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Empiric Antimicrobial Therapy in Severe Sepsis and Septic Shock: Optimizing Pathogen Clearance

Stephen Y. Liang¹ and Anand Kumar²

¹ Division of Infectious Diseases, Division of Emergency Medicine, Washington University School of Medicine, 660 S. Euclid Avenue, Campus Box 8051, St. Louis, MO 63110, USA, sliang@dom.wustl.edu

² Section of Critical Care Medicine, Section of Infectious Diseases, JJ399d, Health Sciences Centre, 700 William Street, Winnipeg, Manitoba, Canada R3A-1R9, akumar61@yahoo.com

Abstract

Mortality and morbidity in severe sepsis and septic shock remain high despite significant advances in critical care. Efforts to improve outcome in septic conditions have focused on targeted, quantitative resuscitation strategies utilizing intravenous fluids, vasopressors, inotropes, and blood transfusions to correct disease-associated circulatory dysfunction driven by immune-mediated systemic inflammation. This review explores an alternate paradigm of septic shock in which microbial burden is identified as the key driver of mortality and progression to irreversible shock. We propose that clinical outcomes in severe sepsis and septic shock hinge upon the optimized selection, dosing, and delivery of highly potent antimicrobial therapy.

Keywords

Septic shock; Sepsis; Infection; Antimicrobial; Antibiotic; Pharmacokinetics; Combination therapy; Survival

Introduction

Significant progress has been made in the care of critically ill patients with severe sepsis and septic shock. While the incidence of severe sepsis and septic shock continues to rise annually in the USA, due in part to increased awareness and recognition, aggressive advances in medical care, and an aging population with many chronic medical comorbidities, in-hospital mortality has declined significantly over the past decade [1, 2]. Taking into account different methodologies for case identification, mortality rates in North America for severe sepsis range anywhere from 12.1 to 25.6 % [1]. Mortality from septic shock remains consistently higher at 30–50 % [2, 3]. Similar mortality rates have been described in other medically advanced countries around the world [4–6]. While systems-based strategies incorporating bundles to guide volume resuscitation and timely

Correspondence to: Anand Kumar.

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antimicrobial therapy have improved clinical outcomes for many patients, severe sepsis and septic shock still carry an unacceptably high mortality. In view of this, we will discuss an alternate paradigm for understanding severe sepsis and septic shock and highlight the role of optimized antimicrobial therapy in pathogen clearance and mortality reduction.

Paradigms of Severe Sepsis and Septic Shock

Contemporary management of severe sepsis and septic shock rests solidly on its conceptualization as an immunologic disease. In this paradigm, bacterial infection triggers the innate immune response, setting in motion a cascade of pro-inflammatory and anti-inflammatory cytokines leading to what we recognize as the systemic inflammatory response syndrome (SIRS). It has been thought that this self-propagating cascade drives the progression to severe sepsis and septic shock with increasing degrees of cellular injury and end-organ dysfunction, irrespective of the initial infectious trigger and its rapid elimination with antimicrobial therapy. Clinical manifestations of this intense inflammatory response include a constellation of coagulopathy, encephalopathy, acute kidney injury, acute respiratory distress syndrome (ARDS), and hypotension due to vasodilation, increased endothelial permeability, and functional adrenal insufficiency. A compensatory anti-inflammatory response may follow in which immunoparalysis predisposes the host to further secondary infection. In the context of this paradigm, sepsis, severe sepsis, and septic shock represent a continuum of increasing disease severity rather than discrete clinical entities with unique pathogeneses.

Pharmacologic efforts to modulate the immunologic cascade through action against inflammatory mediators such as tumor necrosis factor-alpha (TNF α) and interleukin-1 (IL-1) have failed to improve clinical outcomes. Likewise, recombinant human-activated protein C (drotrecogin α), initially thought to have both immunomodulatory and anticoagulant properties prompting its approval as the only non-antimicrobial pharmacotherapeutic for septic shock to date, was ultimately not found to increase survival compared to placebo [7]. Early initiation of goal-directed therapy (EGDT) comprising quantitative resuscitation strategies utilizing intravenous fluids, vasopressors, inotropes, and blood transfusions is another approach that is grounded, in part, on the immunologic paradigm of sepsis. An initial high profile study of EGDT to correct the hemodynamic consequences of circulatory dysfunction from systemic inflammation appeared to indicate reduced mortality in severe sepsis and septic shock [8]. However, recent randomized, multicenter studies paint a more guarded picture about the benefits of this approach [9, 10, 11•].

The immunologic paradigm considers infection solely as the initial trigger for severe sepsis and septic shock. In contrast, the classic microbiologic paradigm proposes that infection is both a foundation and the driving force behind these disease states. In this conceptualization, microorganisms replicate over time within a body site (e.g., lung, urinary tract, blood stream) releasing endotoxins and exotoxins that elicit the host inflammatory immune response. The persistence of infection in the form of total microbial load perpetuates systemic inflammation over time leading to host cellular injury and end-organ dysfunction. Animal models have shown that septic shock due to *Escherichia coli* peritonitis consistently occurs once a defined microbial load in the blood stream has been reached [12]. In

meningococcal disease, a significantly higher burden of plasma *Neisseria meningitidis* DNA and lipopolysaccharide has been identified in patients with fulminant septic shock compared to those without shock [13]. In pneumococcal pneumonia, a high *Streptococcus pneumoniae* load in blood (as measured by polymerase chain reaction) has been found to be independently associated with the occurrence of septic shock and hospital mortality [14]. Shorter time to blood culture positivity, a proxy for high microbial load in the blood stream, has also been linked to severe disease and poorer clinical outcomes in bacteremia secondary to *Staphylococcus aureus* [15, 16] as well as Gram-negative bacilli [17–20].

The microbiologic paradigm suggests that rapid elimination of the underlying focus of infection with effective antimicrobial therapy can quickly terminate the downstream manifestations of severe sepsis and septic shock. There is evidence that infection can be persistent in sepsis and septic shock. In a study of 235 patients admitted to a surgical intensive care unit for sepsis or septic shock, more than three quarters of patients were found at autopsy to have a persistent focus of infection [21]. Of those who lived long enough to receive 7 days of therapy for infection, nearly 90 % still had a continuous septic focus. Clinical experience similarly demonstrates that site cultures may remain positive for a variety of infections for days or longer despite initiation of appropriate antimicrobial therapy. The microbiologic paradigm holds that the inflammatory response of severe sepsis and septic shock cannot be overcome unless the underlying infection has been effectively eradicated.

Absent from both the immunologic and microbiologic paradigm is a clear acknowledgement of the fundamental cause of death in all septic states: irreversible shock. First described by Wiggers in hemorrhagic shock [22], this is the concept that a limited window of opportunity exists to correct shock before death becomes inevitable, often recognized as the “golden hour” in trauma care. Furthermore, Wiggers found that mortality from hemorrhagic shock could not be improved without definitive treatment of the underlying cause of hemodynamic compromise, namely the bleeding lesion. The same can be said of other forms of shock, be it coronary reperfusion for myocardial infarction with cardiogenic shock or thrombolysis of a massive pulmonary embolus that has led to obstructive shock. In septic shock, the underlying cause is the total microbial load. This suggests that survival hinges upon the timely reduction and eradication of infection after the onset of hypotension. Progression of this hypotensive state driven by a persistent microbial load leads to cellular injury, irreversible organ damage, and death in septic shock.

Adapting key components of the immunologic and microbiologic paradigm and incorporating the endpoint of irreversible shock provide a useful integrated conceptual model for thinking about and managing severe sepsis and septic shock (Fig. 1) [23]. Sepsis begins within a nidus of infection with the microbial load increasing over time if untreated. Overlaying this microbial load is the toxic burden (exotoxins, structural toxins, etc.), the inflammatory response, and the cellular dysfunction/injury driven by inflammatory endogenous mediators. Two aspects of the model require special attention. First, host characteristics define a threshold above which cardiovascular reserve can no longer compensate for systemic inflammation-mediated hemodynamic stress leading to septic shock (interrupted line in figure). A healthy individual will have a high shock threshold

reflecting significant physiologic reserves, while those with impaired cardiovascular function at baseline will succumb to septic shock at a lower threshold. Second, the presence of hypotension left unchecked over a finite period of time leads to irreversible organ injury and death. The transition from reversible to irreversible shock will vary depending on the individual genetic predisposition and characteristics of the patient.

In this re-envisioned integrative model of severe sepsis and septic shock, appropriate therapy centers on the rapid reduction of total microbial load to minimize host injury and limit the duration of hypotension. Successful treatment of septic shock is not only time-critical but intimately tied to control of the underlying infection. Delayed and/or ineffective antimicrobial therapy permits microbial replication to continue unchecked, resulting in more time spent above the shock threshold and progression to irreversible shock and death. In light of this proposed model, septic shock and sepsis without shock are cast as two fundamentally distinct diseases rather than as a continuum of severity for a single disease process. From a clinical perspective, refractory hypotension, lactic acidosis, and multiorgan dysfunction coupled with mortality rates exceeding 50 % (similar to other forms of shock) clearly distinguish septic shock from sepsis without shock where less dramatic presentations are associated with mortality rates of approximately 10–15 %. Certain pro- and anti-inflammatory cytokine profiles may be specific to septic shock and adverse outcomes [24–26], further setting this disease apart from sepsis without shock.

Optimizing Antimicrobial Use

The importance of antimicrobial therapy has been long accepted and is well established in modern sepsis care [27]. If our objective in septic shock is the rapid reduction of total microbial load before progression to irreversible shock, then empiric antimicrobial therapy must assume a position of co-primacy in the initial resuscitation with an eye toward optimizing selection, delivery, and cidal activity at the first dose. While many of these concepts are familiar to infectious disease specialists and clinical pharmacists, empiric antimicrobial therapy for severe sepsis and septic shock remains to a great extent the domain of emergency physicians, intensivists, internists, and surgeons caring for these complex critically ill patients on the frontline. A thoughtful and systematic approach to antibiotic utilization in severe sepsis and septic shock maximizes the success of accelerating clearance of microbial burden underpinning these diseases. Efforts to optimize antimicrobial therapy in clinical practice can be broadly divided into the categories of (a) early achievement of therapeutic drug concentrations and (b) optimizing cidal activity of the drug regimen.

Early Achievement of Therapeutic Drug Concentrations

Antimicrobial Appropriateness/Spectrum of Coverage

Empiric antimicrobial therapy for severe sepsis and septic shock should be broad from the start to maximize coverage of potential microorganisms presumed responsible for the underlying infection. Empiric therapy is considered appropriate if the selected antimicrobial has in vitro activity against an isolated microorganism before a causative microorganism can be identified. Delivery of appropriate empiric antimicrobial therapy is critical in early

achievement of therapeutic drug levels because initiation of inappropriate therapy is functionally equivalent to starting no antimicrobial at all.

Inappropriate antimicrobial therapy for blood stream infections has historically been reported in anywhere from 15 to 30 % of patients admitted to the ICU and is associated with increased hospital mortality [28–30], particularly in the setting of severe sepsis and septic shock [31]. In a retrospective study of 5715 patients with septic shock spanning 22 medical institutions in 3 countries, inappropriate initial antimicrobial therapy occurred in almost 20 % of all patients, with 18.8 % occurring in those with community-acquired infections and 28.4 % in those with nosocomial infections [3]. Inappropriate initial empiric therapy was associated with a five-fold reduction in survival from 52 to 10.3 %.

Given the high mortality associated with septic shock, empiric antimicrobial therapy should cover both Gram-positive and Gram-negative bacteria. The probable anatomic site of infection should inform selection of antimicrobials capable of achieving therapeutic drug levels in infected tissue and fluid (e.g., lung, skin, and soft tissue, urine, cerebrospinal fluid). Patient risk factors including chronic comorbid diseases (e.g., diabetes mellitus, chronic kidney disease), immune status, and social history (e.g., travel, incarceration, illicit drug use) should likewise be considered in predicting potentially resistant microorganisms. Recent and/or prolonged hospitalization, antimicrobial use, and prior colonization or infection with a resistant organism should prompt expansion of empiric antimicrobial therapy to cover organisms such as methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and multidrug-resistant Gram-negative bacilli. Empiric antifungal coverage for *Candida* species may be warranted in the setting of severe immunosuppression or neutropenia, prior extensive antimicrobial therapy, or colonization at multiple sites. Local and unit-specific antibiograms provide antimicrobial susceptibility patterns that can guide appropriate antimicrobial selection. Initially unrestricted broad-spectrum antimicrobial therapy in septic shock increases the likelihood that the inciting microorganism will be appropriately covered and reduction of the microbial load driving septic shock can begin.

Early Administration of Antimicrobials

Appropriate empiric antimicrobial therapy must be administered as soon as possible in patients with septic shock. Delayed antimicrobial therapy is strongly associated with increased mortality in severe infections that have the potential to progress to septic shock [32–40]. Animal models of septic shock demonstrate that increased mortality from delayed antimicrobial therapy coincides with the onset of hypotension and lactic acidosis [12]. In a major retrospective study of septic shock, initiation of effective antimicrobial therapy within the first hour after onset of hypotension was associated with a 79.9 % survival to hospital discharge [41•]. With each ensuing hour of delay, survival decreased by 7.6 %, with a survival rate of 42 % at the median delay of 6 h (Fig. 2). This time-dependent deterioration in mortality applied to all assessed clinical syndromes and multiple organisms/organism groups including *Candida* septic shock. In a multicenter, observational, propensity score analysis of 2796 patients with severe sepsis, early administration of broad-spectrum antimicrobials within 1 h of presentation was independently associated with survival [42]. Other studies confirm that early and appropriate antimicrobial therapy is a key determinant

of mortality in severe sepsis and septic shock [43–46]. Likewise, timely anti-fungal therapy is associated with increased survival in patients with septic shock due to *Candida* blood stream infection [47]. In view of this data, empiric antimicrobial therapy should be started immediately (preferably within 30 min) of making the presumptive clinical diagnosis of septic shock in the setting of refractory hypotension. While every effort should be made to secure site-specific cultures to guide microorganism-specific therapy downstream, this should never delay the administration of empiric antimicrobials in patients with septic shock where the window of opportunity to intervene before irreversible shock can be fleeting.

Loading Doses of Antimicrobials

Clearance of pathogenic microorganisms cannot begin until therapeutic serum concentrations of antimicrobials have been achieved. Critically ill patients exhibit significantly altered antimicrobial pharmacokinetics. Apparent volume of distribution (V_d) describes the relative theoretical distribution of a drug within body compartments. In patients with critical illness, interstitial third-spacing, whether from increased capillary permeability in sepsis or aggressive fluid resuscitation needed to treat refractory hypotension, can increase the V_d of hydrophilic antimicrobials that are primarily distributed in the extracellular space [48–50]. Included among these are β -lactams, aminoglycosides, glycopeptides, and lipopeptides. Increased V_d can lead to subtherapeutic concentrations of these antimicrobials when standard dosing regimens are used to treat critically ill patients. Hypoalbuminemia, common in critically ill patients, can lead to an increase in the unbound fraction of antimicrobials that are usually highly protein-bound (e.g., ceftriaxone, ertapenem, aztreonam, daptomycin) thereby decreasing their V_d but increasing subsequent clearance of renally excreted antimicrobials, resulting in serum concentrations that may be suboptimal for treating severe infection [51].

Inadequate serum drug concentrations for coverage of *Pseudomonas* in patients with severe sepsis and septic shock during the initial dosing interval have been demonstrated with piperacillin-tazobactam, ceftazidime, cefepime, meropenem, and other β -lactams using standard intermittent dosing [52–54]. Likewise, aminoglycoside dosing in septic shock is frequently found to be suboptimal and has been associated with increased mortality [55–58]. Insufficient dosing of vancomycin [59–61], fluoroquinolones [62, 63], and colistin [64, 65] has also been described extensively in critically ill patients.

Initial antimicrobial therapy in septic shock should begin with the maximum recommended dose taking into account any increased predisposition to toxicity in a given critically ill patient. There is emerging consensus that loading doses of some antimicrobials may improve clinical outcomes in critically ill patients, particularly when utilizing aminoglycosides [58, 66], fluoroquinolones [67], vancomycin [59, 60], and colistin [64, 65]. Loading doses may also be crucial for early achievement of therapeutic drug concentrations when β -lactams are administered as continuous or extended infusions [68]. Loading doses are also routinely recommended for a broad range of other antimicrobials including tigecycline, fluconazole, caspofungin, and anidulafungin.

Optimization of Antimicrobial Potency

Combination Therapy

To rapidly and effectively clear infecting microorganisms, antimicrobial therapy must be highly potent, i.e., exert a high degree of cidal activity. While more than one antimicrobial is frequently needed to cover the entire spectrum of suspected microorganisms in severe sepsis and septic shock, combination antimicrobial therapy is the use of more than one antimicrobial to target the same microorganism through different pharmacologic mechanisms of action to achieve an additive or synergistic killing effect leading to more rapid clearance of the infection [69–71]. Historically, evidence supporting antimicrobial synergism to this effect can be found with β -lactam/aminoglycoside combinations [72–75]. Similar findings have also been demonstrated for β -lactam/fluoroquinolone combinations [76–79]. However, the overall benefit of combination therapy on clinical outcomes in severe infections associated with sepsis has remained equivocal at best in several metaanalyses [80–82].

Combination therapy may have its greatest benefit in the sickest patients. In a meta-analysis and meta-regression study of over 60 randomized and observational datasets of sepsis and/or septic shock, the pooled odds ratios indicated no overall mortality or clinical response benefit with combination therapy [83]. However, on stratification of datasets, combination therapy (primarily a β -lactam combined with another agent) was consistently found to improve survival and clinical response in groups with a high mortality risk ($>25\%$) on monotherapy (OR 0.51, 95% CI, 0.41–0.64) (Fig. 3) and those with septic shock (OR 0.49, 95% CI 0.35–0.70), even when the analysis was restricted to randomized controlled trials. Likewise, a propensity-matched analysis of a multicenter retrospective cohort of 4662 ICU patients with septic shock demonstrated both clinical and mortality benefit with combination therapy in Gram-positive and Gram-negative infections [84]. In addition, the duration of hypotension was significantly shorter with combination therapy. Notably, the most potent β -lactams including carbapenems failed to demonstrate this benefit presumably due to a very high level of cidal activity for most pathogens that could not be substantially augmented with a supplemental agent. Several recent retrospective studies in critically ill patients have found similar benefits [30, 85–87], particularly with combinations including an amino-glycoside. In contrast, one randomized trial of combined carbapenem/fluoroquinolone therapy has failed to show benefit in severe sepsis and septic shock [88], a result which is congruent with the findings of the earlier noted propensity study [84]. If microbial load indeed drives refractory hypotension and mortality in septic shock, a rational approach may be to incorporate combination therapy in the opening salvo of treatment to acutely reduce this load, stabilize hemodynamic parameters, and avert further organ injury. In theory, combination therapy would only be required while the microbial load is high enough to drive hemodynamic instability, typically several days. Thereafter, a switch to more targeted monotherapy should be entirely effective and preferred.

Antimicrobial Pharmacokinetics and Pharmacodynamics

Optimization of antimicrobial dosing in septic shock plays a crucial role in maximizing killing activity and reducing microbial load before shock becomes irreversible. Significant

evidence suggests that antimicrobial dosing strategies seeking to optimize pharmacokinetic (PK) and pharmacodynamics (PD) indices improve clinical response to infection.

Pharmacokinetic optimization of antimicrobial therapy beyond the first dose can be approached based on principles of antimicrobial effect, namely time-dependent vs concentration-dependent killing. For time-dependent killing agents (e.g., β -lactams, linezolid, clindamycin), optimal antimicrobial effect occurs during the fraction of time (T) when drug concentrations exceed the mean inhibitory concentration (MIC) of the microorganism over a given dosing interval ($fT > MIC$). In critically ill patients with nosocomial pneumonia, bacterial eradication rates with cefmenoxime correlated with greater fractional time above the dynamic response concentration, similar to $fT > MIC$, and translated to shorter durations of therapy required to treat infection [89]. In patients receiving cefepime or ceftazidime for sepsis with bacteremia, those who achieved a $fT > MIC$ of 100 % had significantly greater rate of clinical cure and bacterial eradication compared to patients with $fT > MIC$ of less than 100 % [90]. In a separate study examining cefepime in patients with pneumonia, skin and soft tissue infection, or bacteremia, those with $fT > MIC$ under 60 % were significantly more likely to have poor microbiologic response to therapy [91]. More frequent antimicrobial dosing remains the traditional approach for increasing $fT > MIC$.

Continuous infusion of antimicrobials, specifically β -lactams, provides an alternative strategy for maintaining 100 % $fT > MIC$ in critically ill patients where infecting microorganisms with higher MICs may be encountered. In a randomized controlled trial of 40 septic critically ill patients, those receiving a continuous infusion of piperacillin (2-g loading dose followed by 8g over 24 h) consistently achieved greater $fT > MIC$ and reduction in severity of illness, as measured by APACHE II scores, when compared to those receiving intermittent dosing (3 g every 6 h) [92]. Continuous infusion of meropenem (2-g loading dose followed by 4 g over 24 h) has been associated with greater microbiological cure rates compared to an intermittent high-dose regimen (2 g every 8 h) in a randomized open-label trial of critically ill patients admitted with severe infection [93]. Notably, patients receiving continuous therapy required a shorter duration and total dose of meropenem with clinical outcomes comparable to intermittent dosing. Clinical and microbiological advantages with continuous infusion of ceftriaxone (2 g over 24 h) over intermittent dosing (2 g once daily) have also been demonstrated in critically ill patients with sepsis [94]. A multicenter, randomized controlled trial has found higher rates of clinical cure with continuous infusion of piperacillin-tazobactam, meropenem, and ticarcillin-clavulanate compared to intermittent bolus administration of each antimicrobial [95].

In critically ill patients with *Pseudomonas* infections, extended infusion of piperacillin-tazobactam (3.375 g over 4 h every 8 h) has been associated with improved clinical outcomes as defined by APACHE II scores and 14-day mortality compared to traditional intermittent dosing (3.375 g every 4 or 6 h) [96]. While this retrospective cohort study did not examine intermittent high-dose (4.5 g) therapy, it found significant mortality benefit with extended infusion in the sickest patients (APACHE II score ≥ 17). Other studies have been more divided over the clinical benefit of extended infusion antimicrobials [97–100]. Meta-analyses remain guarded over the advantages of continuous and extended infusion strategies with β -lactams, citing variable methodologies in the existing literature [101–103].

However, stratified analyses of the most critically ill subset of patients in whom benefit is most likely to occur have not been performed. While further studies examining alternative dosing regimens in septic shock are needed, pharmacokinetic data supports antimicrobial dosing at shorter intervals or extended/continuous infusion as an effective means to maximize $fT > MIC$ when employing time-dependent killing agents.

Concentration-dependent killing agents (e.g., fluoroquinolones, aminoglycosides, metronidazole, daptomycin) exhibit optimal antimicrobial effect when the area under the concentration-time curve (AUC) to mean inhibitory concentration (MIC) ratio relative to the dosing interval and normalized to 24 h (AUC_{24}/MIC) and peak antimicrobial concentration (C_{max}) to MIC ratio (C_{max}/MIC) are maximized. Effective AUC_{24}/MIC and C_{max}/MIC ratios vary depending on the antimicrobial and the microorganism targeted. In critically ill patients receiving ciprofloxacin for serious infections, patients who achieved an $AUC_{24}/MIC \geq 125$ had significantly greater rates of microbiologic and clinical cure in a shorter period of time compared to those with an $AUC_{24}/MIC < 125$ [104]. With respect to Gram-negative bloodstream infections, patients receiving ciprofloxacin with $AUC_{24}/MIC \geq 250$ had a 91.4 % cure rate compared with 28.6 % in those with an $AUC_{24}/MIC < 250$ [105]. Specific AUC_{24}/MIC and C_{max}/MIC thresholds have also been linked to improved clinical outcomes and microbiological cure for a range of infections in patients treated with levofloxacin [106, 107]. While no studies have examined whether targeting higher fluoroquinolone AUC_{24}/MIC and C_{max}/MIC ratios improves survival in septic shock, optimization of these parameters reduces the likelihood of subtherapeutic serum drug concentrations. High C_{max}/MIC ratios are also a major determinant of clinical response to aminoglycosides in the treatment of Gram-negative bacterial infections [108], but come with inherent nephrotoxicity that may compound existing acute kidney injury in critically ill patients. Strategies balancing these tensions support higher once daily dosing of aminoglycosides for short durations when the perceived benefit of their use outweighs the risks [109, 110]. It stands to reason that use of the maximum nontoxic dose of a concentration-dependent killing agent hastens clearance of infecting microorganisms and contributes to reduced mortality in severe sepsis and septic shock.

Vancomycin is another antimicrobial that relies upon concentration-dependent killing effects. In patients with MRSA bacteremia, those with AUC_{24}/MIC ratios ≥ 421 were less likely to experience vancomycin failure, as defined by 30-day mortality, persistent signs, and symptoms of infection at the conclusion of therapy, or persistent bacteremia ≥ 7 days [111]. In particular, achieving this threshold AUC_{24}/MIC early on (within 48–72 h) appears to be a key factor in clinical success [112–114]. A vancomycin AUC_{24}/MIC threshold of ≥ 400 has also been linked to significantly shorter time to bacterial eradication and clinical improvement in patients with *S. aureus* pneumonia [115]. In a multicenter, retrospective study of critically ill patients with MRSA septic shock, an independent graded improvement in survival was seen with achievement of vancomycin $AUC_{24}/MIC > 451$ and > 578 [116].

Optimization of antimicrobial potency through selective targeting of PK/PD indices is linked to improved clinical and microbiological cure. While studies in critically ill patients with severe sepsis and septic shock are limited, optimized dosing of antimicrobials likely

expedites microbial clearance and appears to confer a survival advantage in these critically ill patients.

Cidality

Apart from the treatment of endocarditis and meningitis, the perceived superiority of antimicrobials with in vitro bactericidal vs bacteriostatic activity in treating many infections in vivo has not been borne out in most clinical studies [117–119]. However, cidality may yet have relevance in therapy for septic shock, where irreversible shock and mortality are time- and microbial load-dependent. Few studies have examined the efficacy of cidal vs static agents in treating severe infections associated with sepsis or septic shock [120, 121]. While nominally considered cidal, vancomycin has relatively weak cidal activity against methicillin-sensitive *S. aureus* (MSSA). When used to treat MSSA bacteremia, vancomycin has been associated with increased mortality and morbidity compared to treatment with antistaphylococcal penicillins or a first-generation cephalosporin [122–124]. Bacteriostatic agents such as linezolid appear to be no more effective than vancomycin in eradicating *S. aureus* in hospitalized patients with nosocomial pneumonia [125]. It is intuitive that, all other factors being equal, killing (cidal) activity would be preferable to inhibition (static activity) in septic shock; to be sure, additional studies in this population are needed. However, the distinction between bactericidal and bacteriostatic activity for many antimicrobials depends as much on the microorganism as well as the serum concentration of the drug. There is evidence, albeit limited, to support improved clinical responses with cidal therapy in severe infections. In meta-analyses of serious infections treated with tigecycline (a bacteriostatic drug) versus a standard regimen, tigecycline was found to result in inferior survival [126]. Similarly, the only randomized, controlled study to directly compare a fungistatic (fluconazole) versus a fungicidal agent (anidulafungin) for invasive *Candida* infection has demonstrated improved clinical cure with the cidal agent [127]. In another instructive study, the use of chloramphenicol yielded similar initial clinical outcomes compared with penicillin with gentamicin for community-acquired pneumonia in third-world children [128]. However, its use was associated with a significantly higher relapse rate at 1 month suggesting suboptimal microbiologic cure.

While the clinical data supporting a preference for cidality in antimicrobial therapy in septic shock is limited, sufficient evidence exists to encourage consideration of this factor in designing optimal antimicrobial regimens for severe infections.

Maintenance and Tailoring of Antimicrobial Therapy

While the initial management of severe sepsis and septic shock will be spearheaded by frontline clinicians in the emergency department and intensive care unit in the first hours of patient care, a multidisciplinary approach further enhances the effectiveness of antimicrobial therapy. Infectious disease consultation maximizes the appropriateness of empiric antimicrobial therapy [129–131] and has been shown to improve clinical outcomes in serious infections [132–134]. Clinical pharmacists can provide invaluable expertise in improving antimicrobial effects through PK/PD optimization [135], and tailor dosing strategies for complex patients requiring continuous renal replacement therapy (CRRT),

sustained low-efficiency dialysis (SLED), and extracorporeal membrane oxygenation (ECMO) [136].

Reassessment and de-escalation of antimicrobial therapy based on microbiologic culture, susceptibility testing, and clinical improvement not only promote antimicrobial stewardship but has been associated with improved outcomes in serious infections [137–140]. Transitioning to less toxic and/or more effective antimicrobials (e.g., use of β -lactams instead of vancomycin to treat confirmed MSSA) and reducing selection pressure for multidrug-resistant nosocomial infections may explain some of the protective effects of de-escalation. While the limited evidence on de-escalation in septic shock remains variable and further randomized trials are needed [141–143], de-escalation does not appear to adversely impact survival. In the face of resolving septic shock and hemodynamic stabilization, antimicrobial de-escalation is safe and should be considered within 48–72 h of initiating empiric antimicrobial therapy.

Conclusions

Septic shock is a time-critical disease with high mortality that requires not only prompt recognition but rapid and definitive management. We have described an alternate paradigm of severe sepsis and septic shock which combines our current knowledge of the immunologic and microbiologic aspects of this disease with the concept of irreversible shock. In it, we underscore the importance of microbial load as a key driver of mortality. Optimization of antimicrobial therapy in severe sepsis and septic shock is crucial to reducing the microbial load in a prompt and effective manner. Early, appropriate empirical antimicrobial therapy employing aggressive dosing strategies to maximize pharmacokinetic and pharmacodynamic indices and therefore killing activity are vital to reducing mortality. Timely antimicrobial deescalation based on microbiologic identification and susceptibility testing and clinical improvement are likewise essential strategies to conserve the effectiveness of existing antimicrobials and prevent the emergence of resistance.

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Fig. 1. Integrative paradigm of sepsis and septic shock. Reproduced with permission from reference [23]. See text for explanation

Fig. 2.

Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. The *x*-axis represents time (hours) following first documentation of septic shock-associated hypotension. *Black bars* represent the fraction of patients surviving to hospital discharge for effective therapy initiated within the given time interval. The *gray bars* represent the cumulative fraction of patients having received effective antimicrobials at any given time point. Reproduced with permission from reference [41•]

Fig. 3.

Analysis of studies comparing combination antibiotic therapy with monotherapy for reducing mortality of life-threatening infections associated with sepsis. Note that different baseline mortality risk in the monotherapy group is associated with markedly different impact of combination therapy on septic shock on outcome. The size of the squares is proportional to the reciprocal of the variance of the studies. **a** Nonshock or noncritically ill stratified dataset; **b** shock or critically ill stratified dataset; **c** modified dataset provided by study authors. Adapted from reference [83•], reproduced with permission