the >90 known serotypes (Pneumococcal vaccines 1999; MMWR Recomm Rep 2000). Thus, children vaccinated with Prevnar® remain colonized and are susceptible to nonvaccine serotypes. Due to the limited number of serotypes included in Prevnar®, vaccine efficacy is reduced in countries where nonvaccine serotypes are more frequently the cause of disease; for example, Prevnar® protects against only 58% of the serotypes that cause invasive disease in Latin America (Sniadack et al. 1995). Studies are currently being conducted on protein conjugate vaccines composed of CPS from 9 and 11 serotypes. These would improve coverage in developing countries. However, cost of the vaccine and the implementations of policies that ensure its use remain daunting obstacles not only in South American countries but also in most of the world.

5.2 Bacterial Pathogenesis

5.2.1 Microbiology

S. pneumoniae is a gram-positive diplococcus that grows in pairs or short chains and is catalase negative. Most laboratories grow the bacteria on tryptic soy agar supplemented with blood in 5% CO_2. These culture conditions are preferred as blood contains a high level of catalase and *Streptococcus* spp. are facultative anaerobes. Currently, pneumococci are identified in a microbiology laboratory by: α-hemolysis on blood agar plates, catalase negativity, susceptibility to optochin, and solubility to bile salts. Pneumococci are also now identified by detecting ribosomal RNA that is specific to the pneumococcus.

5.2.2 Inflammation Resulting from Infection

Solely a human pathogen, the pneumococcus colonizes the nasopharynx and is spread among humans by aerosol droplets. IPD results from the spread of the pneumococcus from the nasopharynx to the lungs, blood stream, and central nervous system. While attack rates are generally low, such a large number of individuals are colonized that the resulting morbidity and mortality associated with the pneumococcus is tremendous. Pneumococcal disease is characterized by an intense inflammatory response that, in the lungs, results in consolidation of the infected alveoli and the affected lobe. Infected lung tissue progresses through stages of engorgement during which capillaries and epithelial cells become inflamed; fluid, erythrocytes and neutrophils accumulate in the alveoli; and a fibrin mesh develops (red hepatization). Subsequently, the lungs darken (gray hepatization) as leukocytes enter the lesion and the bacteria are engulfed by neutrophils and macrophages.

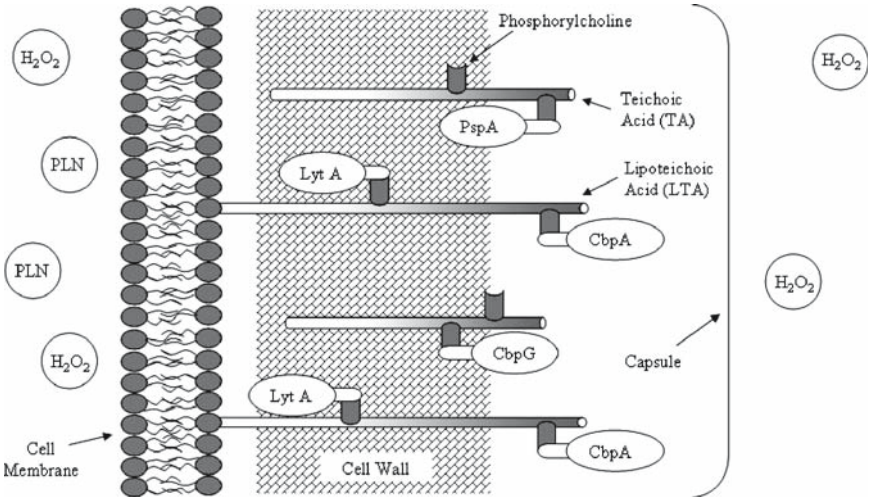

Fig. 5.1 Representation of *S. pneumoniae* cell membrane, cell wall and capsule. Within the bacteria is the toxin pneumolysin (PLN), which is released along with cell wall fragments following lysis of the bacteria. Cell lysis can be the result of cell death or autolysis triggered by cell-wall-acting antimicrobials such as β-lactams. The cell wall consists of peptidoglycan and is covalently linked to teichoic acid (TA). Lipotechoic acid (LTA) extends from the cell membrane through the cell wall. Both TA and LTA contain phosphorylcholine residues that bind to PAFr and serve as anchors to a family of proteins known as choline-binding proteins: choline-binding protein A (CbpA) is an adhesin and mediates attachment to pIgR. Choline-binding protein G (CbpG) is a protease required for replication to high titer in the blood. Pneumococcal surface protein A (PspA) inhibits complement deposition by binding to factor H. Finally, the murein hydrolyse, autolysin (LytA), is also a choline-binding protein. During growth, the bacteria release hydrogen peroxide. This contributes to tissue damage caused by the bacteria

Resolution continues for several days as capsule-specific antibodies provide efficient opsonization and inflammatory mediators dissipate (Tuomanen 2004).

Pneumococcal cell wall, pneumolysin, and hydrogen peroxide are the primary virulence determinants that mediate the inflammation and cytotoxicity that is observed in the lungs (see Fig. 5.1) (Berry and Paton 2000; Canvin et al. 1995). Intratracheal challenge of mice with purified pneumolysin or cell wall products is sufficient to cause edema and the influx of neutrophils that result in pneumonia (Regew-Yochay et al. 2004; Tuomanen et al. 1987). Multiple studies demonstrate that deletion of the genes that encode autolysin (LytA), the bacteria cell wall hydrolase, pneumolysin (Pln), a pore-forming toxin, or pyruvate oxidase, the enzyme that produces hydrogen peroxide, results in attenuated bacteria that are unable to survive in the lungs (Regew-Yochay et al. 2004; Berry and Paton 2000; Berry et al. 1992; Orihuela et al. 2004). These findings suggest that the ability of the pneumococcus to cause inflammation is not incidental but a requirement for its survival in vivo. Importantly, because the pneumococcus is encapsulated, phagocytosis is limited until sufficient capsule-specific antibodies are present. Prior to this, the thick peptidoglycan cell wall layer protects the bacteria from complement-mediated killing.

Inflammation is requisite for clearance of the bacteria. Proinflammatory mediators such as activated complement (activated complement protein C3a, C5a), tumor necrosis factor alpha (TNFα), interleukin (IL)-1, and macrophage inflammatory protein 2 (MIP-2) contribute to the influx of neutrophils (PMNs) and macrophages that are the effector cells in the host defense against pneumococcal pneumonia (Regev-Yochay et al. 2004; Kadioglu et al. 2000). In mice, PMNs appear in the lungs 2–4 h after challenge and increase in number up to 48 h after infection (Dallaire et al. 2001). Not surprisingly, excessive inflammation is detrimental. Continued production of inflammatory mediators and PMN recruitment has been associated with death following intranasal and intratracheal challenge of mice with *S. pneumoniae*. Likewise, studies have documented an association between survival and an earlier disappearance of lung PMNs (Dallaire et al. 2001; Burns et al. 2005). Most recently, Marks et al. have shown that mice depleted of neutrophils and challenged with a serotype 8 isolate of *S. pneumoniae* had less lung damage, longer survival, and less lung apoptosis than control mice (Marks et al. 2007). Thus, an excessive immune response, where the host defense causes tissue damage and lung consolidation, contributes to pneumococcal-associated mortality.

5.2.3 Toll-Like Receptors (TLRs) Detect Microorganisms and Initiate the Innate Host Defense

TLRs are a family of surface receptors that recognize pathogen-associated molecular patterns (i.e., structural components) present in bacteria, viruses and fungi. Binding of ligands to TLRs initiates an intracellular signaling cascade through cytoplasmic intermediates such as TIR, Myd88, and IRAK that ultimately results in NFkB activation and production of proinflammatory cytokines. TLRs are sensors that activate the innate immune system. Thus, deficiencies in TLR functions result in diminished cytokine production and an increased susceptibility to infection (Akira and Sato 2003; Takeda et al. 2003). Pertinent to this review, TLR-2 and TLR-4 are the sensors responsible for the detection of *S. pneumoniae* and are expressed on a wide variety of cell types including mucosal epithelial cells and alveolar macrophages (Armstrong et al. 2004; Saito et al. 2005).

Peptidoglycan (PGN) is the primary constituent of bacterial cell wall, composed of alternating *N*-acetylglucosamine and *N*-acetylmuramic acid residues cross-linked by short peptides. Instilled peptidoglycan can reproduce most of the clinical manifestations of bacterial infections including fever, inflammation, and septic shock. Most of these effects are the result of cytokines that are released from macrophages (Fournier and Philpott 2005; Pichichero et al. 2005). It is now known that peptidoglycan initiates inflammation through its activation of TLR-2. Peptidoglycan binds to lipopolysaccharide-binding protein (LBP) (Weber et al. 2003), which in turn binds to CD14 (Dziarski et al. 1998, 2000; Gupta et al. 1996, 1999). Binding of LBP:peptidoglycan to CD14 induces physical proximity of the CD14:LBP:

peptidoglycan complex with TLR-2/TLR-1 and formation of the TLR-2 signaling complex (Becker et al. 2002; Manukyan et al. 2005).

Pneumolysin is also released by *S. pneumoniae* during bacteria lysis. Pneumolysin binds to cholesterol on the host cell membrane, and at high concentrations oligomerizes and forms lytic pores (Edwards 2004). Low concentrations of pneumolysin have been shown to have multiple effects including stimulating the production of TNFα and IL-1β by human mononuclear phagocytes (Houldsworth et al. 1994), inducing nitric oxide (NO) production from macrophages (Braun et al. 2002), and phosphorylation of p38 MAPK in epithelial cells (Ratner et al. 2005). Evidence now indicates that pneumolysin binds to TLR-4 (Malley et al. 2003). Srivastava et al. (2005) found that macrophages from wild-type mice were significantly more prone to pneumolysin-induced apoptosis than cells from TLR-4-defective mice and pretreatment of epithelial cells with TLR-4 antagonist reduced pneumolysin-mediated apoptosis in wild-type cells (Srivastava et al. 2005). Together, pneumolysin and pneumococcal cell wall act synergistically to activate host cells. In contrast, macrophages from TLR-4-deficient mice were hyporesponsive to pneumolysin and the combination of pneumolysin with cell wall (Srivastava et al. 2005; Malley et al. 2003).

5.3 Inflammation Increases Susceptibility to IPD

The process of inflammation is normally a protective mechanism that is employed by the host to destroy, dilute, or wall off infecting agents. During the past 25 years it has also become evident that aging is associated with chronic low-grade inflammation (Sarkar and Fisher 2006). Studies by multiple investigators have shown that individuals >65 years experience higher levels of proinflammatory cytokines in blood and tissues than healthy young adults Bruunsgaard et al. 2001; Ershler 1993; Paolisso et al. 1998). Age-associated inflammation (AAI) can be the result of multiple factors including chronic underlying diseases, obesity, diabetes, and the aging process itself, a side effect of cellular senescence, and an increased production of reactive oxygen species (Krabbe et al. 2004; Bruunsgaard et al. 1999).

In the lungs, studies by Meyer et al. have shown that the healthy elderly have increased numbers of neutrophils, IL-6, and immunoglobulin in bronchoalveolar lavage when compared to younger subjects (Meyer et al. 1996). Likewise, Meyer et al. observed an increased ratio of CD4+ cells to CD8+ cells (Meyer and Soergel 1999). Examination of tissues from aged rodents supports the notion of AAI and demonstrates that aged mice have higher levels of NFkB activation in the brain, lungs, liver, spleen, and lymphoid tissues (Spencer et al. 1997). Briefly, NFkB serves as the central transcription factor responsible for inflammation (Sarkar and Fisher 2006; Xiao and Ghosh 2005). Tissue samples from aged mice also express higher levels of TNF, IL-6, IL-12, and COX-2 when compared to young adult mice (Spencer et al. 1997). These findings suggest that even when there are no apparent signs of infection or disease, increased levels of inflammation are present in the elderly.

5.3.1 Individuals with Increased Inflammation Have More Frequent and Severe IPD

Increased inflammation is pertinent to pneumococcal disease, as elevated levels of proinflammatory cytokines in the blood have been correlated with an increased incidence of pneumococcal pneumonia and heightened severity of infection. For example, Yende et al. (2005) document that elevated levels of IL-6 and TNFα in the blood are associated with increased risk for CAP. Individuals with the highest levels of TNFα and IL-6 in serum experienced a 1.8- to 2.8-fold increase in the incidence of CAP over a 6.5-year period (upper tertile vs. lower tertile), a finding that was determined to be independent of coexisting medical condition, smoking status, and steroid use. Likewise, studies by Glynn et al. (1999) and Antunes et al. (2002) found that IL-6 correlated best with both disease-specific and generic severity scores for pneumonia. Thus inflammation links age with risk for IPD.

5.3.2 S. pneumoniae Adhesion and Invasion is Dependent on Inflammation

S. pneumoniae attachment and invasion is dependent on activation of NFkB and cellular inflammation. While attachment of the pneumococcus is initially mediated by loose interactions with glycoconjugates (Cundell and Tuomanen 1994), invasion does not occur until the cells become activated (i.e., NFkB is translocated into the nucleus) and the cell expresses the NFkB-regulated host proteins polymeric immunoglobulin receptor (pIgR) and platelet-activating factor receptor (PAFr) to which the pneumococcus binds to (Cundell et al. 1995; Zhang et al. 2000). In healthy adults, cell activation occurs during infection following contact with bacterial components such as peptidoglycan and pneumolysin. In contrast, in the elderly, elevated pIgR and PAFr levels are already present in the lungs, the result of age-associated inflammation or proinflammatory cytokines in blood as a result of underlying disease (see Fig. 5.2 and 5.3). Once the cell is activated, bacterial adherence is increased and invasion is mediated by the bacterial protein choline-binding protein A (CbpA) and phosphorylcholine (ChoP) on the cell wall. CbpA binds to pIgR on epithelial cells, while ChoP binds to PAFr on epithelial and endothelial cells. In general, the pneumococcus is a low-efficiency invader with ~0.2% of the inoculum invading cells (Cundell et al. 1995); nonetheless, invasion is a critical step in the development of IPD and is the mechanism by which the bacterium enters the central nervous system (Orihuela et al. 2004).

5.3.3 pIgR-Mediated Invasion

In the respiratory tract, pneumococcal adherence and invasion is mediated by the bacterial protein CbpA (Orihuela et al. 2004; Zhang et al. 2000). CbpA binds to

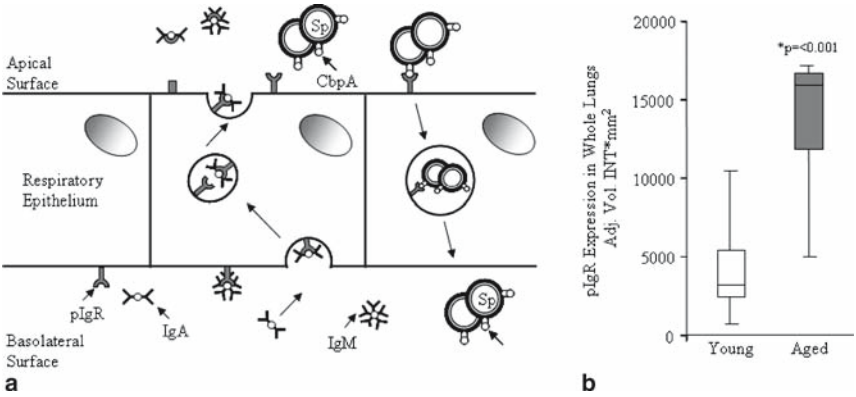

Fig. 5.2 (**a**) pIgR-mediated transport of *S. pneumoniae*. Secretory IgA is the first line of the specific immune defense that is encountered by bacteria invading the lungs. Epithelial cells in the respiratory tract transport polymeric IgA from the basolateral surface to the lumen through a series of vacuoles resulting in the presence of a pIgR/antibody complex on the apical surface. Cleavage of this complex permits the release of the antibody and a portion of the receptor that remains attached to the antibody (secretory component); secretory component protects the antibody from proteolytic degradation. Importantly, unoccupied pIgR on the apical surface is recycled, and returns to the basolateral surface for subsequent attachment to immunoglobulin. *S. pneumoniae* co-opts this system by binding to unoccupied pIgR on the apical surface through CbpA and is translocated through the cell during receptor recycling. (**b**) Elevated levels of pIgR in the lungs of aged mice vs. young. Box plot demonstrating increased expression of pIgR in the lungs of aged (19-month old, $n = 6$) vs. young (4-month old, $n = 6$) female Balb/cBy mice (unpublished finding). Whole lungs were homogenized and levels of pIgR were determined by measuring band intensity on immunoblots. *Box* indicates 25–75% percentile, *horizontal bar* indicates average, *inner* and *outer fence* indicate lowest and highest value

the pIgR machinery and allows translocation of the bacteria to the basolateral surface (see Fig. 5.2) (Kaetzel 2001). Zhang et al. have demonstrated that wild-type, but not CbpA-deficient *S. pneumoniae* adhere to pIgR and are transported to the basolateral surface during receptor recycling (Zhang et al. 2000). This interaction is inhibited by the addition of antibodies to CbpA, antibodies to secretory component (SC), and purified SC, all of which reduce pneumococcal adhesion and invasion. Furthermore, mice deficient in pIgR, and mice deficient in the protein tyrosine kinase $p62^{yes}$, which is required for pIgR transcytosis, demonstrate decreased nasopharyngeal colonization and a delayed onset of bacteremia relative to wild type (Luton et al. 1999). Finally, Rosenow et al. demonstrate that CbpA deficient bacteria colonize the nasopharynx at a 100-fold lower efficiency than wild-type bacteria (Rosenow et al. 1997).

Importantly, pIgR expression is enhanced following NFkB activation and has been observed to be elevated in the lungs of aged mice (see Fig. 5.2b). Zhang et al.

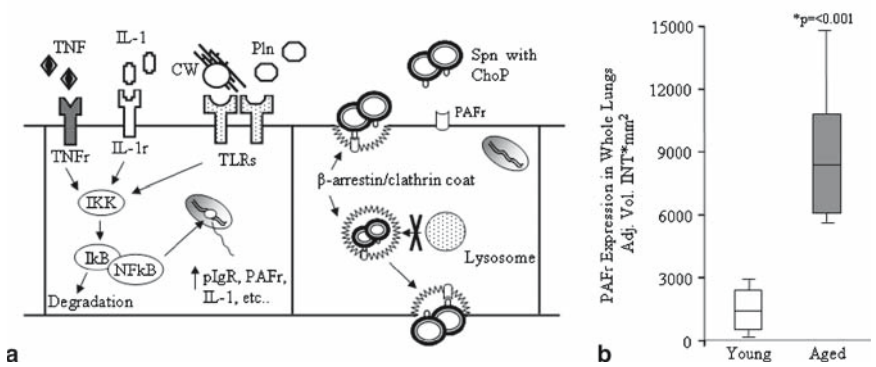

Fig. 5.3 (**a**) Platelet-activating factor receptor (PAFr) and NFkB activation. NFkB activation can be the result of various stimuli such as binding of peptidoglycan (CW) and pneumolysin (Pln) to TLRs and cell exposure to proinflammatory cytokines such as TNF and IL-1. Binding of ligands to their receptors initiates a cell-signaling cascade (not shown) which results in IkB kinase (IKK) activation. IKK then phosphorylates inhibitor kB (IkB) which leads to its dissociation from nuclear-factor kappa B (NFkB). NFkB is then able to enter the nucleus and serve as a transcriptional activator to numerous pro- and anti-inflammatory mediators including PAFr. PAFr on the cell surface binds to phosphorylcholine (ChoP), a component of teichoic and lipoteichoic acid residues on the bacteria. This activates ERK kinases leading to the formation of clathrin-coated vesicles that mediate endocytosis and passage of pneumococci through the cell. (**b**) Elevated levels of PAFr in the lungs of aged mice vs. young. *Box plot* demonstrating increased expression of PAFr in the lungs of aged (19-month old, $n = 6$) vs. young (4-month old, $n = 6$) female Balb/cBy mice (unpublished finding). Whole lungs were homogenized and levels of PAFr were determined by measuring band intensity on immunoblots. *Box* indicates 25–75% percentile, *horizontal bar* indicates average, *inner* and *outer fence* indicate lowest and highest value

have demonstrated that treatment of Detroit cells, a nasopharyngeal cell line, for 12 h with IFNγ increased bacterial adhesion and invasion. Furthermore, Bruno and Kaetzel demonstrate that chronic exposure (2 weeks) of HT-29 cell to TNFα resulted in a 7- to 20-fold increase in the amount of pIgR transcribed (Bruno and Kaetzel 2005). Thus, inflammation increases pIgR expression, which in turn increases pneumococcal attachment and invasion, a finding that explains how AAI may facilitate the development of IPD.

5.3.4 PAFr-Mediated Invasion

S. pneumoniae also attaches to PAFr, the chemokine receptor for platelet-activating factor (Cundell et al. 1995; Zhang et al. 2000). PAFr binding is mediated by phosphorylcholine (ChoP), which is present on the bacterial cell wall and lipoteichoic residues that extend from the cell membrane (see Fig. 5.1). Phosphorylcholine is a

structural component of PAF and it is believed that ChoP acts as a structural analog when binding to PAFr. Unlike PAF, pneumococcus binding to the PAFr does not result in the activation of a G-protein-mediated signal transduction pathway (Radin et al. 2005). Rather, pneumococcal binding results in activation of ERK kinases consistent with activation by β-arrestin. Uptake of the pneumococcus into a vacuole involves clatherin followed by recruitment of β-arrestin scaffold, Rab5, then Rab7 and Rab11. Rab 5 is involved in early endocytosis, Rab 7 is found in the late endosome, and Rab 11 is responsible for vacuole recycling (Seachrist and Ferguson 2003). Overexpression of arrestin in endothelial cells enhances colocalization of the bacteria with Rab 7 and Rab 11 and increases survival of the pneumococci normally killed by the lysozome. Thus it is currently thought that association of β-arrestin with the PAFr vacuole complex contributes to the successful translocation of the bacteria away from the lysozome (Radin et al. 2005). Of note, PAFr-mediated invasion of endothelial cells requires CbpA, although CbpA does not bind PAFr, suggesting the presence of a second stabilizing ligand (Hoskins et al. 2001).

It is well documented that *S. pneumoniae* preferentially binds to cells treated with proinflammatory cytokines. Like pIgR, PAFr is regulated by NFkB (Cundell et al. 1995; Zhang et al. 2000) and is produced de novo following exposure of cells to proinflammatory cytokines, cell wall components, and reactive oxygen species (Silverman et al. 2001). Unlike pIgR, PAFr is expressed ubiquitously on both epithelial and endothelial cells. Binding of bacteria to PAFr is thought to be a principal mechanism by which the bacteria enter the bloodstream and the sole mechanism as to how bacteria translocate across the blood–brain barrier and cause meningitis (Robinson et al. 2001). NFkB-induced expression of PAFr, and the observation that PAFr is elevated in the lungs of aged mice (see Fig. 5.3b) is further evidence that AAI in the elderly increases their susceptibility to infection.

5.4 Age-Related Defects in Immune Function

5.4.1 Reduced Clinical Symptoms may be the Result of Impaired Toll-Like Receptor Function

While chronic low-grade inflammation is associated with aging, a decline in immune function is also a hallmark of aging and leads to increased susceptibility to bacterial infections. One striking example of this phenomenon is the significant number of elderly with pneumonia who present without overt clinical symptoms. It is now known that aging is associated with a decline in TLR functions: age-related changes in TLR expression, TLR signaling, and TLR-dependent induction of proinflammatory cytokines has been shown by various investigators in both humans and mice and may explain why the innate and adaptive immune systems fail to become sufficiently

activated. Renshaw et al. have shown decreased TLR expression on splenic and thio-glycollate-elicited macrophages from aged mice versus controls (Renshaw et al. 2002). Boehmer et al. have shown a reduction in the expression of mitogen-activated protein kinases such as JNK and their phosphorylation in macrophages isolated from the peritoneum of aged mice versus young controls (Boehmer et al. 2004). Finally, Duin et al. have demonstrated age-associated defects in the response of neutrophils isolated from the blood of aged human volunteers to an assortment of TLR ligands versus those isolated from healthy young adults (Van Duin et al. 2007). Thus, TLR dysfunction is one explanation for the lack of symptoms observed in some of the elderly with pneumonia. Future studies are warranted to determine if TLR defects occur in the lungs, their affect on alveolar macrophages, and to determine their impact during respiratory tract infection in an aged animal.

5.4.2 Other Age-Related Defects

Age-related immune dysfunctions are not limited to TLRs. For example, alveolar macrophages are decreased in number and are not efficient at presenting antigens to T-cells. Neutrophils have impaired chemotaxis and phagocytosis. Both macrophages and neutrophils demonstrate a decreased capacity to produce reactive oxygen species; nor is the adaptive immune system unaffected. Studies document a reduction in clonal expansion and function of antigen-specific T and B cells, a diminished ability to generate high-affinity protective antibodies against infectious agents, and a diminished and/or altered cytokine profile produced by T-helper cells. In summary, the elderly immune system becomes deficient at multiple levels and the collapse of these systems contributes to the susceptibility of the elderly to all infectious disease (Plackett et al. 2004).

5.5 Anti-inflammatory Drugs as Therapeutics

Worsening of clinical symptoms after initiation of antibiotic treatment during sepsis or meningitis has long been observed and has led to the use of corticosteroids and other agents concomitant or prior to the first antibiotic dose for immunosuppression. Cell wall active antibacterials (e.g., β-lactams) cause bacterial lysis and in the case of the pneumococcus, releases cell wall components and pneumolysin that enhance inflammation through TLR-2 and TLR-4. Bacteriostatic antibiotics, which inhibit RNA and protein synthesis, delay or even circumvent bacterial lysis, thus reducing inflammation. Given that much of the damage during pneumococcal infection is host-driven, investigators continue to examine the potential of anti-inflammatory drugs as therapeutics. While many, such as macrolides, have proven potential (Amsden 2005), we will discuss the use of statins as a possible prophylactic therapy.

5.5.1 Statins Inhibit NFkB Activation

Statins, 3-hydoroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are among the most widely prescribed drugs in the United States. They are prescribed to treat hypercholesterolemia and inhibit the synthesis of cellular cholesterol. While statins can reduce plasma cholesterol by as much as by 30–55%, it is increasingly evident that statins also have potent anti-inflammatory properties that are independent of their lipid-lowering ability. Currently, it is believed that statins inhibit lipid raft formation and prenylation of signaling molecules, thereby inhibiting cell signal relaying and NFkB activation (Maron et al. 2000). Decreased NFkB activation during infection inhibits the production of inducible nitric oxide synthase (iNOS) and lowers the expression of acute-phase proteins, cytokines, and adhesion molecules. Statins also increase the production of endothelial nitric oxide synthase (eNOS). Unlike iNOS, which increases NO production at the nanomolar level and contributes to the development of shock, eNOS increases NO at a picomolar level and serves to preserve microvasculature tone and tight-junction integrity (McGown and Brookes 2007).

In the last 5 years more than 100 published findings have shown that statins inhibit NFkB activation in a wide variety of tissues and disease conditions. For example, Pravastatin inhibited endothelial cell activation after irradiation and decreased the resulting inflammatory response in mice (Gaugler et al. 2005). Similarly, Simvastatin inhibited NFkB activation and the expression of adhesion molecules in human endothelial cells activated with TNFα (Hilgendorff et al. 2003). Prospective and retrospective studies now indicate that statins are protective against acute bacterial infection. Statin therapy is associated with a decreased rate of sepsis (19% nonstatin group, 2.4% statin group, $p = <0.001$) (Almog et al. 2004), and increased survival in patients with multiple organ dysfunction syndrome (MODS) as a result of sepsis (mortality = 72% nonstatin group, 35% statin group, $p = <0.001$) (Schmidt et al. 2006). Finally, statin therapy has been associated with reduced mortality in patients with CAP (Mortensen et al. 2005) and associated with reduced risk of pneumonia in patients with diabetes (0.49 odds ratio/0.35–0.69, 95% confidence interval), a known risk group for IPD (Van de Garde et al. 2006). Thus, statin therapy offers potential prophylaxis for individuals who are at high risk for IPD, presumably by decreasing pIgR and PAFr expression. It currently remains unclear if statins may be used as a treatment during acute infection.

5.6 Summary

An abundance of evidence indicates that: (1) inflammation occurs in the elderly, (2) inflammation increases susceptibility to *S. pneumoniae* infection, (3) pneumococcal infection causes inflammation, and (4) excessive inflammation is detrimental. Thus, in

the elderly, physiological factors are in place for the development of a positive feedback loop that contributes to patient mortality. Because inflammation underpins these mechanisms, therapies that block inflammation, such as statins, have the potential to protect against IPD.

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Chapter 6
Nonspecific Removal of Sepsis Mediators

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6.1 Introduction

Sepsis is a growing clinical problem in our society, with an estimated annual incidence rate of above 300 cases per 100,000 people and mortality that exceeds 30% in those individuals suffering the disease (Esteban et al. 2007; Angus et al. 2001). Despite apparent recent successes in the treatment (Bernard et al. 2001), sepsis morbidity and mortality remain very high. This implies that new efforts are needed to translate to the clinical practice the huge information that preclinical research has generated in the past decade about the mechanisms of sepsis.

One of the problems is that sepsis entails multiple disorders in different organs and systems, the individual contribution of each one, or the dominance of a particular one, in the disease process being unclear. Initially, sepsis was considered a disorder due to an uncontrolled inflammatory response (Hotchkiss and Karl 2003). However, clinical interventions directed to the inflammatory elements did not reduce morbidity and mortality associated with the disease (Hotchkiss and Karl 2003). Since inflammation and coagulation are tightly linked, and sepsis-associated coagulopathy is almost universal in patients with severe sepsis, antithrombotic-targeted therapy has been clinically investigated with an apparent success, though controversial and limited (Costa et al. 2007; Nadel et al. 2007). Recent data also suggests that most deaths from sepsis are due to an extensive death of immune mediator cells (Hotchkiss and Nicholson 2006). Therefore, in 15 years we have moved from immunostimulation to immunosuppression as cause of sepsis, with one stop in coagulation disorders.

Are we talking about the same disease? Are all these findings different steps in the same disorder? Do they reflect a particular response of the host depending on genetic factors? Honestly, we do not know the answers to these questions yet. The numerous reasons proposed to explain the failure of the different therapies attempted in sepsis probably reflect more a hopeful expectation, such as targeting a single mediator would be enough to modify all events that take place in sepsis, than a real evidence. On the other hand, tailoring the therapy to an individual patient is something desired in medicine for many diseases, and sepsis is not an exception, but so far has been very difficult to achieve. In the meanwhile,

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approaches addressed for nonspecific removal of sepsis mediators appear an attractive option to restore organism homeostasis and improve the morbidity and mortality of this disease.

6.2 Why a Nonspecific Approach?

The predominant theory for many years considered sepsis an uncontrolled production of inflammatory molecules as per the data generated in clinical and preclinal studies (Waage et al. 1987; Remick et al. 1987). This prompted several clinical trials with the goal of blocking tumor necrosis factor (TNF) or interleukin (IL-1) (Remick 2003). These trials did not show a significant improvement in patient survival, though a meta-analysis of TNF inhibitors suggested a better outcome in treated patients (Marshall 2003). An often explanation for the failure of these trials was that the anti-inflammatory agents were not administered quickly enough, but there may be others. An inflammatory mediator must be elevated and detectable to be implicated in the pathogenesis of sepsis. The problem is that cytokines and other inflammatory mediators may have considerable local effects without detectable changes at plasma levels (Remick 2007). Thus, a recent clinical trial in sepsis showed that neonates with sepsis improved after treatment with IL-1 receptor antagonist, even though IL-1 was not detected in plasma (Goldbach-Mansky et al. 2006), and recovery was associated with a decrease in IL-6 plasma levels.

Other studies have shown that intensive care unit (ICU) patients have reduced production of both TNF and IL-6 in response to endotoxin stimulation (Heagy et al. 2000, 2004), while IL-10 production was not impaired (Rigato and Salomao 2003). These data suggest that instead of a hyperinflammatory response, septic patients might present an anti-inflammatory or immunosuppressive response, which has been attributed to the apoptosis of cells of the innate and adaptive immune system (Hotchkiss and Nocholson 2006). Apoptosis causes the deletion of critical effector immune cells and the release of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGFβ), and suppresses the release of proinflammatory cytokines. However, similarly to what happened with anti-inflammatory treatments, use of immunostimulants such as granulocyte macrophage colony-stimulating factor or interferon-γ did not modify survival in septic patients (Root et al. 2003; Dries et al. 1994).

Something analogous to what happens with inflammation occurs with the dysfunction of coagulation in sepsis. Activation of the coagulation cascade can be produced by several noninfectious insults, such as thermal injury, pancreatitis, and trauma. In this case, the activation of coagulation is associated with an inflammatory response through TNF-α release and complement activation (Esmon 2000). In sepsis, along with the activation of coagulation through the proinflammatory cascade, there is also a direct activation of coagulation by infectious toxins that upregulate tissue factor (TF) in endothelial cells, leading to the formation of thrombin and fibrin clots (Tapper and Herwald 2000). However, the procoagulant

activity in sepsis is not limited only to the endothelium, since TF is also present in circulating activated monocytes. Thrombin is also generated by these cells, allowing an unlimited supply of TF and a generalized activation of coagulation. This leads to the depletion of natural antithrombotic factors, such as protein C, antithrombin (AT), and TF pathway inhibitor (TFPI), turning the hemostatic system into an appropriate target for sepsis intervention. Unfortunately, as what happened with the anti- and proinflammatory treatments, clinical studies failed to demonstrate a benefit for recombinant TFPI or AT (Warren et al. 2001), and only activated protein C appears to yield a limited benefit.

All these data suggest that the inflammatory and coagulation responses in sepsis are multifaceted, not clearly classified as augmented or decreased, and probably with more unknown elements than those that we know. This has led to the rationale for nonspecific elimination of circulating mediators in sepsis by continuous extracorporeal removal mechanisms. The consideration of these techniques as potential therapeutic options in septic patients is also a consequence of the advances of technology. Continuous renal replacement therapies (CRRTs) have progressively evolved from a therapy of last resort for acute renal failure to a standardized technique for critically ill patients. This has created a new scenario where the CRRT is foreseen as a possible therapeutic approach in critical care patients with multiple organ dysfunction syndrome (MODS), regardless of whether the patients exhibit a renal failure or not (Ricc et al. 2004).

6.3 Continuous Renal Replacement Therapy

Replacement of the renal function may be performed through hemodialysis (HD) or hemofiltration (HF). HD is achieved by diffusive clearance along with a concentration gradient from blood to a dialysate through a semipermeable membrane. Small molecules (urea, creatinine, potassium) diffuse rapidly and are efficiently removed, whereas larger solutes that diffuse poorly are cleared slowly. HD is performed intermittently for the treatment of patients with chronic renal failure (CRF) or acute renal failure (ARF) without hemodynamic compromise to restore metabolic and/or fluid balance.

HF is based on convective mass transport. A transmembrane pressure drives both fluid and solutes through a membrane selected for its high hydraulic permeability, allowing removal of larger solutes than HD. Convective removal of a solute (sieving coefficient) depends on transmembrane pressure (TMP), on molecular weight (MW) and structure of the solute, as well as on the cutoff point of the membrane. HF may be performed intermittently but it is usually executed as CRRT, namely continuous veno-venous hemofiltration (CVVH). CRRT includes other techniques also, such as the continuous veno-venous hemodialysis (CVVHD), which uses diffusion as the main mechanism to remove solutes, and continuous veno-venous hemodiafiltration (CVVHDF), which combines both HD and HF. Most of the filters used in these techniques have an adsorption property, which is

defined as the molecular adherence to the surface or interior of a semipermeable membrane. Thus, CRRT may include three types of depurative mechanisms: convection, diffusion, and adsorption.

Different strategies have been investigated for renal replacement in critical care patients, making CRRT the most extensively used therapy in clinical practice. The reason is that many patients in ICU are hemodynamically unstable and cannot tolerate the subtraction of the blood volume required for intermittent HD. Despite that some authors settled that alternate-day HD should no longer be considered adequate for critically ill patients with acute renal failure (Schiffl et al. 2002), no study has obtained conclusive results of the benefits of CRRT versus intermitent HD (Kellum and Bellomo 2000; Vinsonneau et al. 2006; Ronco and Bellomo 2007).

A high percentage of septic patients develop ARF, exceeding 50% in the case of septic shock. Combination of sepsis and ARF usually leads to MODS, which is associated with more than 80% mortality. Thus, many septic patients require an intensive care support that most of the times includes mechanical ventilation and renal replacement therapy (Schrier and Wang 2004). CVVHD or CVVHDF have been proposed for renal replacement in septic patients, based on a better control of azotemia (Ricci et al. 2006; Saudan et al. 2006; Page et al. 2005). Other authors recommended the use of slow extended dialysis, which appears to be associated with equivalent cardiovascular stability and solute control as CRRT in septic patients (Kumar et al. 2004). However, CRRT have become extensively used in septic patients with renal failure because of their apparent ability to remove, along with the small MW solutes, middle MW molecules that would include cytokines and other sepsis mediators (Kellum et al. 1998).

6.4 CRRT and Cytokine Removal

Nonspecific elimination of circulating cytokines and other inflammatory mediators by CRRT has been a matter of controversy ever since it was first proposed. In 1976, Burton created the term *hemofiltration*, and one year later Kramer developed the continuous arteriovenous hemofiltration (CAVH) technique (Kramer et al. 1977), which used a systemic arteriovenous pressure difference in an extracorporeal circuit to continuously produce an ultrafiltrate. The limited capacity of this procedure to remove nephrotoxins led to the development of pump-driven techniques (Peachey et al. 1998; Storck et al. 1991). In 1991, CAVH was compared to pump-driven hemofiltration (PDHF), showing a better survival rate in the PDHF group that appeared related to a faster elimination of toxic mediators (Storck et al. 1991). These would include nephrotoxins and other toxins as suggested by the improvement in cardiovascular function with HF observed in animals after endotoxin injection and the impairment of hemodynamics in healthy animals with the infusion of the *septic ultrafiltrate* (Grootendorst et al. 1992).

Complications related to the arterial access lead to the development of veno-venous pump-driven techniques which have become extensively used for CRRT in intensive

care units (Bellomo et al. 1993a,b). The expansion of these techniques was associated with the introduction of biocompatible membranes in the procedures that decreased the generation of inflammatory mediators by the system itself (Schiffl et al. 1994). In this setting, Bellomo et al. suggested that CRRT might remove cytokines (TNF-α and IL-1) from the circulation of septic patients (Bellomo et al. 1993b).

Since then, several studies have shown the presence of inflammatory mediators in the ultrafiltrate fluid from septic patients with CRRT. However, a few demonstrated a significant decrease in plasma concentrations of these mediators with the ultrafiltrate usually removed for renal replacement (Table 6.1) (Heering et al. 1997; Sander et al. 1997; Hoffmann et al. 1995). This discrepancy between the presence of inflammatory mediators in ultrafiltrate fluid and their lack of reduction in plasma suggest a constant production of mediators during sepsis. Similarly, HF has been associated with hemodynamic improvements in critically ill patients and animal models of acute endotoxic shock without a correlation with the decrease in cytokine plasma concentrations (Sanchez-Izquierdo et al. 1997; Kamijo et al. 2000; Rogiers et al. 1999; Mink et al. 1999).

Table 6.1 Mediators clearance with CRRT

Author	Study	Modality	Membrane	Ultrafiltrate dose	Ultrafiltrate analysis	Plasma reduction
Rogiers et al. (1999)	Dogs	HVHF	PS	6 l/h	TNF	No
Bellomo (2000)	Dogs	HVHF	AN69	80 ml/kg/h	ET-1, PGF1α	No
Bellomo (1993b)	Humans	CVVHD	AN69	–	TNF IL-1	No
Sanchez-Izquierdo Riera (1997)	Humans	CVVH	AN69	300 ml/h	TNF, IL-6	No
Hoffmann. et al (1995)	Humans	CVVH	PA	2 l/h	TNF, IL-2, IL-6	C3a
Journois et al. (1996)	Humans (pediatric)	HVHF	AN69	5 l/m^2	TNF, IL-10	IL-1, IL-6, IL-8
Heering et al. (1997)	Humans	CVVH	PS	1 l/h	TNF, IL-1, IL-2R, IL-8	No
Sander et al. (1997)	Humans	CVVH	AN69	1 l/h	TNF, IL-6	No
De Vriese et al. (1999)	Humans	CVVH	AN69	1.5–2.7 l/h	TN IL-6, IL-1	No
Kamijo et al. (2000)	Humans	CVVH	AN69	500–1,000 ml/h	IL-6	No
Cole et al. (2001)	Humans	HVHF	AN69	80 ml/kg/h	C3, C5, IL-10	Transitory changes
Ghani et al. (2006)	Humans	HVHF	PS	100 ml/kg/h	IL-6	IL-6

AN69 polyacrylonitrile; *HVHF* high volume hemofiltration; *PA* polyamide; *PS* polysulphone; *ET* endothelin; *PG* prostaglandin

Convective techniques of CRRT (CVVH) have been considered more efficacious for cytokine removal than diffusive techniques (CVVHD) in septic patients (Table 6.1) (Kellum et al. 1998). The rationale is that HF might remove higher MW molecules than HD. This benefit of convective techniques has been recently argued by one study that suggested no benefit from CVVH compared to CVVHD for the removal of both small and middle MW molecules, which include cytokines (Ricci et al. 2006). However, it should be noted that the clearance of middle MW molecules was higher with CVVH than with CVVHD, though it did not reach the statistical significance ($p = 0.055$). On the other hand, the effect of CRRT on cytokine removal and blood pressure appeared not only be explained by convective or diffusive clearance of the mediators, suggesting other mechanisms of clearance (Bellomo et al. 2000). This led to propose adsorption to the membrane as the main clearance mechanism of cytokines, being most pronounced immediately after installation of a new membrane and decreasing steadily thereafter by a rapid saturation of the membrane (Goldfarb and Golper 1994; De Vriese et al. 1999). Nevertheless, in this case, the same study that questioned the benefit of the convective versus diffusive techniques has presented more solid data that minimizes the contribution of adsorption to remove inflammatory mediators (Ricci et al. 2006).

Therefore, mediators related to sepsis may be found in the ultrafiltrate fluid from septic patients during CRRT, suggesting their removal by this technique, though the plasma level of these mediators does not change. Then, why do hemodynamics and clinics improve with CRRT in septic patients? Ronco et al. proposed the "peak concentration hypothesis" to explain these events. This considers the response to sepsis in a network perspective, where absolute values are less relevant than relative ones and small decreases might induce major balance changes. Thus, the clinical and hemodynamic benefits of CRRT in sepsis may be due to the ability of this technique to lower peaks of mediators such as the pro- and anti-inflammatory, pro- and anticoagulant, and likely others, reducing their toxic effects and leading to a nearly normal inmunohomeostasis (Ronco et al. 2001).

6.5 CRRT in Sepsis

Several factors influence the potential beneficial effects of CRRT in sepsis. These include the amount of ultrafiltrate, the moment of initiation, and the permeability of the filter used for CRRT.

6.6 Ultrafiltrate Dose

In chronic hemodialysis patients, hemodialysis dose might affect morbidity and mortality (Gotch and Sargent 1985). A similar correlation between outcome (survival) and dose of treatment with CRRT (volume of ultrafiltrate) was also suggested in ischemic or septic ARF (Storck et al. 1991). Subsequently, animal studies confirmed this link between dose of ultrafiltrate and survival in sepsis (Table 6.2) (Rogiers et al. 1999; Yekebas et al. 2001).

Table 6.2 Clinical response to CRRT

Author	Study	Modality	Ultrafiltrate dose	Clinical improvement
Grootendorst et al. (1992)	Pigs	HVHF	150 ml/kg/h	HMD, RESP
Lee et al. (1998)	Pigs	HVHF	50–75 ml/kg/h	RESP, SURV
Rogiers et al. (1999)	Dogs	HVHF	200 ml/kg/h	HMD
Bellomo *(2000)*	Dogs	HVHF	80 ml/kg/h	HMD
Yekebas (2001)	Pigs	HVHF	100 ml/kg/h	HMD, SURV
Hoffmann et al. (1995)	Humans	CVVH	2 l/h	HMD
Journois et al. (1996)	Humans (pediatric)	HVHF	5 l/m^2	RESP
Sander et al. (1997)	Humans	CVVH	1 l/h	No improvement
Heering et al. (1997)	Humans	CVVH	1 l/h	HMD
Oudemans-van Straaten et al. (1999)	Humans	HVHF	3.8 l/h	HMD, SURV
Kamijo et al. (2000)	Humans	HVVC	500–1,000 ml/h	HMD
Ronco *(2000)*	Humans	HVHF	45 ml/kg/h	SURV
Honore et al. (2000)	Humans	HVHF	116 ml/Kg/h	HMD, SURV
Cole et al. (2001)	Humans	HVHF	80 ml/kg/h	HMD
Cornejo et al. (2006)	Humans	HVHF	100 ml/kg/h	HMD, SURV
Ratanarat et al. (2005)	Humans	PHVHF	85 ml/kg/h (6–8 h) + 35 ml/kg/h (16–18 h)	HMD, SURV
Ghani et al. (2006)	Humans	PHVHF	100 ml/kg/h (6 h) + 35 ml/kg/h (18 h)	HMD

HMD hemodynamic; *RESP* respiratory; *SURV* survival; *PHVHF* pulse HVHF

The largest clinical trial evaluating the impact of different ultrafiltration doses in critically ill patients with ARF, either septic or not, randomized patients to ultrafiltration rates of 20 ml/kg/h (group 1), 35 ml/kg/h (group 2), and 45 ml/kg/h (group 3). The survival rate was significantly lower in group 1 (41%) compared to groups 2 (57%) and 3 (58%), indicating that a minimal renal dose of 35 ml/kg/h is required to replace renal function in critically ill patients with ARF. In the subgroup of patients with sepsis, survival was 47% in group 3 compared to 18% in group 2 and 25% in group 1. Though the differences did not reach statistical significance, the authors postulated that sepsis patients might benefit from an ultrafiltrate dose >35 ml/kg/h (sepsis dose) (Ronco et al. 2000). Since then, different doses of hemofiltration have been investigated in patients with septic shock (Table 6.2).

In a group of septic shock patients with organ dysfunction, the hemodynamic parameters increased regularly during HF treatment with ultrafiltration rates between 40 and 60 ml/kg/h. The improvement of hemodynamics was associated with a beneficial effect on 28-day mortality (46% vs. 70%) (Joannes-Boyau et al. 2004). In addition, the efficacy of HF with ultrafiltration of 35 l in 4 h was evaluated in patients with refractory septic shock. Improvement in hemodynamics was observed in 11 of the 20 patients studied. Of these, 9 (81%) were alive on day 28, while all nonresponders died within one day. The observed mortality was significantly lower than the APACHE II, SAPS II predicted mortality, being patient's weight and the time from ICU admission to HF the factors associated with a clinical

response. The fact that the weight was a factor associated with improvement emphasizes the relevance of the volume of ultrafiltration, since the study used a fixed ultrafiltration rate per hour instead of adjusting this to patient's weight (Honore et al. 2000). Other studies investigated different doses of ultrafiltration (85, 80, or 70 ml/kg/h during 6–12 h) (Oudemans-van Straaten et al. 1999; Cole et al. 2001; Ratanarat et al. 2005; Cornejo et al. 2006; Jiang et al. 2005), suggesting an improvement in hemodynamics and short-term patient survival compared to the conventional doses used in CRRT for ARF (Table 6.2). Bouman has summarized the different doses of ultrafiltration in three groups (Bouman et al. 2007):

- Low volume hemofiltration (LVHF): <30 ml/kg/h
- High volume hemofiltration (HVHF): 30–50 ml/kg/h
- Very high volume hemofiltration (VHVHF): >50 ml/kg/h

It should be noted that the concentration of mediators in the ultrafiltrate in studies with HVHF and VHVHF has shown inconsistent results (Table 6.1). Thus, some studies found an increase for removal of several cytokines, along with a drop in their plasma levels, in HVHF or VHVHF compared to LVHF for CRRT (Journois et al. 1996; Ghani et al. 2006). This fall in cytokines was not always associated with better hemodynamic effects in HVHF or VHVHF compared to LVHF (De Vriese et al. 1999). In contrast, other studies found a level of cytokines in the ultrafiltrate of HVHF negligible, and suggested adsorption as the major mechanism for mediator removal with these techniques (Cole et al. 2001). These variations may reflect particular differences with the HF methods or the technical difficulties involving the analysis of cytokines.

HVUF or VHVUF are not innocuous to the patients and may be associated with problems related to the vascular access and others such as hypothermia or ionic disorders. In addition, it requires a rapid change in drug dosing to compensate all the drugs that will undergo an extracorporeal clearance. On the other hand, when the filtration fraction (FF: the ratio between ultrafiltration and plasma flow) exceeds 30% with these techniques, TMP gradient progressively increased and membrane fouling occurred. This complication might be avoided by using the replacement solution before passage through the filter (predilution), though it might reduce efficiency compared with dilution after passage through the filter at similar ultrafiltration volumes. Finally, HVUF and VHVUF are expensive techniques that need a very well-trained team to perform. In this setting, short intermittent VHVUF sessions and maintenance with a HVUF rate around 35 ml/kg/h appear as the best way to balance the potential benefits and adverse effects of these techniques in septic patients with ARF. The problem is that the best dose and period for VHVHF have not been defined yet.

6.7 When CRRT Should Begin?

Sepsis is a "continuum" process that may develop MODS. Early antibiotics and hemodynamic goal-directed therapy (EGDT) are included in actual practice guidelines because they have proven a benefit for septic patients (Dellinger et al. 2004).

It seems reasonable to consider that removing or reducing the peak of mediators in an early phase of the sepsis may avoid MODS instauration. Experimental animal studies have confirmed this postulate showing that early HF treatment increases survival (Mink et al. 1999). The problem is that in experimental studies HF techniques are started before or shortly after the microbial challenge, whereas in clinical practice CRRT is started when shock and ARF are already established. The exception may be one study in patients with pancreatitis where HF was performed without ARF. It showed that HVUF and early treatment (within 48 h after onset of abdominal pain) was associated with significantly better survival that in the group of patients with late (96 h) LVUF (Jiang et al. 2005).

Several parameters have been studied for an earlier indication of CRRT in critically ill patients. These include the initiation of CRRT with a BUN < 60 mg/dl, which improved the survival of trauma patients with ARF compared to beginning with a greater renal dysfunction. As we indicated previously, the time from ICU admission to HVUF was significantly shorter in septic patients with refractory shock that improved with the treatment (<7 h) than in nonresponders (>12 h) (Gettings et al. 1999; Piccinni et al. 2006). Interestingly, two responders with delayed times (>12 h) died despite an improvement in the hemodynamic status, suggesting that even though cardiovascular reserve may be present, delay in treatment may lead to the development of a lethal injury (Honore et al. 2000). Other authors have used the acute respiratory failure commonly present in septic patients to initiate HF. When PaO_2/FiO_2 ratio was lower than 250, CVVH improved survival compared to an historical control group (Weksler et al. 2001). The exception to these studies is the one from Boumann that did not find differences in survival nor in recovery of renal function in severely ill patients with ARF with early (7 h) HVUF versus late (42 h) LVUF (Bouman et al. 2002).

In summary, early CRRT is associated with hemodynamic improvement and an apparent better survival rate in septic patients developing ARF. The problem is that for the moment there is no agreement about what indicator should be used for the initiation of therapy. On the other hand, there is a lack of studies analyzing HF in patients without ARF, since the majority of studies analyze early therapy HF in patients with at least established acute renal injury, which already implies the presence of MODS. The preliminary results obtained in the few studies that attempted HF without renal dysfunction warrant the application of these techniques to septic and other critically ill patients, if they can prove a benefit in prospective randomized clinical trials.

6.8 Membrane and Pore Size

Both membrane and solute characteristics (geometry, charge, MW, and protein binding) determine the degree of removal by ultrafiltration and adsorption in HF and HD. Important membrane-related determinants are pore characteristics (size, distribution, and density), pH, charge, and surface (Clark et al. 1999).

For some membranes, in particular the negatively charged polyacrylonitrile (AN69) membrane, adsorption appeared to be the main mechanism of mediator removal (De Vriese et al. 1999; Kellum and Bellomo 2000), though a recent study has questioned this effect (Ricci et al. 2006).

Filter permeability may dramatically influence the removal of plasma mediators. Conventional membranes usually have a pore size of about 5 nm, allowing the removal of molecules up to a MW of about 30 kDa. High cutoff membranes have pore sizes of about 10 nm, allowing the elimination of molecules with MW up to 50 kDa. The use of high cutoff membranes to increase cytokine removal has been discussed since it was first proposed. An animal septic model compared 100 kDa with 50-kDa pore size filters for HF, showing an increased survival rate in the 100-kDa group (8 times higher), though it was associated with an increased protein concentration in the ultrafiltrate (Lee et al. 1998).

The impact of filter permeability in the treatment of septic patients is unclear. In vitro studies using large filter pore size (100 kDa) for HF showed a significantly better clearance of cytokines by an augment of ultrafiltration rate from 1 to 6 l/h, without changes in the albumin clearance (Uchino et al. 2002). In a small observational study, intermittent HF with high cutoff membranes (HCOM–HF; in vitro cutoff of 100 kDa) led to a slight improvement of organ failure in 16 patients with septic shock and ARF combined with high IL-6 removal. However, there was a cumulative protein loss of almost 7.6 g/12 h (Morgera et al. 2003). The same authors performed a small randomized controlled trial in 30 patients with sepsis comparing HF with standard membranes (30 kDa) with HCOM–HF (60 kDa). Ultrafiltrate dose was 2.5 l/h in both groups. HCOM–HF was superior to HF allowing bigger decrease in norepinephrine dose and higher cytokine removal (IL-1 and IL-6) with significant decline of cytokine plasma levels (Morgera et al. 2006). Other study compared HD with HCOM membranes (HCOM–HD) during 4 h and HD with high flux during 4 h, in septic patients with ARF. HCOM–HD, but not HD with high flux, achieved substantial diffusive clearance of several cytokines (IL-6, IL-8, and IL-10). However, during HCOM–HD, cumulative albumin loss into the effluent was 7.7 g versus less than 1.0 g for HD with high flux (Haase et al. 2007). All these data suggest that HCOM could be a good option to increase cytokine removal. The main drawback of this method is the loss of proteins and its associated complications. Whether the benefit of HCOM may be added to that achieved with other strategies such as HVUF rates is unclear for the moment.

6.9 Other Therapies

In an attempt to increase cytokine removal, new strategies have been proposed: Total plasma exchange tries to replace *bad molecules by good molecules* with plasma transfusion; adsorption therapies with special cartridges aim to increase cytokine removal; and nonselective extracorporeal therapies like coupled plasma filtration adsorption (CPFA) combine both adsorption and convection techniques.

6.10 Plasmapheresis

Plasma exchange therapies (PE) separate plasma from whole blood by centrifugation or filtration mechanisms, and replace with human plasma. Plasma replacement could be a good option in septic patients because of the potential benefits of factor replacement. Experience in septic patients with PE is reduced, though most of the studies showed beneficial effects. Stegmayr et al. used PE as rescue therapy in 76 patients with severe MOF observing an increase in survival (86% vs. 33% APACHE II expected survival) (Stegmayr et al. 2003). The largest published trial included 106 septic patients and was associated with a decreased mortality in PE group of 20% (33% vs. 53.8%) (Busund et al. 2002). Finally, in pediatric patients with proved infection, PE was associated with a trend toward fewer organs failing, though it did not have an impact on mortality (Reeves et al. 1999).

6.11 Adsorption Techniques

These methods use cartridges containing materials such as resin-coated beads or fibers that bind the desired mediators. Endotoxin is one of the most important mediators of sepsis that have been targeted for adsorption. Multiple methods of removing endotoxin from blood or plasma have been developed utilizing various ligands such as polymyxin B, albumin, ofloxacin, bactericidal/permeability-increasing protein, endotoxin inhibitor, and cationic antibacterial protein 18 (Nillson et al. 2005).

Major clinical experience is related to the use of polymixin B cartridges (PMX-F) in gram negative infections. A recent meta-analysis including over 1,425 septic patients (978 treated with PMX-F) observed improvement in hemodynamics, PaO_2/FiO_2 ratio, endotoxin removal, and mortality in patients treated with the cartridges However, possible publication bias and lack of binding lead to the conclusion that further studies are needed to confirm the potential benefits of this therapy (Cruz et al. 2007).

6.12 Coupled Plasma Filtration Adsorption

Coupled plasma filtration adsorption (CPFA) is a blood purification technique in which blood passes through a plasmafilter separating a predetermined percentage of plasma. This plasma continues through a cartridge that removes mediators via nonselective adsorption. Plasma is then returned to combine with blood that subsequently can pass through a hemofilter for CRRT if needed. This technique showed in animal models a reduction in cytokine plasma concentrations and improvement in survival (Tetta et al. 2000). Clinical studies reported hemodynamic and gas exchange improvements with CPFA treatment (Formica et al. 2003). The main limitation of this technique is the lack of comparative studies with HF or HD, which does not allow us to conclude whether CPFA may give an additional benefit to the latter techniques or not.

Our own group, in a small uncontrolled trial, treated ten septic shock patients with severe MOF with either CPFA or HF with HVUF, observing a similar hemodynamic and gas exchange response in both groups (Perez et al. 2007).

6.13 Conclusion

Sepsis is the major cause of mortality in critically ill patients. The physiopathology pathways of the disease are complex and incompletely understood even now. Adequate and early antibiotic administration, infection focus eradication, and EGDT, continue to be the main cornerstones of sepsis therapy. Interventions designed to block the synthesis or the action of a particular component of the sepsis cascades have been attempted in the last years, but have not achieved the expected benefits.

CRRT in septic patients who develop ARF have produced benefits that go beyond the replacement of renal function. Peak reduction of cytokines and other sepsis mediators have been proposed to be responsible for the improvements observed in septic patients with CRRT. Ultrafiltrate dose, filter pore size, and membrane adsorption properties appear to be the issues that may convert CRRT in a therapeutic alternative to septic patients. Thus, ultrafiltration of at least 35 ml/kg/h should be the regular practice in critically ill patients when CRRT is needed, regardless of whether the patients are septic or not. The use of higher doses of ultrafiltration and high cutoff filters require more investigation and standardization before they can be recommended. For the moment, CRRT with short intermittent VHUF sessions (6–8 h) and maintenance with a HVUF rate around 35 ml/kg/h appear the best way to balance the potential benefits and adverse effects of these techniques in septic patients with renal injury or ARF.

Scientific evidence is too low to recommend the use of continuous replacement therapies as adjunctive treatment for septic patients without ARF. Similarly, the use of plasma exchange and adsorption techniques is a promising field but need to be compared to CRRT to appreciate the potential benefits. However, the potential benefit of the continuous replacement therapies and other blood exchange techniques to treat septic and other critically ill patients regardless of renal failure constitutes one of the more appealing therapeutic approaches for the critical care medicine in the twenty-first century.

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Chapter 7
Optimal Antibiotic Use in Severe Community-Acquired Pneumonia

Alejandro Rodríguez, Mónica Magret, and Jordi Rello

7.1 Introduction

Community-acquired pneumonia (CAP) is the main cause of death due to infectious disease in the developed countries. Although the incidence is not available in most countries, it represents more than 600,000 hospital admissions in the United States (Barlett et al. 2000) and 50,000 in the United Kingdom each year (Hirani and Macfarlane 1997). The cost is higher for nonsurvivors than for survivors (around $7,500 of an in-hospital case) (Fine et al. 1997).

Since the use of penicillin, the mortality rates of severe CAP have not decreased significantly despite advances in antimicrobial therapy and technical improvements in the ICU. Fine et al. (1997) reported that only 10% of hospitalized patients are admitted to ICU, and that the mortality rate in intubated patients reaches 40%. This mortality rate depends on the interaction between the host factors (age, comorbidities, genetic predisposition, and immunocompromise), microorganism characteristics, and optimal antibiotic use (Luján et al. 2006) (Fig. 7.1). In a recent study, Waterer et al. (2001a,b) suggest that CAP patients with septic shock appear to have different genotypes than those with hypoxemic respiratory failure without shock.

The constant increase in the number of elderly and immunocompromised patients (those receiving steroids, organ transplant recipients, HIV patients), the better survival rates of patients affected by chronic illness, and the need for appropriate empirical antibiotics administration are reasons that justify continuing research, focused on improving the diagnosis, defining risk factors that influence outcome, and assessing new therapies.

Usually, at the time of initiation of the empirical antibiotic treatment, the responsible microorganism is not identified. In the last decade, different societies (Infectious Disease Society of America – IDSA, American Thoracic Society – ATS, and British Thoracic Society – BTS) have published guidelines to help physicians in the management of CAP (Barlett et al. 2000; ATS 1993; BTS 2001).

Several studies (Malone and Shaban 2001; Dean et al. 2006; Mortensen et al. 2004) on patients with severe CAP (SCAP) have emphasized the importance of appropriate empirical therapy in reducing disease-related mortality; however, the optimal regimen has not been well defined from large case series. The use of

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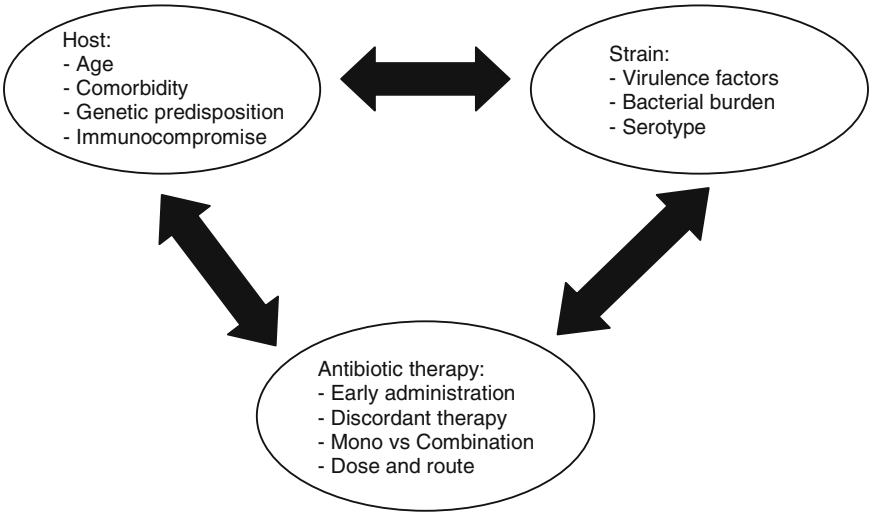

Fig. 7.1 Interaction factors influencing survival in severe community-acquired pneumonia

empiric antimicrobial therapy concordant with international guidelines is associated with decrease mortality among patients with CAP. One study reported a 4.4-fold reduction in mortality if the ATS therapy guidelines were followed (Malone and Shaban 2001). Other authors have observed similar results (Dean et al. 2006; Mortensen et al. 2004). However, these studies have limitations, such as the use of administrative databases, focus on specific patient groups, such as those with bacteremic pneumococcal pneumonia (Waterer et al. 2001a,b; Baddour et al. 2004), or low risk of mortality (Brown et al. 2003). Recently, our group (Bodí et al. 2005) reported the first study to evaluate the impact of the adherence to IDSA guidelines for severe episodes of CAP admitted to ICU. Multivariate analysis found associations between higher mortality rate and age, APACHE II score, immunocompromise, and nonadherence to IDSA guidelines for antibiotic treatment. Interestingly, adherence to IDSA guidelines was the only potentially modifiable factor for improving the prognosis of ICU patients with SCAP.

Considering the few information about treatment of critically ill patients with SCAP, we focused this chapter on the antimicrobial treatment of a subgroup of patients admitted to ICU due to SCAP, specially, on the optimal antibiotic use.

7.2 Antibiotic Therapy: New Concepts

Until now, the in vitro susceptibility of the microorganisms was considered the reference aspect for the antibiotic efficacy for pneumonia (Pea and Viale 2006), and was used to define the concept of “appropriate therapy.” Indeed, other factors must be considered to achieve what we call “appropriate,” “adequate,” or “optimal” antibiotic therapy for pneumonia (Rello and Mallol 2006) (Fig. 7.2). The “appropriate”

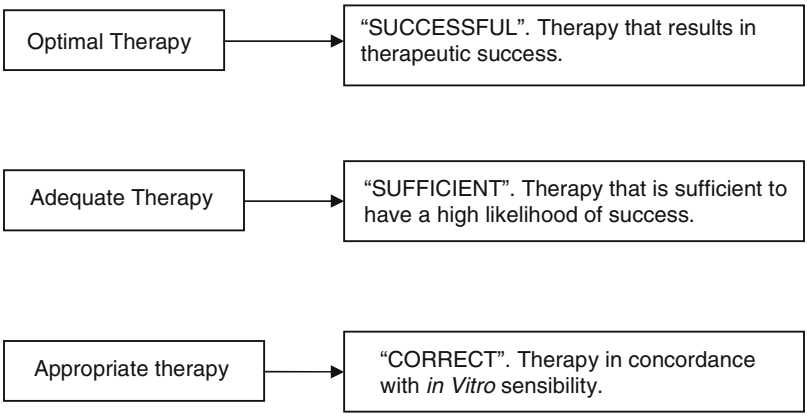

Fig. 7.2 New concepts about antibiotic therapy

or concordant antimicrobial therapy only refers to the in vitro susceptibility. Thus, the main synonym of "appropriate" is "correct." Although fundamental, this might not suffice for the optimal care of critically ill patients. Timely administration of appropriate antimicrobial therapy, particularly in the subset of patients with highest severity, is a crucial factor to improve survival (Houck et al. 2004). In addition, most of the dosing regimens are administered regardless of the infection site and the pathophysiological conditions of the patients. Antibiotic effective concentrations should be guaranteed at the infection site. In critically ill patients, this can be a very difficult goal to achieve considering their complex pathophysiological conditions. Mechanical ventilation increases over 50% the volume of distribution of drugs (Pinder et al. 2002). Thus, higher doses of antimicrobial agents may be required to achieve adequate concentration in the site of infection (Pea and Viale 2006). Therefore, "adequate" antimicrobial therapy should take into account the interaction between the bacterial pathogen and the antimicrobial agent at the minimal inhibitory concentration (MIC). Adequate antibiotic therapy would be the prescription that is sufficient to have a high likelihood of success, beyond the "appropriateness" of the choice. Finally, "optimal" therapy for pneumonia should consider additional factors in addition to the in vitro susceptibility and the penetration into the infectious site, like the anti-inflammatory effects of antibiotics. Thus, "optimal" therapy is that one that results in therapeutic success (Pea and Viale 2006; Rello and Mallol 2006; Wunderink 2004) (Fig. 7.3).

7.3 Management of SCAP

The adequate management of SCAP includes the appropriate antibiotic treatment, management of septic shock, control of the inflammatory response, and ventilatory support. However, in this chapter we will focus only on antibiotic treatment.

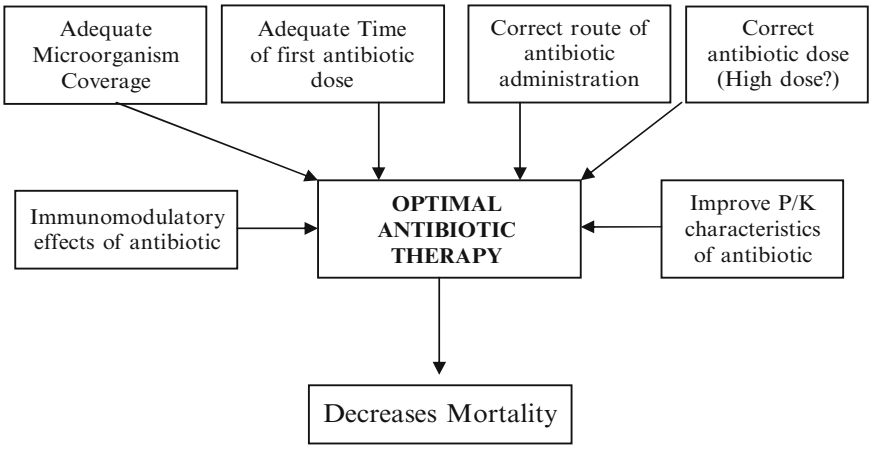

Fig. 7.3 Optimal antibiotic therapy (modified from Pea and Viale 2006)

7.3.1 Antibiotic Treatment

Several studies have demonstrated that an inadequate empiric antibiotic treatment is associated with a significant increase in mortality (Pachón et al. 1990; Torres et al. 1991; Rello et al. 2006; Niederman et al. 1993; Gordon et al. 1996). Inadequate antibiotic treatment is defined as the therapy administered during the first two days of pneumonia onset, which is inactive (intermediate or resistant) in vitro to the responsible microorganism (Luján et al. 2006).

In most cases, the antibiotic treatment begins in an empiric way, covering the most frequent microorganism and considering the risk factors of each patient. However, there is no uniformly accepted definition of SCAP. Many studies have described an entity referred to as SCAP, without providing a specific definition, and requiring only that the patients had been admitted to the ICU (Fine et al. 1997; Waterer et al. 2001a,b; Mortensen et al. 2004; Houck et al. 2004). This has led to tremendous variability in both, the patients and the mortality rate described as SCAP. The ATS has attempted to provide a working set of criteria for this illness (Niederman et al. 1993). In their initial statement, SCAP was characterized by the presence of any of the following features: (1) respiratory rate > 30/min; (2) PaO_2/FiO_2 ratio < 250; (3) need for mechanical ventilation; (4) bilateral, multilobar, or rapidly expanding infiltrates; (5) shock, and (6) oliguria or acute renal failure. However, 65% of all patients admitted to the hospital had at least one of the severe pneumonia features (Gordon et al. 1996). Thus, we still need a more specific definition that better defines a population needing ICU admission for SCAP. We believe that probably patients having shock or needing mechanical ventilation fit in the best definition of SCAP, and these ICU admission criteria have been considered in recent IDSA/ATS guidelines (Mandell et al. 2007).

A major goal of therapy is the eradication of the infecting organism, with resultant resolution of the clinical disease. Appropriate drug selections dependent on the causative microorganism and its antibiotic susceptibility. Acute pneumonia can be caused by a wide variety of pathogens. However, *Streptococcus pneumoniae, Legionella sp*., and *Haemophilus influenzae* are the main pathogens to cover (Bodí et al. 2005). Until more accurate and rapid diagnostic methods are available, the initial treatments for most patients remain empirical and physicians should consider specific risk factors for each patient (gram-negative pathogens) (Rello et al. 1996, 2003). Recently, in the community setting have appeared methicilin-resistant *Staphylococcus aureus* (MRSA) as severe pulmonary infections (pneumonia or empyema) (Kollef and Micek 2006). At difference to healthcare-associated MRSA, community-acquired MRSA is more susceptible to a wider class of antibiotics but it continues being more virulent, since it usually produces the Panton-Valentine leukocidin (PVL) that makes necrotizing pneumonia. At this time, in contrast to the observed one in America, the community-MRSA is not a frequent pathogen isolated in Europe.

S. pneumoniae is the most frequent microorganism in SCAP. Interestingly, a higher mortality rate for CAP patients has not been reported from countries with high levels of in vitro resistance for *S.pneumoniae* compared with those with lower resistance rates (Lode et al. 2003). Therefore, it is important to emphasize that in vitro resistance may not have the anticipated impact on the outcome.

The most recent IDSA/ATS Guidelines (Mandell et al. 2007) recommend for patients admitted to ICU to begin with a wide spectrum antibiotic treatment. The combination therapy with two different antibiotics that include a potent antipneumococcal β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus a macrolide (level II evidence) or a respiratory fluoroquinolone (level I evidence) is the treatment suggested for critically ill patients. Because septic shock and mechanical ventilation are the clearest reasons for ICU admission, the majority of ICU patients would still require dual therapy. However, these recommendations were not obtained from clinical trials and have been extrapolated from nonsevere cases, in conjunction with case series and retrospective analyses of cohorts with SCAP (Mandell et al. 2007). In fact, many of these trials involved a discretionary use of antibiotic and most were pharmaceutical trials that deliberately excluded ICU patients. Thus, the implications of empirical antibiotic therapy for ICU patients with severe CAP remain unknown.

7.3.2 Mono- or Combination Therapy

Only 20% of CAP patients require hospitalization, and the mortality rate is lower than 10%, regardless of the antibiotic regimen received. Up to 10% of all hospitalized patients with CAP are finally admitted to ICU. This group of patients represents only a small fraction of all of the CAP cases, but in terms of mortality, it is the most important strata.

In the last ten years, many different studies have evaluated the impact of the dual antibiotic treatment for SCAP on mortality. These retrospective and observational studies (Waterer et al. 2001a,b; Baddour et al. 2004) have showed higher rates of survival in patients who are treated with a combination antibiotic therapy. However, the studied population included patients with pneumococcal bacteremic CAP and their conclusions might not be extrapolated to the treatment of all patients with SCAP. Three of these retrospective studies (Waterer et al. 2001a,b; Baddour et al. 2004; Martínez et al. 2003) reported that the benefit was higher in patients with SCAP who received a combination therapy. Indeed, Waterer et al. (2001a,b) observed an 11.3% absolute mortality difference (18.2% vs. 6.9%, $p = 0.02$) favoring the dual therapy. After controlling for comorbidities and the APACHE II score predicted mortality, there was a 6.4-times increased risk of death associated with monotherapy (95% CI 1.9–21.7). However, all deaths occurred in patients with a PSI score over 90, and therefore there was no mortality difference between antibiotic strategies in milder disease. In addition, Baddour et al. (2004) reported that there was a substantial 14-day survival advantage in favor of the combination therapy when the analysis was restricted to patients with severe disease (23.4% vs. 55.3%, $p = 0.001$). Finally, Martínez JA et al. (2003) examined 409 patients with bacteremic pneumococcal pneumonia. The authors evaluated the outcome of patients according to the use of monotherapy with a β-lactam or combination therapy with a β-lactam plus a macrolide. After a stepwise logistic regression analysis, shock, age > 65 years, infection with resistant pathogens, and dual therapy were associated with mortality. The association between initial combination therapy and a lower in-hospital mortality rate remained significant after the exclusion of patients who died ≤ 48 h after admission (OR= 0.4, CI 0.17–0.92).

Although the consistent findings of these studies are very suggestive, they all suffer from one or more significant limitations, predominantly arising from the retrospective nature and the special population considered. The lack of controlled trial data in SCAP admitted to ICU is also a problem with respect to the assessment of the impact of antibiotic therapy on survival according to different levels of illness. Recently, Rodríguez et al. (2007) have shown, in a secondary analysis of a prospective multicenter and observational cohort study including 529 ICU patients with SCAP, that the adjusted 28-day in-ICU mortality was similar ($p = 0.99$) for the combination antibiotic therapy and the monotherapy in the absence of shock. On the other hand, in patients with shock, combination antibiotic therapy was associated with significantly higher 28-day adjusted in-ICU survival (hazard ratio= 1.69; 95% CI 1.09–2.6; $p = 0.01$). These data suggest that ICU patients at higher risk of death (in shock) will derive greater benefit from therapeutic interventions focusing survival (Rello and Rodríguez 2003). On the other hand, this finding strongly suggests that combination therapy does not increase ICU survival in CAP patients with lower risk of death (without shock). Thus, the potential benefits of combination therapy may be limited to the most severely ill patients.

The impact of the combination therapy on mortality in critically ill patients with SCAP is still debated by some investigators questioning whether dual therapy contributes to an improved survival, or if they are secondary to benefit from aggressive initial therapy (Hook et al. 1983), or conversely monotherapy could be indicative

of other limitation being placed on treatment. The benefit of combination therapy may be due to: (a) the presence of undetected copathogens, as atypical bacteria, (b) antibiotic synergy, or (c) immunomodulatory effects of macrolides or fluoroquinolones.

Suggested antibiotic regimens for inpatients include a β-lactam combined with a macrolide or monotherapy with a respiratory fluoroquinolone (Mandell et al. 2007). Although *S. pneumoniae* remains to be the leading pathogen in CAP, the rationale for a macrolide supplement or fluoroquinolone monotherapy lies in its ability to cover intracellular (atypical) pathogens as *Legionella pneumophila; Chlamydia pneumoniae, and Mycoplasma pneumoniae*. However, only coverage for *L. pneumophila* is recommended for patients in intensive care units.

Controversy still exists in the literature regarding the need to use antimicrobials covering atypical pathogens when initially treating hospitalized CAP patients. A recent international multicenter study (Arnold et al. 2007) observed a significant global presence (about 20%) of atypical pathogens in CAP. The authors reported that patients treated with atypical coverage had lower time to clinical stability (3.2 days vs. 3.7 days, $p < 0.001$), lower length of stay (6.1 days vs. 7.1 days, $p < 0.01$) and lower CAP-related mortality (3.8% vs. 6.4%, $p = 0.05$). However, since few patients required admission to ICU, the role of atypical microorganisms (different to *L. pneumophila)* in ICU patients with CAP remains unknown. In contrast, a meta-analysis (Shefet et al. 2005) found no difference in mortality between regimens with coverage of atypical pathogens and regimens without such a coverage, persisting in all subgroup analysis. In addition, there was a nonsignificant trend toward clinical success when covering the atypical pathogens, but this advantage disappeared when they evaluated high quality methodological studies alone.

The studies, which documented polymicrobial CAP, rely primarily on serologic conversion to diagnose atypical microorganisms, and no such search for atypical pathogens. Waterer et al. (2001a,b) observed that the coverage of these microorganisms did not contribute to the apparent benefit of dual therapy after the multivariate analysis. Our findings (Bodi et al. 2005) agree with the study of Mundy et al. (1998) who observed infrequent identification of atypical pathogens in a prospective series of patients hospitalized at the Johns Hopkins. Thus, the impact of the atypical pathogens in critically ill patients in SCAP seems to be scarce.

Although appealing, the possibility that the antibiotic combination had a synergistic effect on killing activity is difficult to support. There is certainly no data suggesting synergic activity of β-lactams and macrolides. In fact, there is good evidence that no such synergy exists for either cephalosporin/macrolide (Lin 2003) or penicillin/macrolide (Deshpande 2003) combination against *S. pneumoniae*. Thus, ICU patients with SCAP should receive a combination antibiotic therapy with β-lactam and macrolide or fluoroquinolone only to cover *Legionella pneumophila*.

Other possibility is the immunomodulatory effect of the macrolide or fluoroquinolone that is independent of their antibacterial activity. Although fluoroquinolones exhibit some immunomodulatory effects, it is the macrolides that have been most investigated. Experimental and clinical data on the anti-inflammatory effects of macrolides was recently reported (Waterer et al. 2001a,b; Lode et al. 2003; Schultz et al. 1998). Macrolides have shown to reduce the tumor necrosis factor (TNF) and IL-6 production by whole blood after stimuli with heat-killed pneumococci (Schultz

et al. 1998). In addition, macrolides appear to enhance polimorphonuclear activity against pneumococci even when the isolates are macrolide resistant, (Cuffini et al. 2002) and to reduce the IgG-mediated lung damage in rats, again probably by the reduction in both TNF and IL-1β release from the alveolar macrophages (Tamaoki et al. 1999). It is worth noting that macrolides have become widely used in panbronchiolitis and cystic fibrosis with their efficacy attributed to immunomodulation rather than antibacterial effects (Schultz 2004). All fluoroquinolones modestly impair rat macrophage chemotaxis (Labro 2000) and transendothelial neutrophil and monocyte migration (Uriarte et al. 2004). However, only moxifloxacin and gatifloxacin inhibited IL-8 production. These actions on endothelial cells may contribute to the inhibitory effects of fluoroquinolones seen in experimental sepsis models, but their clinical relevance is uncertain (Parnham 2005).

The controversy about which is the best dual therapy for SCAP treatment remains unresolved. Several studies (Waterer et al. 2001a,b; Baddour et al. 2004; Martínez et al. 2003) have found that the use of a β-lactam plus a macrolide is associated with significantly lower mortality. Conversely, few studies have examined the combination of β-lactam with fluoroquinolones versus other combination therapies. A recent study (Mortensen et al. 2006) observed that the empiric use of a β-lactam plus a fluoroquinolone was associated with higher 30-day mortality when compared to other guideline-concordant regimes for patients hospitalized with SCAP. This study has the common limitations of observational and retrospective analysis. However, it is in accordance with a recent study of Metersky et al. (2007) who studied the relationship between the initial antibiotic regimen and mortality in a large cohort of Medicare beneficiaries who were hospitalized with bacteremic pneumonia. These authors observed that, compared to patients who received no atypical coverage, patients treated with a macrolide had a lower risk of adjusted in-hospital mortality (OR = 0.59, 95% CI 0.40–0.88; $p = 0.01$) and of 30-day mortality (OR = 0.61, 95% CI 0.43–0.87; $p = 0.007$). Interestingly, there were no significant associations between fluoroquinolones and patients outcome (OR = 0.94, 95% CI 0.69–1.28). Conversely, other studies (Gleason et al. 1999; Burgess and Lewis 2000) found no significant differences between the use of this combination and others. Nevertheless, the mortality rate observed in these trials is much lower than the mortality rate reported for CAP critically ill patients, and it is possible that the patients included in these trials are different from those included in observational studies. Since most studies showing the importance of adding a macrolide to a β-lactam regimen for SCAP are retrospective, only a prospective randomized double-blind trial will resolve whether combination therapy is truly more effective than monotherapy for SCAP. The strength of the association demonstrated in clinical trials provides significant justification to suggest that combination therapy with a macrolide should be the first line option of antibiotic treatment for ICU patients with SCAP.

Finally, in patients with certain risk factors like severe structural lung disease (bronchiectasias), recent antibiotic exposure, or recent hospitalization, *P. aeruginosa* can be present in the setting of SCAP (Barlett et al. 2000). Rello et al. (2003), in a recent study, have shown that patients with SCAP who need intubation have a significant

risk of *Pseudomonas aeruginosa* or *Legionella* infection. Recently, Bodí et al. (2005) showed that COPD, malignancy, and rapid X-ray spread were factors associated with severe pneumonia by *P.aeruginosa*. Due to all of these findings and the high mortality rate of *P.aeruginosa* pneumonia, in all intubated patients with SCAP and risk factors (COPD, malignancy, previous antibiotic therapy, or rapid X-ray spread), we recommend empirical initial antibiotic treatment with two antipseudomonal agents. However, this initial antibiotic treatment should provide appropriate coverage to penicillin-resistant *Streptococcus pneumoniae* and *Legionella spp*., the most frequent pathogens observed in CAP.

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Chapter 8
Dose Adjustment and Pharmacodynamic Considerations for Antibiotics in Severe Sepsis and Septic Shock

Andrew Udy, Jason Roberts, Robert Boots, and Jeffrey Lipman

8.1 Introduction

Prescription of antibiotics in the critically ill is a complex process. It requires consideration of the likely causative organism/s, an appreciation of the underlying pathophysiological state and how this dynamic process influences drug distribution, metabolism and elimination. Associated organ dysfunction, fluid shifts and altered immune status are common, and each can influence the efficacy of many antimicrobial agents. This chapter will focus on the prescription of antibiotics commonly used in the treatment of critically ill patients with severe sepsis or septic shock. Early appropriate antimicrobial therapy remains the cornerstone of successful treatment in this group (Kollef et al. 1999; Ibrahim et al. 2000; Garnacho-Montero et al. 2003; Valles et al. 2003). Pharmacokinetic and pharmacodynamic principles will be reviewed, with the aim to optimize dosing and improve outcome. There are similar considerations concerning the use of antifungal and possibly antiviral agents in the critically ill; however, a wider discussion of these agents is beyond the scope of this chapter.

8.2 Applied Clinical Pharmacology

Successful treatment of an infection involves optimizing the interaction between the host, the pathogen and the antibiotic (Nicolau 1998). Recommended antibiotic regimens have often been derived from studies on healthy volunteers or non-critically ill patient groups, making extrapolation to dosing in severe sepsis difficult. Key considerations involve a variety of pathophysiological changes associated with sepsis, and their effects on the pharmacokinetic and pharmacodynamic parameters of the chosen antibiotic. This process is dynamic, and ongoing evaluation of illness severity, organ function and the resuscitation status are necessary to allow the timely adjustment of antibiotic dosing.

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8.2.1 Pharmacokinetic Considerations

Pharmacokinetics (PK) refers to the study of changes in drug concentration over time. The primary PK parameters of importance to antibiotics include:

- *Volume of distribution (Vd)*. Apparent (hypothetical) volume of fluid that contains the total amount of administered drug, at the same concentration as that measured in plasma.
- *Clearance (CL)*. Volume of plasma effectively cleared of the drug per unit time. Total clearance is the sum of the clearances for each eliminating organ or tissue.
- *Plasma half-life ($T_{1/2}$)*. Time required to decrease the plasma concentration by one half.
- C_{max}. The peak concentration achieved by a single dose.
- C_{min}. The lowest concentration during a dosing period.
- *Area under the curve (AUC)*. The area under the plasma concentration–time curve.

Antibiotics can be classified by their affinity for water (hydrophilic) or lipids (lipophilic). Where hydrophilic drugs are typically distributed in extracellular water, lipophilic drugs may distribute intracellularly and into body fat, favouring bioaccumulation. Protein binding of antibiotics either to albumin or alpha-1 acid glycoprotein (AAG) effects their distribution throughout the body and their biological effect. More highly bound drugs generally have a longer duration of action and a lower volume of distribution. The free drug concentration is important for clinical effect, and is influenced by plasma protein levels and binding competition from other drugs. Consideration of these basic pharmacokinetic factors can be used to determine whether appropriate concentrations of the antibiotic are being delivered to the target area (Nicolau 2003).

8.2.2 Pharmacodynamic Considerations

The pharmacodynamic (PD) effect of antibiotics refers to the ability of the antibiotic to kill or inhibit the growth of the infective organism. How this is effected by an antibiotic's PK properties is referred to as "pharmacokinetics-pharmacodynamics or PK–PD characteristics" but will be termed "pharmacodynamics" (PD) here. PD parameters include:

- $T > MIC$. The time for which a drug's concentration remains above the minimum inhibitory concentration (MIC) for bacterial growth during a given dosing period
- C_{max}/MIC. The ratio of the maximum antibiotic concentration ($C_{\max}$) to the MIC of the pathogen
- AUC_{0-24}/MIC. The ratio of the area under the concentration time curve during a 24-hour time period to the MIC of the pathogen (see Fig. 8.1)

Pharmacodynamically, the rate and extent of an antibiotic's bactericidal activity is dependent on the interaction between drug concentrations at the site of infection, bacterial load, phase of bacterial growth and the MIC for the pathogen (Nicolau 2003). It follows that a change in any of these factors will affect the PD profile of the antibiotic against a particular pathogen and may affect the outcome of therapy.

8.3 Kill Characteristics of Different Antibiotic Classes

Different antibiotic classes can be generally classified by their bacterial killing characteristics: concentration-dependent killing and time-dependent killing (Fig. 8.1 and Table 8.1). An understanding of these PD properties should be considered for appropriate dose adjustment in individual patients.

These kill characteristics have been determined from in vitro and ex vivo studies and describe the PK measurements that represent optimal bactericidal activity (Nicolau 2003). The β-lactam group of antibiotics have a time-dependent kill characteristic, and as such T > MIC is the best predictor of antibiotic efficacy (Nuytinck et al. 1988; Craig 1998). Maintaining adequate plasma concentrations throughout the dosing interval is essential. In contrast, aminoglycosides have a concentration-dependent (or time-independent) kill characteristic where effect is determined by C_{max}/MIC (Craig 1984; Schentag et al. 1984; Vogelman and Craig 1985, 1986; Moore et al. 1987; Vogelman et al. 1988; Leggett et al. 1989; Roosendaal et al. 1989; Bakker-Woudenberg and Roosendaal 1990; Bouvier d'Yvoire and Maire 1996; Mouton and Vinks 2005). The higher the peak concentration achieved above the MIC, the greater will be the bacterial kill. Fluoroquinolones are more complex, being initially reported to be C_{max}/MIC dependent, although subsequent studies have also found that AUC_{0-24}/MIC is important (Forrest et al. 1993; Gunderson et al. 2001). The pharmacodynamic parameters associated with efficacy for other antibiotics are described in Table 8.1.

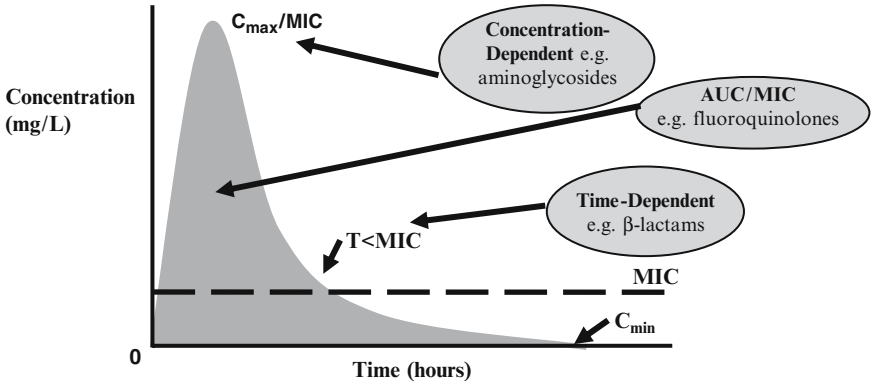

Fig. 8.1 Pharmacokinetic and pharmacodynamic parameters of antibiotics on a concentration vs. time curve

Table 8.1 General PK and PD characteristics of various antibiotics

Antibiotic	Vd (L/kg)	Serum half-life ($T_{1/2}$, h)	Protein binding	Clearance	Post-antibiotic effect	Kill characteristic	PD parameter	Tissue penetration
Aminoglycosides (Mangione and Schentag 1980; Pharmacia Australia 2005)	0.2–0.3	2–3	Low	Renal (Chambers and Sande 1996)	Yes	Concentration dependent	C_{max}/MIC	Poor
β-lactams (Swabb et al. 1983; Barbhaiya et al. 1992; Lipman et al. 1999a, 2001, 2003; Levitt 2003)	ECW	0.5–2 h (longer for ceftriaxone (Stoeckel 1981))	Low (except ceftriaxone (Stoeckel 1981) and flucloxacillin)	Renal (McKindley et al. 1996) (some exceptions)	Gram (+) organisms only	Time dependent	T > MIC	Variable
Carbapenems (Mouton et al. 2000)	ECW	1 h (Ertapenem – 4 h)	Low (except Ertapenem)	Renal	Yes	Time dependent (Turnidge 1998b)	T > MIC	Good
Vancomycin (Cunha 1995a)	0.2–1.25	4–6	30–55%	Renal (Rybak 2006)	Yes (MacKenzie and Gould 1993)	Concentration and time dependent	AUC_{24}/MIC	Poor
Teicoplanin (Brogden and Peters 1994; Wilson 2000; Barbot et al. 2003)	0.9–1.6	80–160	90%	Renal	Yes (MacKenzie and Gould 1993)	Concentration and time dependent	AUC_{24}/MIC	Poor
Quinupristin/dalfopristin (Bernard et al. 1994; Chant and Rybak 1995; MIMS Australia 2005a)	Q = 0.45 *D = 0.24*	1.3–1.5	Q = 23–32% *D = 50–56%*	Hepatic	Yes (E. faecium (Aeschlimann and Rybak 1998) & *S. aureus* (Griswold et al. 1996))	Concentration dependent	AUC_{24}/MIC	Poor

Daptomycin (Woodworth et al. 1992; Dvorchik et al. 2002, 2003)	0.09	5.8–11.6	92%	Renal	Yes	Concentration dependent	C_{max}/MIC	Poor
Tigecycline (Meagher et al. 2005a,b; Muralidharan et al. 2005; Rubinstein and Vaughan 2005)	7–10	37–66	73–79%	Hepatic	Yes (Projan 2000)	Time dependent	AUC_{24}/MIC	Excellent
Telithromycin (Namour et al. 2002; Gattringer et al. 2004; Kasbekar and Acharya 2005; Nguyen and Chung 2005)	2.7–2.9	10–13	60–70%	Renal	Yes	Concentration dependent (Odenholt et al. 2001; Jacobs et al. 2003)	C_{max}/MIC	Variable
Clindamycin (Fass and Saslaw 1972; DeHaan et al. 1973; Gordon et al. 1973; Mann et al. 1987b; Rovers et al. 1995; Mueller et al. 1999)	0.6–1.2	1.5–5	65–90%	Hepatic	Yes (*B. anthracis*) (Athamna et al. 2004)	Time dependent	T > MIC	Excellent
Linezolid (MacGowan 2003; Stalker et al. 2003; Boselli et al. 2005)	0.5–0.6	3.5–7	31%	Hepatic and renal	Yes (*B. anthracis*) (Athamna et al. 2004)	Time dependent	AUC_{24}/MIC	Good
Ciprofloxacin (MICROMEDEX 1974–2005; Brittain et al. 1985; Bennett et al. 1994)	1.2–2.7	3 (4–5 in the elderly)	20–40%	Hepatic	Yes	Concentration and time dependent	AUC_{24}/MIC	Excellent (Smith et al. 2000)

(continued)

Table 8.1 (continued)

Antibiotic	Vd (L/kg)	Serum half-life ($T_{1/2}$, h)	Protein binding	Clearance	Post-antibiotic effect	Kill characteristic	PD parameter	Tissue penetration
Levofloxacin (Chien et al. 1997, 1998)	0.9–1.36	6–8.9	24–38%	Renal	Yes	Concentration and time dependent	AUC_{24}/MIC	Excellent (Smith et al. 2000)
Moxifloxacin (Chien et al. 1997; Stass et al. 1998; Stass 1999)	2.45–3.6	9.3–15.6	39–52%	Hepatic	Yes	Concentration and time dependent	AUC_{24}/MIC	Excellent (Smith et al. 2000)
Gatifloxacin (MICROMEDEX 1974–2005; Nakashima et al. 1995)	1.98–2.3	6.5–9.6	20%	Hepatic	Yes	Concentration and time dependent	AUC_{24}/MIC	Excellent (Smith et al. 2000)
Azithromycin (Zuckerman 2004; Chiu et al. 2002)	13–31	40–68	7–50%	Hepatic	Yes	Concentration and time dependent	AUC_{24}/MIC	Excellent

ECW extracellular water

8.3.1 Post-antibiotic Effect

Most antibiotics demonstrate a post-antibiotic effect (PAE): the continued suppression of bacterial growth for prolonged periods when drug concentrations fall below the MIC of the bacteria (Rodvold 2001). β-lactams demonstrate a modest PAE against gram-positive organisms but no PAE (except carbapenems) against gram-negative organisms (Bustamante et al. 1984; Tauber et al. 1984; Gudmundsson et al. 1986; Craig and Ebert 1991; Fantin et al. 1991; Craig 1993, 1998; Tessier et al. 1999; Rodvold 2001; Drusano 2004). Aminoglycosides demonstrate a significant PAE (>3 h), the duration of which is concentration dependent (Craig 1984; Vogelman and Craig 1985, 1986; Moore et al. 1987; Vogelman et al. 1988; Roosendaal et al. 1989; Bakker-Woudenberg and Roosendaal 1990; Mouton and Vinks 2005). Fluoroquinolones also possess a prolonged PAE (Lode et al. 1998; Turnidge 1998a). Interestingly, the PAE of an agent can change in states of altered immune function, being reduced in neutropenia (Klatersky 1986; Kapusnik et al. 1988; Fisman and Kaye 2000) or in critically ill patients with sepsis. However, this has not been widely characterized for all antibiotics.

8.3.2 Post-β-lactamase Inhibitor Effect

Post-β-lactamase inhibitor effect (PLIE) refers to a period of continued suppression of bacterial growth after removal of a β-lactamase inhibitor (also known as a suicide inhibitor) (Thorburn et al. 1996). It has been shown to occur in vitro for amoxicillin plus clavulanate (Thorburn et al. 1996) and more recently ceftazidime plus sulbactam (Lavigne et al. 2004). This effect may be utilized in treating extended-spectrum β-lactamases (ESBLs), and enable reduced β-lactam doses (Thorburn et al. 1996). However, scarce clinical evidence exists for the clinical relevance of PLIE.

8.3.3 Inoculum Effect

The inoculum effect refers to the activity of certain antibiotics in the presence of a large bacterial load (initially described with *E. coli*). High bacterial concentrations make third generation β-lactams less effective (Kim 1985), and is thought to be due to the production of β-lactamases (Levison 1995). Broader spectrum β-lactams, including fourth generation cephalosporins have a clinical advantage in this respect (Phelps et al. 1986; Hoepelman et al. 1993; Jauregui et al. 1993). In clinical practice, the identification of bacterial load is difficult and thus dose changes on the basis of these observations are not indicated at this time. However, this does underscore the importance of early effective broad-spectrum antibiotic therapy in the critically ill.

8.4 Sepsis

While a definition and conceptual framework for sepsis is continuing to evolve, the process is most widely thought of as a systemic inflammatory response syndrome (SIRS) triggered by an overwhelming infection (Bone et al. 1992; Calandra and Cohen 2005). Severe sepsis occurs upon failure or dysfunction of at least one organ, and septic shock is defined by hypotension in the setting of severe sepsis, unresponsive to fluid resuscitation. The pathogenesis of sepsis is complex (Parrillo 1993; Grocott-Mason and Shah 1998; Calandra and Cohen 2005; Rice and Bernard 2005), and research in this area is an ongoing process. While much effort has been directed at cellular and humoral targets to limit the associated inflammatory and coagulation cascades (Rice and Bernard 2005), none of these interventions have been found to be as important or effective as optimal early antibiotic therapy (Kollef et al. 1999; Garnacho-Montero et al. 2003; Harbarth et al. 2003; Hugonnet et al. 2003; MacArthur et al. 2004; Rice and Bernard 2005; Kumar et al. 2006). The host's recognition of and response to the invading microorganism largely determine the degree of pathophysiological disturbance and clinical sequelae. Therefore, knowledge of the pathophysiological and pharmacokinetic changes in sepsis are necessary to ensure optimal prescription of antibiotics (Kieft et al. 1993; Joukhadar et al. 2001).

8.4.1 Pathophysiological Changes in Sepsis that can Affect Pharmacokinetics

Figure 8.2 schematically depicts the pharmacokinetic changes that can occur due to the altered pathophysiology during sepsis.

8.4.1.1 Altered Capillary Permeability

Endotoxins from bacteria or fungi can stimulate the production of a variety of endogenous mediators (van der Poll 2001), which may effect the vascular endothelium directly or indirectly. This can result in either vasoconstriction or vasodilatation with altered distribution of blood flow, endothelial damage and increased capillary permeability. This capillary leak syndrome results in fluid shifts from the intravascular compartment to the interstitial space (Nuytinck et al. 1988; Gosling et al. 1994) known as "third spacing". For water-soluble drugs, this will result in an increase in Vd, decreasing the plasma concentration. It is uncommon for the Vd of lipophilic agents to be affected by "third spacing".

8.4.1.2 Hypoalbuminaemia

Hypoalbuminaemia is a frequently encountered problem in the critically ill. It may develop de novo in severe sepsis as a consequence of increased protein capillary leak, fluid loading, increased catabolism and under-feeding. A low plasma albumin

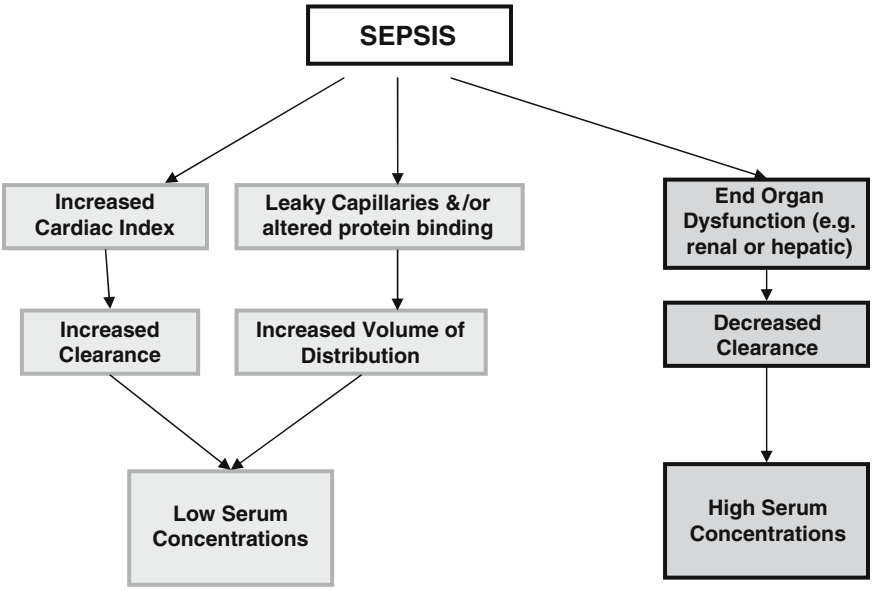

Fig. 8.2 Basic pathophysiological changes that can occur during sepsis and their subsequent pharmacokinetic effect

concentration results in a reduction in oncotic pressure and encourages fluid extravasation and interstitial oedema formation. This will increase the Vd of hydrophilic antibiotics such as aminoglycosides. The Vd will also be increased for agents that are highly albumin bound and renally excreted (e.g. ceftriaxone and teicoplanin), resulting in a greater free-fraction of drug and higher renal clearances (Rowland 1990; Pea and Furlanut 2001; Barbot et al. 2003).

Recent work in critically ill patients with severe sepsis treated with 2-g IV ceftriaxone (protein binding ~ 90%) once daily has demonstrated an increase in Vd and an almost doubling of drug clearance in those patients with normal renal function but severe hypoalbuminaemia (Joynt et al. 2001). This implies that in patients with severe hypoalbuminaemia and normal renal function, optimum dosing with ceftriaxone may involve either shortening the dosage interval or administration by continuous infusion (Joynt et al. 2001). An increase in the Vd of amikacin (protein binding ~10%) has also been noted in patients with haematological malignancies and hypoalbuminaemia (Romano et al. 1999). It may also have a role in contributing to low trough levels in critically ill children treated with teicoplanin (Sanchez et al. 1999). In summary, consideration should be given to different dosing regimes for hydrophilic antimicrobials in critically ill patients with severe hypoalbuminaemia, to ensure adequate drug concentrations.

8.4.1.3 Post-surgical Drains

Indwelling surgical drains are a source of hidden drug loss. Patients post major abdominal and thoracic surgery can lose drug via this route (Buijk et al. 2002b),

and it may contribute to sub-therapeutic levels of hydrophilic antibiotics. The effect is an increase in Vd and clearance perhaps necessitating higher and/or more frequent doses in these patients.

8.4.1.4 Burns

Patients with severe burns deserve individual consideration. Not only do they have complex pathophysiological changes, they are also prone to recurrent infection. The first phase of the burns injury lasts approximately 48 h and is characterized by intra-vascular hypovolaemia secondary to loss of protein-rich fluid across the capillary membrane. This may result in a reduction in renal pre-load and reduced elimination of renally cleared antibiotics. Increasing interstitial oedema and ongoing fluid loading can result in an increase in the Vd of hydrophilic antibiotics, leading to low plasma concentrations. The second phase is characterized by a hypermetabolic state, with a subsequent increase in renal blood flow and glomerular filtration rate (Lesne-Hulin et al. 1997; Weinbren 1999) lasting several days to weeks.

Several pharmacokinetic studies (Zaske et al. 1976; Loirat et al. 1978; Brater et al. 1986; Walstad et al. 1988; Yoshida et al. 1993; Lesne-Hulin et al. 1997; Weinbren 1999) have shown increased clearance of hydrophilic and moderately lipophilic agents during this second phase. As such, higher doses of aminoglycosides are required in burns patients (Hollingsed et al. 1993), and more frequent dosing of glycopeptides is also advocated (Boucher et al. 1992). Regular measurement of trough concentrations is essential to avoid sub-therapeutic levels (Rice 1992). Further detailed review of pharmacokinetic considerations for different antibiotic agents in burns patients is beyond the scope of this chapter, but given the complex pathophysiological changes that occur, and the wide inter-individual variation, therapeutic drug monitoring (TDM) is recommended in this setting.

8.4.1.5 Creatinine Clearance can be Increased or Decreased

Serum creatinine concentration alone is a poor measure of renal function. In the critically ill population, elevated creatinine clearance has been demonstrated despite a serum value within the normal range (Lipman et al. 2001, 2002). Hypotension is a common clinical manifestation of the inflammatory response associated with sepsis, and initial volume loading with intravenous fluids is a cornerstone of early treatment (Rivers et al. 2001). If hypotension persists, vasoactive agents (some of which may be “inoconstrictors”) are often utilized (Dellinger et al. 2008) producing higher than normal cardiac indices in these patients (Parrillo et al. 1990; Parrillo 1993; Pea et al. 2000). In the absence of significant organ dysfunction, this results in increased renal blood flow and higher creatinine and drug clearance (Di Giantomasso et al. 2002, 2003, 2005) and is a major reason to consider modification of drug dose/dosing intervals in the critically ill (Pinder et al. 2002; Lipman et al. 2003).

As sepsis progresses, significant myocardial depression can occur which leads to a decrease in organ perfusion (Parrillo et al. 1990). Myocardial insufficiency and abnormalities of the macrovascular circulation are compounded by failure of the microcirculation. The resultant end-organ cellular injury may progress to multiple organ dysfunction syndrome (MODS) (Marshall 2001). This often includes renal and/or hepatic dysfunction with failure of homeostatic and excretory mechanisms. Drug elimination half-lives can be prolonged and result in increased antibiotic concentrations and/or accumulation of metabolites (Power et al. 1998).

8.4.1.6 Determining Renal Function in Critically Ill Patients with Sepsis

Accurate knowledge of renal function is a critical factor for dosing antibiotics, as most of these agents are eliminated by the kidney. However, assessment of renal function in the critically ill patient with sepsis is not straightforward. Accepted norms for calculating creatinine clearance (as a marker of renal function) in "normal" ward patients, such as the Cockroft-Gault method (Cockroft and Gault 1976), and the Modified Diet in Renal Disease (MDRD) study (Levey et al. 1999) are not accurate in the critically ill (Roberts et al. 2005). As such, the most effective way to calculate renal function remains using either an 8-, 12- or 24-h creatinine clearance collection (Wells and Lipman 1997a,b; Pong et al. 2005), although recent work has suggested a 2-h creatinine clearance may be an adequate substitute (Herrera-Gutierrez et al. 2007). If acute renal failure occurs, such that the patient needs renal replacement therapy (RRT) with either intermittent haemodialysis or continuous renal replacement therapy, further considerations for appropriate antibiotic dosing are introduced.

8.4.1.7 Renal Replacement Therapy

Various methods of RRT are available to remove nitrogenous waste products and fluid, and the subsequent effect on antibacterial pharmacokinetics is complex. A detailed review of this subject is beyond the scope of this chapter, although for RRT, the extent of any direct change in drug clearance has often not been investigated. Metabolic and homeostatic factors that need consideration include changes in total body water, albumin and acute phase protein levels, muscle mass, blood pH, bilirubin concentration, renal, hepatic and cardiac function (Joy et al. 1998a,b). The size of the molecule, degree of protein binding, route of elimination, electrostatic charge and Vd will all influence the potential effects of RRT (Joy et al. 1998a,b; Bugge 2001). Technical factors including the type of filter used, blood flow rate, ultrafiltration rate, use of counter current dialysis and membrane interactions, and whether the dialysis is intermittent or continuous are also important considerations (Freebairn and Lipman 1993a,b; Schetz et al. 1995; Joy et al. 1998a,b; Pinder et al. 2002; Trotman et al. 2005). Often the need for RRT is transient in the septic patient, and as native renal function improves, the challenge for the practising clinician is to adjust doses accordingly to ensure therapeutic drug concentrations.

8.5 Duration of Antibiotic Therapy for Critically Ill Patients with Sepsis

Little data exist to rationally guide the duration of antibiotic treatment in critically ill patients. However, increasing awareness of the risks of prolonged courses of broad spectrum agents has led towards shortening the length of treatment. Most courses of antibiotics in ICU are given for an empirical duration based upon site of infection and pathogen. Some data exist to modify durations based upon clinical response.

The Infectious Disease Society of America (IDSA) guidelines on management of community-acquired pneumonia (CAP) in adults (Bartlett et al. 2000) suggests that length of treatment should be guided by clinical factors, such as response, severity and co-morbidities. Specifically, they note that pneumonia caused by *Streptococcus pneumoniae* should be treated until the patient has been afebrile for at least 72 h. Similar recommendations are made for management of neutropenic patients with cancer based upon duration of fever and neutrophil count (Bartlett et al. 2000). Published guidelines can be consulted when considering other systemic infections (Therapeutic Guidelines Antibiotic 2006).

The Surviving Sepsis Campaign (Dellinger et al. 2008) recently produced updated treatment guidelines for the management of severe sepsis and septic shock. These guidelines recommend a typical seven- to ten-day course of antibiotic therapy that should be guided by microbiological results and clinical response. Importantly, the appropriateness of the anti-infective therapy should be reviewed regularly to ensure adequacy of treatment and allow de-escalation where possible (Dellinger et al. 2008). The pathophysiological sequelae of severe sepsis and septic shock are transient and dynamic in nature, and changes in drug distribution, metabolism and elimination can be expected throughout the patients' course. Although there is little literature to guide specific dosage adjustment in critically unwell patients – particularly for many of the newer antimicrobials – daily review of the appropriateness of antibiotic dosage should be undertaken.

8.6 Implications of Under-dosing in Sepsis

The most important clinical consequence of under-dosing in severe sepsis and septic shock is treatment failure. Effective antibiotic therapy is essential to optimize patient outcome (Cunha 1995b; Kollef et al. 1999; Garnacho-Montero et al. 2003; Harbarth et al. 2003; MacArthur et al. 2004). Developing dosing regimens that maximize the rate of response in patients with sepsis is important for accelerating patient recovery, but also in minimizing the development of antibiotic resistance. Under-dosing with β-lactams may facilitate the development of antibiotic resistance, particularly if plasma concentrations fall below the threshold (MIC) for more than half the dosing interval (Fantin et al. 1994). Inappropriately low dosing of ciprofloxacin has also been associated with the emergence of resistant bacterial strains (particularly Enterococci,

pseudomonas and MRSA) (Hyatt and Schentag 2000; MacGowan et al. 2000; Zhou et al. 2000), and for gram-negative bacteria, this may occur when $AUC_{0-24h}/MIC < 100$ (Thomas et al. 1998; Schentag 1999). Other studies have also shown that a high AUC_{0-24}/MIC can reduce the development of resistance with quinolone antibiotics (Ross et al. 2001; Tam et al. 2005; LaPlante et al. 2007).

The mutant prevention concentration (MPC) is defined as the drug concentration required to prevent emergence of all single step mutations in a population of at least 10^{10} bacterial cells (Zhao and Drlica 2001). Therefore, at drug concentrations above the MPC, at least a second step mutation is required for bacterial survival. Consequently, the MPC represents an important target for determining optimal dosing regimens that will minimize the selection of drug-resistant organisms (Dong et al. 1999). If drug levels are maintained at concentrations between the MIC and MPC for an organism, there is selective antibiotic pressure favouring the growth of single-step resistant mutants. This range of antibiotic concentrations is referred to as the mutant selection window (MSW) (Zhao and Drlica 2001) and has been defined for many of the fluoroquinolones and some β-lactams against various organisms (Firsov et al. 2003, 2006; Knudsen et al. 2003; Zinner et al. 2003; Croisier et al. 2004; Olofsson et al. 2006). The clinical relevance of the MSW remains unclear although future dosing regimes will likely focus on optimizing drug exposure to minimize the development of antibioitic resistance (Olofsson and Cars 2007).

Sub-optimal dosing of aminoglycosides may lead to adaptive resistance by virtue of a period of reduced drug uptake by the microorganism. Dosing to achieve improved C_{max}/MIC ratios appear to reduce this (Daikos et al. 1991; Xiong et al. 1997), although this is probably more a function of extended dosing intervals. In vitro data from Henderson-Begg et al. have also demonstrated that bacterial mutability can occur with sub-therapeutic aminoglycoside exposure (Henderson-Begg et al. 2006). Development of resistance has also been documented for carbapenems (Fink et al. 1994), and extended infusions may be more beneficial (Roberts et al. 2007b).

Existing dosing regimes for many antibiotics used in crtically ill patients will need re-evaulation in the context of onging investigation in this area. Many patients may be potentially under-dosed, with subsequent selection of resistant mutants. Higher doses, albeit within the limits of patient tolerability, must be considered in order to optimize patient response and prevent the development of further resistant infections.

8.7 Antibiotic Classes

Below, aminoglycosides, β-lactams, glycopepetides, fluoroquinolones and other various antibiotics used in critically ill patients with sepsis and septic shock are considered. General PK and PD characteristics have been tabulated for ease of reference for the reader (Table 8.1). A summary of the potential effects of the septic state on drug handling, clinical application and dosing implications for critically ill patients is also addressed (see Table 8.2).

Table 8.2 Changes in PK characteristics with sepsis and organ dysnfunction, and implications for dosing

Antibiotic	Increase in Vd with sepsis	Decrease in C_{max} with fluid shifts	Clearance in sepsis without organ dysfunction	Effects of organ dysfunction	Possible dosing adjustments in severe sepsis	Therapeutic drug monitoring
Aminoglycosides	Yes (Nuytinck et al. 1988; Gosling et al. 1994; Buijk et al. 2002a)	Yes	↑ (Beckhouse et al. 1988; Bakker-Woudenberg and Roosendaal 1990; Triginer et al. 1990; Dager 1994)	↓ CL with renal dysfunction	↑ dose/↑ dosing frequency (with rapid CL)	Yes (Prins et al. 1993; Begg et al. 1995; Nicolau et al. 1995)
β-Lactams	Yes (Kieft et al. 1993; Joynt et al. 2001; Lipman et al. 2001)	Yes	↑	↓ CL with renal dysfunction (Barbhaiya et al. 1992; McKindley et al. 1996; Lipman et al. 2003)	↑ dosing frequency/ infusion	No
Carbepenems	Yes (Mouton et al. 2000; Kitzes-Cohen et al. 2002; Novelli et al. 2005)	Yes	↑ (Mouton et al. 2000; Kitzes-Cohen et al. 2002; Novelli et al. 2005)	↓ CL with renal dysfunction (Gibson et al. 1985; Konishi et al. 1991; Leroy et al. 1992; Mouton et al. 2000)	↑ dosing frequency/ infusion	No
Vancomycin	Yes	Yes	↑	↓ CL with renal dysfunction (Riley 1970; Matzke et al. 1984; Elting et al. 1998)	↑ dose (40 mg/kg/ day IV)	Yes (ensure trough > 15 mg/L)
Teicoplanin	Yes	Yes	↑	↓ CL with renal dysfunction	6 mg/kg IV 12-hourly × 3, then 6 mg/kg IV daily	Yes (Wilson 2000; Rybak 2006)

Tigecycline	Unlikely	Unlikely	Unlikely	↓ CL with cholelithiasis	100 mg LD, then 50 mg IV 12-hourly	No
Quinupristin/dalfopristin	Yes	Yes	Unknown	Unknown	7.5 mg/kg IV 8-hourly	No
Daptomycin	Yes	Yes	↑	↓ CL with moderate renal dysfunction	4 mg/kg IV daily	No
Telithromycin	Unknown	No	↑	↓ CL with moderate renal dysfunction	800 mg PO daily	No
Clindamycin	No	Yes	Unknown	↓ CL with hepatic dysfunction	600 mg IV 8-hourly	No
Linezolid	Yes	Yes	↑(Adembri et al. 2008)	No dose adjustment required	600 mg IV 12-hourly	No
Ciprofloxacin	No	Yes	Not influenced	↓ CL with renal impairment and intra-abdominal pathology	↑ Frequency dosing (400 mg IV 8-hourly)	No
Levofloxacin	No	Yes	Unknown	↓ CL with renal dysfunction	↑ dose (500–1000 mg IV daily)	No
Moxifloxacin	No	Yes	Not influenced		400 mg IV daily	No
Gatifloxacin	No	Yes	Unknown	↓ CL with renal dysfunction	400 mg IV daily	No
Azithromycin	Unlikely	Unlikely	Unlikely	No dose adjustment with hepatic impairment (Mazzei et al. 1993)	500 mg IV daily	No

CL clearance; *PO* per oral dose; *IV* intra-venous dose; *LD* loading dose

8.7.1 Aminoglycosides

Aminoglycosides (gentamicin, tobramycin and amikacin) have three important properties: (a) high, widely spaced doses cause less toxicity than smaller more frequent doses (Zhanel and Ariano 1992; Barza et al. 1996; Munckhof et al. 1996; Ali and Goetz 1997; Bailey et al. 1997; Olsen et al. 2004); (b) high doses produce better kill curves and clinical response (Moore et al. 1987) and (c) a significant PAE, limiting bacterial re-growth should drug concentrations fall below the MIC (Vogelman and Craig 1985, 1986; Moore et al. 1987; Vogelman et al. 1988; Roosendaal et al. 1989; Rodvold 2001; Olsen et al. 2004; Mouton and Vinks 2005). Single daily dosing for aminoglycoside antibiotics (extended interval dosing – EIAD) has been shown in prospective human clinical trials (Marik et al. 1991a,b; Van der Auwera et al. 1991; Prins et al. 1993; Olsen et al. 2004) and numerous meta-analyses (Barza et al. 1996; Munckhof et al. 1996; Ali and Goetz 1997; Bailey et al. 1997) to produce less toxicity and comparable if not superior clinical outcomes. This is also established in patients with organ dysfunction (Barclay et al. 1994; Hatala et al. 1997; Fisman and Kaye 2000).

In vitro studies have shown enhanced bacterial phagocytosis by leukocytes after exposure to aminoglycosides (post-antibiotic leukocyte enhancement – PALE) (McDonald et al. 1981). Neutropenia or a low leukocyte count, as shown in animal models (Kapusnik et al. 1988), may render aminoglycosides less effective (Klatersky 1986). However, specific dose modifications cannot be commended at this time.

Administration of high dose (7 mg/kg if normal renal function; amikacin requires 28 mg/kg) once-daily aminoglycosides is recommended. However, in our experience, where renal function is supra-normal and trough-level monitoring suggests that doses higher than 7 mg/kg are required, increasing the frequency to 18-hourly rather than an increased dose should be considered. The C_{max}/MIC ratio conferred by 7 mg/kg is generally at least 10, thereby maximizing bacterial killing (Kashuba et al. 1999; Rodvold 2001; Buijk et al. 2002a). Higher doses probably have no additional bactericidal effect. With renal impairment, dose reductions to 3–5 mg/kg 24-hourly may be required. Longer dosing intervals (36- or 48-hourly) may be necessary if this lower dose is inadequately excreted. Monitoring by trough levels should occur in this situation, although alternative agents can be considered. Variability in peak aminoglycoside plasma concentrations in critically ill patients (Zaske et al. 1980; Chelluri and Jastremski 1987; Mann et al. 1987a; Beckhouse et al. 1988; Dasta and Armstrong 1988; Fuhs et al. 1988; Chelluri et al. 1989; Reed et al. 1989; Townsend et al. 1989; Triginer et al. 1990; Dager 1994) may be due to an increased Vd (Table 8.2), and is correlated with illness severity (Marik 1993). This underscores the need for therapeutic drug monitoring.

Although in "normal" ward patients there are various methods for monitoring aminoglycoside dosing, including trough levels, published nomograms (Begg et al. 1995) and Bayesian computer software (Burton et al. 1985; Duffull et al. 1997; Kirkpatrick et al. 2003), their applicability in the critically ill is limited due to changes in Vd or the need for non-conventional dosing. Such situations require ensuring trough levels are <0.5 mg/L (preferably undetectable) prior to subsequent

dosing. Some consideration to minimizing the duration of therapy is also important, as the total dose of aminoglycoside is strongly correlated with the risk of both ototoxicity and nephrotoxicity.

8.7.2 β-Lactam Antibiotics

The β-lactam group of antibiotics consists of penicillins, cephalosporins, carbapenems and monobactams. Carbapenems will be considered separately because of their different pharmacodynamic properties. With the time-dependent kill characteristics of β-lactams (Nuytinck et al. 1988), once the antibiotic concentration falls below the MIC, any remaining bacteria multiply almost immediately (Craig 1984; Schentag et al. 1984; Vogelman and Craig 1985, 1986; Vogelman et al. 1988; Leggett et al. 1989; Roosendaal et al. 1989; Bakker-Woudenberg and Roosendaal 1990; Mouton et al. 1997). In the absence of any PAE, the serum concentration of a β-lactam antibiotic should exceed the MIC for 90–100% of the dosing interval (Turnidge 1998b). Concentrations of β-lactam antibiotics should be maintained at 4–5 times the MIC during each dosing period (Vogelman and Craig 1985, 1986) as bacterial killing is maximal at these concentrations (Mouton and den Hollander 1994; Angus et al. 2000).

Unlike aminoglycosides, neutropenia may not reduce the antibacterial effect of β-lactams significantly, but relapse of infection when antibiotic therapy is ceased is documented (Roosendaal et al. 1986; Craig 2003). This supports the common practice of continuing β-lactam therapy until the patient's white cell count normalizes. Standard bolus administration (for example, of cephalosporins) produces unnecessary peak and trough concentrations below the MIC for much of the dosing interval (Young et al. 1997; Lipman et al. 1999a,b, 2001). It follows that an improved PD profile is obtained with either more frequent dosing (Turnidge 1998b; Lipman et al. 1999b) or continuous infusions (Mouton et al. 1997; Young et al. 1997; MacGowan and Bowker 1998; Turnidge 1998b; Georges et al. 1999; Lipman et al. 1999a,b; Tessier et al. 1999; Angus et al. 2000; Burgess et al. 2000; Jaruratanasirikul et al. 2002; Boselli et al. 2003; Tam et al. 2003).

Sepsis without organ dysfunction can lead to increased β-lactam clearance and low plasma concentrations (Bakker-Woudenberg and Roosendaal 1990; Young et al. 1997; MacGowan and Bowker 1998; Gomez et al. 1999; Lipman et al. 1999a,b, 2001; Angus et al. 2000; Hanes et al. 2000). In two of these studies, the clearance of cefepime and more recently cefpirome, were linearly correlated with creatinine clearance (Lipman et al. 1999b, 2001). PK–PD modeling found that the T > MIC could be predicted by creatinine clearance, and that plasma concentrations of these antibiotics were low when using a standard dosing regimen (Lipman et al. 1999b, 2001). Dosing adjustment according to increased renal function is an important PK consideration to ensure optimal therapy, and may require increased dosing, or preferably increased frequency of dosing to ensure T > MIC is maximized.

Furthermore, an increased Vd in the critically ill (Gomez et al. 1999; Hanes et al. 2000) demands dosage adjustment (Table 8.2). Joukhadar et al. (2001) showed that an increased Vd in patients with septic shock results in unbound piperacillin concentrations that can be 5–10 times lower in the extracellular fluid of subcutaneous tissue compared with serum levels after a piperacillin bolus dose.

Administration by continuous infusion optimizes the PD profile of β-lactams (Mouton and den Hollander 1994; Fry 1996; Lipman et al. 1996; Mouton et al. 1997; Turnidge 1998b). Numerous studies have been performed comparing administration by continuous infusion versus bolus dosing (Mouton et al. 1997; Angus et al. 2000; Hanes et al. 2000; McNabb et al. 2001; Nicolau et al. 2001; Georges et al. 2005; Lorente et al. 2005a; Roberts et al. 2007a,b). These have largely shown comparable therapeutic efficacy, although Roberts et al. in their prospective randomized controlled trial found clinical and bacteriologic superiority when administering ceftriaxone 2-g as a continuous intravenous infusion compared to a once-daily bolus dose in patients receiving four or more days of treatment (Roberts et al. 2007a). Continuous infusion has also been reported to result in a reduction in total daily dose; shorter duration of treatment (MacGowan and Bowker 1998); decreased nursing time for administration; possible reduction in formation of resistant bacteria (Young et al. 1997; Klepser et al. 1998) and lower expenditure on patient therapy(Kollef et al. 1999; Krueger et al. 2002).

Recently, Lodise and colleagues performed a retrospective cohort study in 194 critically ill patients with *Pseudomonas aeruginosa* infections, receiving piperacillin-tazobactam by intermittent infusion (over 30 min) or extended infusion (over 3 h) (Lodise et al. 2007). In patients with an APACHE II score greater than 17 ($n = 79$), use of an extended infusion had a lower 14-day mortality rate (12.2% vs. 31.6%; $p = 0.04$) (Lodise et al. 2007). It is likely that the clinical advantage for infusion will be most notable in critically ill patients being treated for gram-negative infections. The benefit of continous- or extended infusions in this setting probably relates to the lack of a significant PAE of β-lactams (except carbapenems) against these organisms.

8.7.3 Carbapenems

Carbapenems (meropenem, imipenem and panipenem) are a separate class of β-lactam antibiotics. In similarity with other β-lactams, they demonstrate time-dependent killing (Table 8.1) and have minimal side effects (Mouton et al. 2000). Increased seizure activity has been noted with imipenem and is a potential adverse effect for all carbapenems, particularly in infants, the elderly and those with renal impairment (Barrons et al. 1992; Day et al. 1995; Norrby et al. 1995; Laethem et al. 2003). In vitro models have shown that carbapenems require less T > MIC for bacteriostatic activity (20%) and bactericidal activity (40%) (Drusano 2003) as compared with other β-lactams. This is most likely secondary to the carbapenem PAE (Bustamante et al. 1984).

Administration by continuous infusion to maximize T > MIC remains a topical issue for carbapenems particularly as this seems less important compared to other β-lactams. Some preliminary data suggest clinical superiority of administration by continuous infusion in critically ill patients (Lorente et al. 2005b) with avoidance of concentration-related toxicity (Craig 1998; Drusano 2003) and pharmacoeconomic advantages from reduced total daily dose (Kotapati et al. 2004). Recently, Lorente et al. performed a retrospective cohort study in 89 patietns with gram-negative bacilli ventilator-associated pneumonia treated with meropenem administered by bolus or continuous infusion (Lorente et al. 2006). This paper described superior clinical cure rates in the continuous infusion group compared with the bolus group (90.5% vs. 59.6%; $p < 0.001$) (Lorente et al. 2006). The principal disadvantage is drug stability for 24-h infusions. Meropenem may only be stable for a maximum of 8 h requiring a new infusion to be made when a bolus would normally be administered (Thalhammer et al. 1999; Krueger et al. 2005). Generally a designated intravenous line to avoid drug incompatibility problems is required. Further prospective research to determine the clinical efficacy of administering carbapenems as a continuous or extended infusion is required.

8.7.4 Glycopeptides

The specific interpretation of the PD properties of glycopeptides is not fully understood. Vancomycin will be preferentially discussed as representative of the glycopeptides due to its more prevalent usage. Vancomycin is well known to induce PAE and has PD properties in common with both aminoglycosides and β-lactams. Some data suggest that the bactericidal activity of vancomycin is time dependent (Saunders 1994; Larsson et al. 1996; Lowdin et al. 1998). Similar results have been obtained for teicoplanin in a rabbit endocarditis model (Chambers and Kennedy 1990). However, an in vitro study (Duffull et al. 1994) found no difference in rates of killing of *S. aureus* by vancomycin when given as continuous infusion or bolus dose suggesting that T > MIC is not necessary for optimal bacterial killing. C_{max}/MIC was found to predict efficacy in a non-neutropenic mouse peritonitis model for *S. pneumoniae* and *S. aureus* suggesting that glycopeptides might show concentration-dependent killing against some organisms (Knudsen et al. 2000). Whether this PD effect is primarily due to the presence of neutrophils in this model is unknown.

Other studies have proposed that AUC_{0-24}/MIC is the most important PK–PD parameter correlating with efficacy for vancomycin (Craig 2003; Rybak 2006). As such, the optimal dosing regimen for administration of vancomycin remains unknown (Duffull et al. 1994; Saunders 1994; James et al. 1996; Wysocki et al. 2001; Rello et al. 2005). The data is confused, as despite adequate vancomycin trough concentrations being maintained by dosing 6-, 8- or 12-hourly or by continuous infusion, there is a lack of definitive evidence of PD efficacy and no evidence linking concentrations to either outcome or toxicity (Saunders 1994; MacGowan 1998). Wysocki et al.

(2001) find no significant difference in clinical efficacy between continuous infusions and bolus dosing, but Rello et al. (2005) described the clinical superiority of continuous vancomycin infusions in a subset of patients treated for ventilator-associated pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Thus, while the economic advantages of reduced dosage of vancomycin by continuous infusion have been described (Wysocki et al. 2001), the clinical relevance of this remains unclear. However, dosing strategies to improve AUC_{0-24}/MIC in critically ill patients with neutropaenia may be prudent, as research suggests this is the most important PD parameter in animal neutropenic models (Rybak 2006).

To optimize dosing of vancomycin in critically ill patients with sepsis, maintenance of trough levels of at least 15–20 mg/L are required (MacGowan 1998). In our experience, higher doses than those conventionally recommended (similar to paediatric doses of 40 mg/kg/day) may be needed to optimize plasma concentrations (Gous et al. 1995). For teicoplanin, when there is no renal impairment, dosing at 6 mg/kg 12-hourly for three doses, followed by 6 mg/kg 24-hourly thereafter, is recommended. Therapeutic drug monitoring is indicated only when high doses (12 mg/kg/day) are used or to avoid toxicity. Current practice suggests that teicoplanin concentrations be maintained above 10 mg/L (15–20 mg/L for endocarditis) (Rybak 2006).

Vancomycin poorly penetrates into solid organs, particularly the lung (Cruciani et al. 1996; Bodi et al. 2001). Thus, if the source of sepsis is thought to be in the lung, the co-prescription of rifampicin as dual therapy has been advocated (Burnie et al. 2000; Bodi et al. 2001). Therapy with rifampicin is frequently avoided due to its potential for drug interactions through CYP3A4 inuduction. Use as a single agent is not recommended because of its propensity to cause bacterial resistance (Lipman 2005). Alternatively, high dose vancomycin (aiming for trough concentrations ≥20 mg/L) has been suggested (Lipman 2005) for sepsis originating in solid organs. Other antibacterial agents provide better penetration of the epithelial lining fluid of the lung and thus therapy with either fusidic acid (Turnidge 1999), linezolid (Conte et al. 2002), tigecycline (Peterson 2005) or televancin (Reyes et al. 2005) may be preferred. Teicoplanin does not provide any specific clinical advantages and newer drugs will likely take its place as a vancomycin subsititute.

8.7.5 Fluoroquinolones

Fluoroquinolone antibiotics include ciprofloxacin, moxifloxacin, levofloxacin and gatifloxacin. These are a relatively new class of antibiotics, and other than for ciprofloxacin, there is little data to guide dosing in critically ill patients. As such, ciprofloxacin will be discussed in preference where information is not available.

Although achieving a C_{max}/MIC ratio of 10 for ciprofloxacin is the critical variable in predicting bacterial eradication (Preston et al. 1998), Forrest et al. (1993) concluded that achieving an AUC_{0-24hr}/MIC > 125 is associated with a successful clinical outcome in critically ill patients with gram-negative infections. For gram-positive

organisms, an AUC_{0-24hr}/MIC of only 30 is required (Nix et al. 1992; Forrest et al. 1993; Piddock and Dalhoff 1993; Goss et al. 1994), although fluoroquinolones should not be used as single agent treatment of gram-positive infections. The dose recommended to achieve these PD parameters for ciprofloxacin is 400 mg IV 8-hourly in adults and this need not be changed during sepsis unless renal dysfunction occurs (Lipman et al. 1998; Gous et al. 2005). However, pharmacodynamic analysis has shown that this maximum dose has a 55% probability of achieving the AUC target of 125 (Sun et al. 2005) and as such larger doses or different dosing regimens may be recommended in the future. There is growing evidence for increased dosing of levofloxacin in critically ill patients with sepsis (1,000 mg daily) (Viale and Pea 2003; Graninger and Zeitlinger 2004), and with more safety and efficacy data, further increases in recommended doses may occur for other fluoroquinolone antibiotics as well.

All fluoroquinolone antibiotics demonstrate good tissue penetration (Gous et al. 2005). Ciprofloxacin is hepatically metabolized, although dose adjustment is recommended by the manufacturers' product information (MIMS Australia 2005b) in renal dysfunction to prevent accumulation of drug and metabolites (Hoffken et al. 1985). However, Jones has shown impaired ciprofloxacin clearance with renal impairment only when the patient had concomitant bowel or liver pathology (Jones 1997).

As referenced in previous sections of this chapter, under-dosing of fluoroquinolones may be implicated in selecting resistant sub-populations of infecting organsims. Although dosing to achieve specific pharmacodynamic end points has been associated with improved outcomes (Forrest et al. 1993), higher doses or alternative dosing regimens may be needed to minimize the development of resistance. Achieving a high $AUC_{0-24hrs}$/MPC has been shown to predict the prevention of resistant mutants (Olofsson et al. 2006), and may become the aim of dosing strategies in the future.

8.7.6 Tigecycline

Tigecycline is a member of the glycylcyclines which are novel tetracyclines with gram-positive and gram-negative activity. Tigecycline has shown rapid and extensive penetration into body tissues, and was shown to have 74% penetration into inflammatory fluid (Meagher et al. 2005a). Tigecycline displays time-dependent killing against *Streptoccus pneumoniae*, *Haemophilus influenzae* and *Neisseria gonorrhea* (Petersen et al. 1999) but AUC_{0-24}/MIC is more likely to be correlated with efficacy (Meagher et al. 2005a,b), due to the agent's long half-life and prolonged PAE. More research into the pharmacodynamic principles of tigecycline is needed.

Tigecycline should be reserved for infections caused by multi-resistant organisms. While a higher (100 mg loading dose then 50 mg 12-hourly) and lower dosing regimen (50 mg loading dose then 25 mg 12-hourly) has been previously trialled (Postier

et al. 2004), the superior clinical and bacteriologic success of the higher dosing regimen suggests that it may be more suitable for critically ill patients with sepsis.

8.7.7 Telithromycin

Telithromycin is the first ketolide marketed and has properties very similar to macrolide antibiotics. Telithromycin has been shown to have good extracellular penetration with therapeutic levels in respiratory tissues (Muller-Serieys et al. 2004), sites of inflammation (blister fluids 38% above plasma (Namour et al. 2002)) and in neutrophils (Kasbekar and Acharya 2005). However, poor penetration in muscle and adipose tissue (Gattringer et al. 2004) has been reported. Telithromycin also exhibits long post-antibiotic effects and post-antibiotic sub-MIC effects enabling once-daily dosing (Odenholt et al. 2001; Jacobs et al. 2003).

No evidence exists to support altered dosing in patients with "third spacing", and current evidence suggests that no dose adjustments are required in patients based on weight (Shi et al. 2004). In moderate to severe renal impairment (CrCL 30 ml/min), doses should be halved (from 800 mg 24-hourly to 400 mg 24-hourly) (Shi et al. 2004). No dose adjustment is required in hepatic disease (Kasbekar and Acharya 2005). Telithromycin is a potent inhibitor of the metabolic enzyme CYP3A4 and should be used with caution with midazolam and triazolam (potential to prolong Q-Tc), HMG-CoA reductase inhibitors or "statins" (risk of myopathy), digoxin, metoprolol and theophylline (elevated drug levels). Phenytoin and other enzyme inducers may reduce telithromycin levels. Telithromycin is available only in oral dosage form and is recommended at 800 mg daily for 7–10 days for community-acquired pneumonia.

8.7.8 Azithromycin

Azithromycin is a macrolide derivative more appropriately referred to as an "azalide" antibiotic, and is most commonly employed in the treatment of atypical respiratory pathogens in patients presenting with severe community-acquired pneumonia. Its structure in comparison with macrolides results in greater tissue penetration and longer plasma half-life, increased activity against gram-negative organisms and decreased activity against some gram-positive organisms (Piscitelli et al. 1992). Mean tissue concentrations are 10–100-fold greater than plasma concentrations (Foulds et al. 1990). Azithromycin is also actively taken up by white blood cells that carry the antibiotic to the site of infection (Amsden 1996).

AUC_{24}/MIC appears to be the PD parameter most closely associated with clinical efficacy, although concentrations at the site of infection rather than in plasma are more likely to correlate with antimicrobial effects (Firsov et al. 2002). Recent work has suggested that AUC_{24}/MIC values ≥ 25 are needed to achieve and maintain bactericidal activity against *S. pneumoniae* (Sevillano et al. 2006). Given the extensive

tissue distribution of azithromycin, changes in Vd are unlikely to occur with severe sepsis, although there is no data currently available on the PK changes of this agent in the critically ill. The recommended dose is 500 mg daily for 3–5 days in the treatment of suspected atypical pneumonia.

8.7.9 Daptomycin

Daptomycin is a novel lipopolypetide antimicrobial agent with good activity against most gram-positive pathogens. Although it was discovered 20 years ago, it has been marketed only recently with limited clinical studies to provide data on toxicity. Dosing should be adjusted in renal impairment. Early trials correlated muscle weakness, myalgia and marked increases in creatinine phosphokinase (CPK) with 12-hourly dosing (Tally et al. 1999), leading to the present recommendation of 4 mg/kg/24 h by intravenous daily bolus.

C_{max}/MIC is the PD parameter associated with clinical efficacy (Safdar et al. 2004). Daptomycin has a prolonged PAE of 2–6 h in MSSA and MRSA (Pankuch et al. 2003) and 1–2.5 h in *S. pneumoniae* (Safdar et al. 2004). Distribution is likely to be limited to the extracellular fluid spaces and third spacing may result in reduced C_{max}. It distributes rapidly into inflammatory fluid but does not reach the plasma concentrations, probably due to differences in the protein content of this fluid (Wise et al. 2002). If patients develop moderate to severe renal impairment (CrCl < 30 ml/min), then the frequency should be extended to 48-hourly dosing (Schriever et al. 2005). The effect of hypoalbuminaemia in hepatic impairment on unbound daptomycin concentration remains unknown, but patients should be monitored for changes in CPK if this occurs.

It has been suggested that daptomycin requires the presence of free calcium ions in a growth medium for activity against gram-positive organisms (Andrew et al. 1987). The effect this may have in humans with low serum calcium concentrations is unknown. In the acutely septic presents with low serum calcium levels, consideration should be given to correcting the serum calcium concentration and closely monitoring the clinical response. Daptomycin should be reserved for serious infections caused by MRSA, VRE and MRSE that do not respond to vancomycin.

8.7.10 Quinupristin/Dalfopristin

Quinupristin/dalfopristin (Q/D) is a combination of two injectable streptogrammins with demonstrated efficacy against multi-resistant gram-positive organisms. In vitro studies have shown significant CYP3A4 inhibition by Q/D, and care should be exercised when administering other drugs that are also inhibitors, substrates for, or inducers of this enzyme system (MIMS Australia 2005a). Q/D is thought to have concentration-dependent efficacy with 99.9% killing of isolates of vancomycin-resistant *Enterococcus*

faecium (VREF) in vitro best correlated a high ratio of Q/D concentration to minimum bactericidal concentration (MBC) (Aeschlimann and Rybak 1998). Some authors have suggested that AUC_{0-24}/MIC is the primary parameter correlated with efficacy (Craig 2001). Hepatic dysfunction may result in altered metabolism of Q/D or may cause unpredictable effects from other CYP3A4 metabolized drugs from unknown inhibition.

Little information exists to guide dosing of quinupristin/dalfopristin in critically ill patients with sepsis. If penetration to the infection site is considered impaired, then co-administration with another antibiotic (e.g. linezolid or a glycopeptide) is recommended (De Gaudio and Di Filippo 2003). Q/D is recommended to be dosed at 7.5 mg/kg intravenous administration 8-hourly for VREF and 7.5 mg/kg intravenous administration 12-hourly for complicated skin and skin structure infections with *Staphylococcus aureus* (methicillin-susceptible) (MIMS Australia 2005a).

8.7.11 Lincosamides

The lincosamide antibiotics include clindamycin and lincomycin. Clindamycin is widely distributed throughout the body and achieves therapeutic concentrations in most body compartments (Fass and Saslaw 1972; Nagar et al. 1989; Mueller et al. 1999). It is extensively hepatically metabolized and renally excreted with its clearance reduced in hepatic dysfunction (Avant et al. 1975). Lincomycin has similar properties to clindamycin although distribution into tissues may not be as wide (Gwilt and Smith 1986). While lincomycin is also extensively hepatically metabolized (Bellamy et al. 1967), its clearance is reduced in both severe renal and hepatic impairment (Bellamy et al. 1967).

T > MIC has been determined to be the pharmacodynamic factor correlated with efficacy. Free drug levels of lincosamides should exceed the MIC of the infective pathogen for at least 40–50% of the dosing interval (Craig 2001). Lincosamides are indicated for suspected/confirmed anaerobic infections in critically ill patients with sepsis due to their extensive distribution characteristics. Standard doses should be used for clindamycin (1,200–2,700 mg in three or four divided doses) unless significant hepatic impairment is present. Lincomycin dosing (600–2,400 mg 8-hourly dependent on the severity of infection) should be reduced in the presence of either significant renal or hepatic impairment.

8.7.12 Linezolid

Linezolid is the first of a new class of antimicrobials called the oxazolinediones. It widely distributes into tissues including inflammatory fluids, extracellular lining fluid and CSF (MacGowan 2003; Boselli et al. 2005). Linezolid is mostly metabolized and then renally cleared although no dose adjustment is recommended in renal dysfunction (Brier et al. 2003) or hepatic dysfunction (MacGowan 2003).

In animal models, T > MIC was the major predictor of efficacy with *S. pneumoniae* in a murine thigh infection model (Andes et al. 1998) and a rat pneumonia model(Gentry-Nielsen et al. 2002). In both models T > MIC of 40–45% was the best predictor of outcome. Subsequent animal models using *S. pneumoniae*, *S. aureus* and pneumococci have predicted that an AUC_{0-24}/MIC ratio of 50–80 correlate well with efficacy (Andes et al. 2002). A 600-mg 12-hourly dose should achieve this ratio in humans against susceptible organisms with MICs up to 2–4 mg/L. There is some information to suggest that maximal *S. aureus* killing may occur with T > MIC for 100% of the dosing interval (Craig 2003).

Linezolid can effect warfarin activity resulting in a decrease in the mean international normalized ratio (INR) (Azie et al. 2000). As such warfarin dosing should be carefully monitored. Linezolid is also a reversible non-selective inhibitor of monoamine oxidase (MAO) (MacGowan 2003), and can have interactions with other inhibitors resulting in an uncontrolled vasopressor response.

In the majority of patients, linezolid is safe and well tolerated for up to 28 days at 600 mg twice daily (French 2003). Evidence exists that therapy longer than 14 days can rarely cause reversible myelosuppression (Gerson et al. 2002), although a causal relationship has not been established. As such patients prescribed linezolid should have blood counts ordered weekly if two or more weeks of treatment is indicated (French 2003).

8.8 PK/PD Modelling

As outlined in the previous sections of this chapter, severe sepsis can result in a number of changes in PK parameters for different antibiotics. As such, Vd and clearance for these agents can be notably different in this patient population compared with healthy volunteers. In addition, inter-individual variation can be substantial, and individualization of the dosing regimen may be necessary to achieve optimal results. Determining creatinine clearance (as a key marker of drug elimination) and mathematical modelling of drug distribution will allow tailoring of dosing regimens to individual patients.

The application of pharmacokinetic/pharmacodynamic modelling in guiding the individualization of antibiotic doses in critically ill patients with nosocomial gram-negative infections has been investigated (Mohr et al. 2004). In their study, Mohr et al. demonstrated the applicability of mathematical modelling to achieve optimal PD profiles in individual patients, and subsequent clinical and microbiological improvement (Mohr et al. 2004). Similarly, creatinine clearance has recently been demonstrated to be a good marker of cefpirome clearance and could potentially be used to individualize cefpirome therapy (Roos et al. 2007). Recent work by Dailly et al. has recommended the use of a simple formula for individualizing ceftazidime dosage administered by continuous infusion in patients with haematological malignancies (Dailly et al. 2006). This work serves to underscore the importance of considering PD and PK parameters in dosing of antibiotics in critically ill patients and further work is needed to allow early identification of high risk patients.

8.9 Conclusion

Current antibiotic regimens have mostly been derived from trials with patients who are not critically ill. Optimizing antibiotic regimens in patients with sepsis requires an understanding of the pathophysiological changes that affect antibiotic dosing in severe sepsis and the different kill characteristics of the various antibiotic classes.

Certain antibiotics may have a high Vd, and hence lead to a low C_{max} during sepsis. It follows that under-dosing may occur if a high peak is needed (e.g. aminoglycosides).

The Vd of antibiotics that distribute primarily into extravascular water, namely aminoglycosides, vancomycin and, to a lesser extent, β-lactams, changes with clinical illness severity. Dosing may need to be altered during the course of illness irrespective of renal or hepatic function, something not commonly described for non-critically ill patients.

In many critically ill patients, despite a normal serum creatinine, supra-normal creatinine clearance, and as a consequence more rapid drug elimination can be demonstrated. High drug clearances lead to sub-therapeutic levels and increase the likelihood of treatment failure and the development of resistant microorganisms. In relation to the aminoglycosides, this means that not only are large doses required to be administered, but these antibiotics may also need dosing more frequently. Similarly, β-lactams and fluroquinolones should, in such patients, be dosed more frequently than suggested in non-sepsis patients.

Treatment of sepsis remains a significant challenge given persistently high mortality and morbidity rates. Data suggest that effective antibiotic therapy remains the most important intervention available to the clinician. In treating sepsis, the clinician must be cognizant of the various pathophysiological and subsequent PK–PD changes that can occur, and how these may influence drug concentration, and hence outcome.

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