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An alternate pathophysiologic paradigm of sepsis and septic shock

Implications for optimizing antimicrobial therapy

Anand Kumar

Section of Critical Care Medicine; Section of Infectious Diseases; Health Sciences Centre; Winnipeg, MB Canada

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The advent of modern antimicrobial therapy following the discovery of penicillin during the 1940s yielded remarkable improvements in case fatality rate of serious infections including septic shock. Since then, pathogens have continuously evolved under selective antimicrobial pressure resulting in a lack of significant improvement in clinical effectiveness in the antimicrobial therapy of septic shock despite ever more broad-spectrum and potent drugs. In addition, although substantial effort and money has been expended on the development novel non-antimicrobial therapies of sepsis in the past 30 years, clinical progress in this regard has been limited. This review explores the possibility that the current pathophysiologic paradigm of septic shock fails to appropriately consider the primacy of the microbial burden of infection as the primary driver of septic organ dysfunction. An alternate paradigm is offered that suggests that has substantial implications for optimizing antimicrobial therapy in septic shock. This model of disease progression suggests the key to significant improvement in the outcome of septic shock may lie, in great part, with improvements in delivery of existing antimicrobials and other anti-infectious strategies. Recognition of the role of delays in administration of antimicrobial therapy in the poor outcomes of septic shock is central to this effort. However, therapeutic strategies that improve the degree of antimicrobial cidality likely also have a crucial role.

Introduction

Septic shock and sepsis-associated multiple organ failure remain the most common cause of death in intensive care units of the medically advanced nations. Historically, the mortality associated with sepsis and septic shock has been approximately 50–75%.[1-3] The primary advance in the therapy of septic shock was the development of modern (i.e., β-lactam) antibiotic therapy 70 years ago which resulted in a reduction in sepsis-associated mortality to the 30–50% range.[1,2] However, the past 50 years has seen a gradual year-to-year increase in the incidence of sepsis.[4] As a result, total deaths have increased substantially.[4] Current estimates suggest a doubling of total United States cases of severe sepsis from 800 000 annually to 1.6 million cases by 2050 with an increase in population of only 33%.[5] Currently, severe sepsis and septic shock cases account for approximately 10–15% of all intensive care unit (ICU) admissions with approximately 25% of cases of sepsis[6] and 50–75% of cases of severe sepsis progress to septic shock.[7] Septic shock alone represents between 5% and 8% of all ICU admissions.[8,9] Despite major advances in technology and constant refinement of our understanding of sepsis pathophysiology, numerous clinical trials have failed to produce any new drugs with consistent beneficial effects on this patient population. Even the efficacy of the only novel non-antimicrobial pharmacotherapy of sepsis and septic shock approved since the advent of modern antimicrobials, activated protein C, has recently been questioned and the product removed from the market.[10-12]

Correspondence to: Anand Kumar; Email address: akumar61@yahoo.com
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Current Paradigm: Immunologic Model

Part of the reason for the failure to develop effective novel therapies may be a fundamental misunderstanding of the pathophysiology of septic shock. The currently accepted immunologic paradigm suggests that sepsis is present when systemic activation of inflammatory pathways (i.e., systemic inflammatory response syndrome [SIRS]) is triggered by infection.[13] This paradigm holds that the disorder is caused by an infection which initiates an immunologic (inflammatory cytokine and eicosanoid)/coagulation cascade that propagates independently of the underlying infectious trigger.[14,15] This view of sepsis as a syndrome that is only indirectly related to the underlying infection is reflected in the classic figure by Bone and colleagues showing the relationships between SIRS and infection (**Fig. 1**).[13] The figure indicates that sepsis is defined by the co-occurrence of infection and SIRS but there is no clear suggestion (in the figure) that uncontrolled infection drives the development of SIRS.

That is appropriate given current thinking. In this view, progression of the syndrome (and a counter-inflammatory, "immunoparalytic" phase of illness[16,17]) will occur as a consequence of inflammatory cellular signaling despite the rapid elimination of the pathogen through administration of cidal antimicrobial

therapy[14] (Fig. 2). The concept is one of an inflammatory cytokine and coagulation "cascade" that can progress to higher degrees of severity independently of the initial infection trigger. In this model, sepsis, severe sepsis (sepsis with organ failure), and septic shock (sepsis with cardiovascular failure) are considered to be related disorders of increasing severity but sharing a similar basic underlying pathology, one of direct endogenous mediator-driven cellular dysfunction and injury. Septic shock, in particular, is considered an epiphenomenon to the underlying cellular injury induced by these mediators rather than a discrete clinical entity with a distinct pathogenesis and pathophysiology. Overwhelming meningococcemia with septic shock, a condition in which an exquisitely antimicrobial-sensitive organism can be quickly eliminated but where massive tissue damage may still occur is the archetypal infectious syndrome that best fits this paradigm. Notably, the pivotal clinical trial of bactericidal permeability increasing (BPI) protein, an immunomodulatory agent developed as a meningococcal anti-sepsis compound actually exhibited some evidence of benefit in meningococcal sepsis.[18] However, other less sensitive pathogenic microorganisms that more frequently cause septic shock fit this archetypical profile less well. Perhaps because of this issue, the variety of immunomodulatory therapies that were developed based on this immunologic paradigm of sepsis have, almost uniformly, failed to improve outcomes in clinical trials.[19] The source of the efficacy of drotrecogin-alfa (activated), the one novel product to have shown a potential benefit in sepsis (at least in the initial pivotal study), may have been its potent anticoagulant rather than immunomodulatory activity since heparin also seems to exert a similar benefit.[20,21]

The Classic Paradigm: Microbiologic Primacy

The reason for the general failure of immunomodulatory strategies for treatment of sepsis may be that the underlying paradigm fails to accurately reflect the disease process. The primacy of active infection in driving the immunologic "cascade" of sepsis pathophysiology may be underappreciated in the currently accepted immunologic paradigm of sepsis. A key deficiency of this immunologic model of sepsis is that most pathogens cannot be eliminated quickly despite cidal antimicrobial therapy[22-27] and likely persist during the period that immunomodulatory therapies (most of which are, in fact, immunosuppressive) might be initiated. A recent autopsy study of sepsis suggested that a persistent septic focus could be found in approximately 75% of 235 surgical ICU patients who died of sepsis/septic shock and in almost 90% of those succumbing in the ICU after at least 7 d of treatment.[28]

Another view of septic shock derives from the more classic microbiologic paradigm of life-threatening infection and sepsis. In this model, infection is the key driving element of sepsis and septic shock. The septic process begins with a nidus of infection (peritonitis, pneumonia, etc.) (Fig. 3). Within that focus, the organism replicates and, untreated, the microbial infectious load increases over time. Overlying that process, the microbial pathogens release a variety of exo- and endotoxins (toxic burden) which

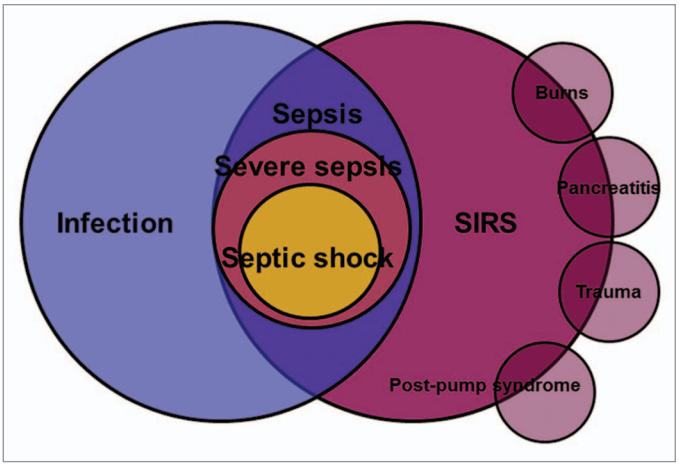

Figure 1. SIRS, sepsis, severe sepsis, and septic shock. SIRS, systemic inflammatory response. Adapted from reference 13. See text for explanation.

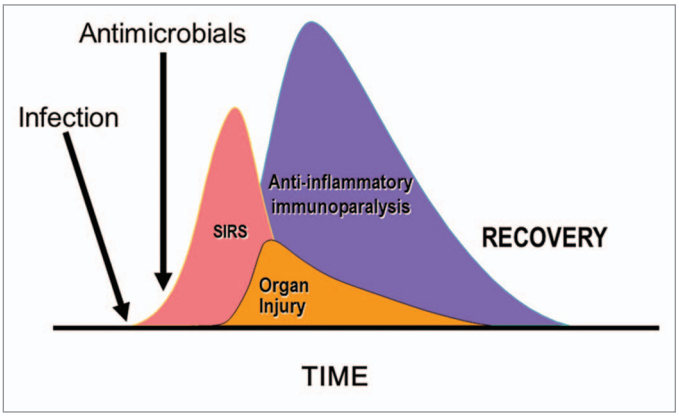

Figure 2. Immunologic view of sepsis and septic shock. SIRS, systemic inflammatory response. Adapted from reference 14. See text for explanation.

have antigenic properties. These stimulate a further overlay of endogenous mediators including inflammatory cytokines such as TNF-α, IL-1β, IL-6, HMGB1, and eicosanoids such as prostaglandin E2, prostacylin, thromboxanes, leukotrienes (inflammatory response). The result is cellular dysfunction which can be manifested as tissue injury and, ultimately, organ dysfunction including septic shock (cellular dysfunction/tissue injury). The central aspect of this model is that the microbial infectious load substantially drives downstream responses including the development of organ dysfunction and septic shock. This paradigm, which forms the basis of standard antimicrobial therapy of sepsis and septic shock, suggests that elimination of the underlying infection should terminate the downstream inflammatory/coagulant basis for tissue injury and organ dysfunction.

A New Composite Model: Integrating Shock

The microbiologic primacy model of sepsis, like the immunologic model, also fails to recognize a key element in mortality

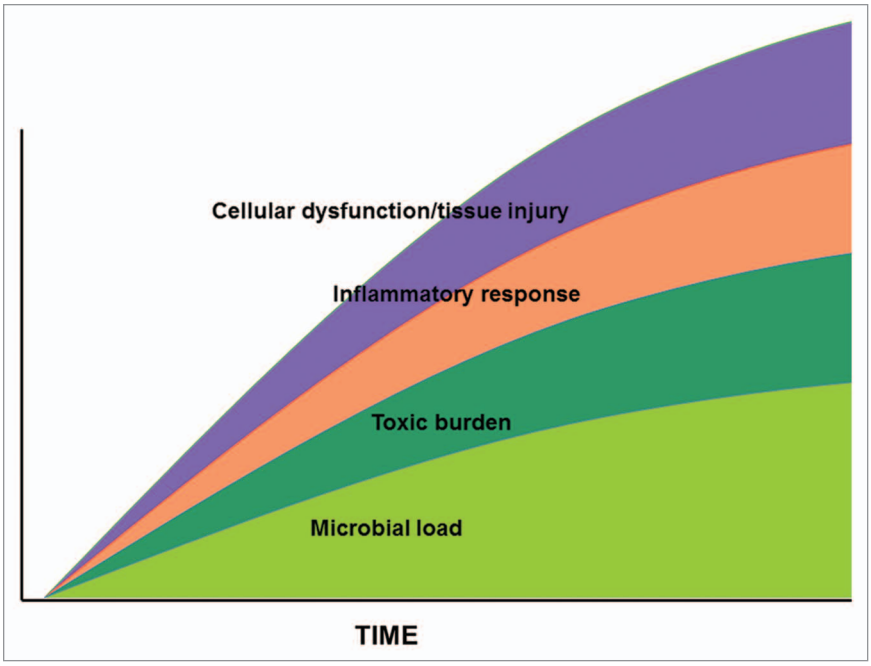

Figure 3. Microbiologic view of sepsis and septic shock. See text for explanation.

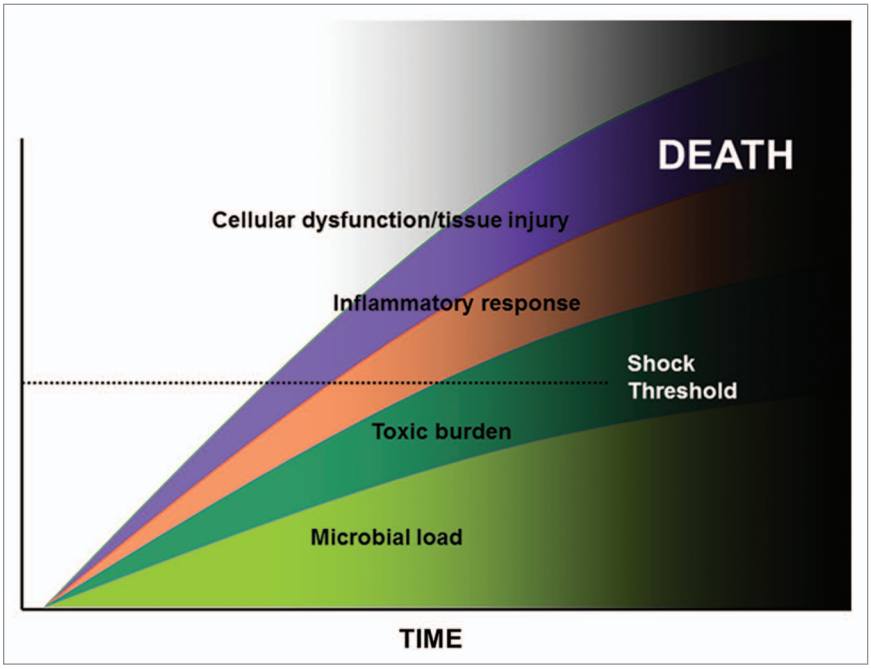

Figure 4. Composite view of sepsis and septic shock. See text for explanation.

of septic states, the concept of irreversible shock as originally described by Wiggers.[29] This concept suggests that shock, irrespective of the etiology, can only be tolerated for a limited time. Once present, shock will become irreversible with inevitable progression to death if the condition is not reversed within a short period of time. This concept is directly associated with the idea of the "golden hour" first demonstrated in the context of hemorrhagic/traumatic shock but applicable to various forms of critical injury particularly other shock states. Many studies have now shown that early definitive intervention (i.e., correction of the underlying problem) within a short time of potentially lethal injury has a major impact on survival. Patients with such injury can be maintained for a limited period of time with non-definitive support modalities (e.g., blood products for hemorrhagic shock, intra-aortic balloon pump for myocardial infarction-associated cardiogenic shock, pressors for all forms of shock) but mortality will not be improved without definitive elimination of the underlying source of hemodynamic instability (e.g., thrombolysis,[30] angioplasty[31] or bypass for cardiogenic shock due to myocardial infarction, embolectomy or thrombolysis of massive pulmonary embolus causing obstructive shock,[32] or definitive repair/control of a bleeding lesion causing hypovolemic shock[33]).

Septic shock can be viewed through a similar prism. In this circumstance, the underlying source of shock is the total microbial load. This paradigm of septic shock implies that the speed with which the inciting infection is reduced to a sub-critical thresh-hold after the onset of persistent or recurrent hypotension (as a marker of shock) will be of paramount importance in survival. The presence of shock becomes a central driver in the genesis of irreversible organ injury rather than an incidental epiphenomenon. A conceptual model that incorporates the key elements of this infectious paradigm of sepsis, immunologic elements from the model described previously and the concept of irreversible shock can be created and used to predict key aspects of pathogenesis of septic shock and develop novel approaches to effective therapy. This construct is similar to the infectious diseases model of septic shock with two major additions (**Fig. 4**). First, the hatched line indicates the point at which inflammatory mediator-associated cellular dysfunction and tissue injury manifest as septic shock. This threshold will be highly variable between individuals. Those with impaired cardiovascular reserve will go into shock at lower levels of cellular dysfunction/tissue injury. Young, healthy persons may require a substantially greater degree of inflammatory stimulation to reach the same shock threshold. The second new element to the model is that the presence of shock (as commonly manifested by persistent/recurrent hypotension) sets the patient on the path toward irreversible organ injury. At some indeterminate point after onset of hypotension (depending on the degree of hypotension, comorbid contributors, and genotype of the patient), the patient

will become irreversibly committed to death. Because of genotypic variations in the host and pathogen and clinical variability in the infection, the exact point at which the injury becomes irreversible for a given patient cannot be determined at present. However, the progression is similar for all patients.

This model suggests that the appropriate approach to therapy of septic shock should be to rapidly reduce the infectious load so that the period of time in shock (irrespective of whether vasopressor are able to maintain blood pressure) before reduction of the microbial load to a subcritical threshold is limited (i.e., minimize the period that sufficient organisms are present to generate shock) (**Fig. 5**). Based on the model, this should limit the risk that the indeterminate pathophysiologic point at which recovery is no longer possible in septic shock is passed. The issue of time/delay-dependent irreversibility of the injury and irreplaceability of the injured organ are critical to this model. Other conditions where these conditions exist in advanced nations include meningitis/encephalitis, necrotizing pneumonia, and necrotizing soft tissue infections. The mortality risk for other potentially eligible conditions may be somewhat more context-specific. Delays of antimicrobial therapy of endocarditis with valve failure or non-necrotizing pneumonia with respiratory failure may be fatal in areas where valve replacement and mechanical ventilation are unavailable but should be survivable in advanced nations.

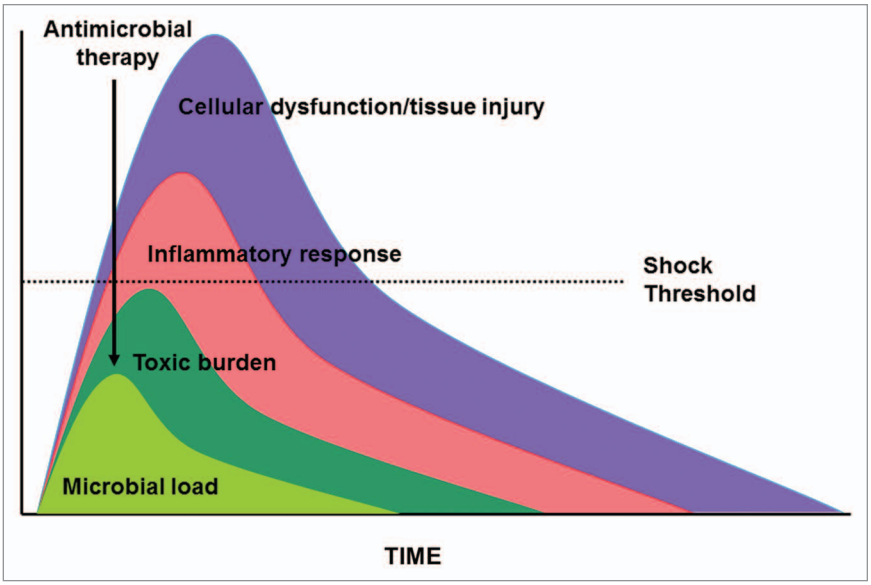

Figure 5. Impact of appropriate antimicrobial therapy in sepsis and septic shock. See text for explanation.

There are two major pathophysiologic implications of this model of injury in septic shock. First and foremost, this model suggests that septic shock and sepsis without shock (including sepsis with organ failure other than shock) are fundamentally different diseases rather than a simple continuum of severity of a single syndrome. The difference lies in the time-/delay-dependent risk of irreversible and irreplaceable organ injury. The simplest line of evidence for this proposal is the commonality of the stark clinical features (hypotension, lactic acidosis, substantial exhaustion of compensatory physiologic responses, etc.) and high (>50%) mortality of septic shock and other shock syndromes of any etiology in contrast to the relatively milder clinical features and lower (approximately 15%) mortality of sepsis or severe sepsis.[34] A pathophysiologic basis for the proposition that sepsis without shock and septic shock represent distinct clinical entities is suggested in the different profiles of associated endogenous mediators[35,36] and evidence of hypotension-associate immune dysfunction in septic shock (compared with sepsis without shock).[37] Moreover, if this model correctly describes sepsis and the shock syndromes, there should be a commonality of gene expression responses among all shock syndromes whereas distinct differences would exist between responses of those of sepsis and septic shock. However, this remains to be proven.

The second major implication of this model is that the time delay of effective antimicrobial therapy from onset of hypotension is a surrogate for an increasing microbial burden of organisms. Again, there is evidence to support this contention. We have shown that the onset of shock in a rodent model of *E. coli* peritonitis/septic shock consistently occurs at a defined microbial organism load in blood.[38] Even as varying numbers of organism are implanted into the animal, the time of onset of shock remains constant relative to the density of organisms in the blood. This issue can be difficult to study in humans because of the variability in infecting organism. However, meningococci are remarkably consistent in their growth characteristics. Several studies have demonstrated that earlier antimicrobial therapy is critical in outcome of severe meningococcal disease. One study has demonstrated that increasing severity of the clinical syndrome (fulminant septic shock vs. meningitis or sepsis without shock) is associated with a higher burden of neisserial DNA and LPS in plasma of patients with meningococcal disease.[39] In another study, logistic regression analysis demonstrated that blood bacterial load predicted outcome of meningococcal shock.[40] Delays in antimicrobial therapy were associated with outcome only in univariate analysis and all deaths were associated with blood bacterial loads of $>10^5$ cfu/mL bacteria. Other studies similarly have demonstrated that the increasing organism burden is associated with increased morbidity and mortality in serious infections.[41] For example, the risk of septic shock and death in serious pneumococcal and gram-negative infections increases with organism burden[42-44] and mortality of *S. aureus*, *E. coli*, and *K. pneumoniae* bacteremia increases with shorter times to blood culture positivity (a surrogate marker of higher bacterial blood counts).[45-49] Conversely, appropriate early antimicrobial therapy has been shown to be associated with both improved clinical outcomes and more rapid bacterial clearance in studies of *Acinetobacter* bacteremia in the critically ill.[50] Similarly, the speed of bacterial eradication in 24 h in vitro time kill studies of antibiotic combination therapy have been shown to correlate strongly with clinical and

Table 1. Antimicrobial determinants of pathogen clearance in septic shock

1) Early antimicrobial therapy
a. Initiate microbially-appropriate therapy
b. Ensure maximally rapid initiation (avoid delays)
c. Utilize a loading dose when possible
2) Antimicrobial potency
a. Ensure antimicrobial cidality
b. Optimize pharmacokinetic indices
i. Time-dependent agents
ii. Concentration-dependent agents
c. Utilize combination therapy with antimicrobials possessing different mechanisms of action
3) Supplemental therapies
a. Source control

bacteriologic outcomes in severely ill patients with *Pseudomonas* infections.[51]

Optimizing Pathogen Clearance

One of the central testable hypotheses that derive from this composite model is that the rapid clearance of pathogens will be the central determinant of outcome in septic shock. In the remainder of this review, we will focus on the application of antimicrobial optimization principles deriving from the concept of microbiologic load/infectious burden as a driver of the pathophysiology of septic shock. Notable among the implications of this model of sepsis progression is that optimization of antimicrobial therapy (i.e., acceleration of microbial clearance) will have the most dramatic impact in septic shock rather than sepsis without shock. Relevant antimicrobial factors to consider are listed in **Table 1**. Supplemental antimicrobial therapies (source control), antitoxin/immunomodulatory strategies, and supportive measures (fluid and pressor resuscitation) will not be discussed in this review.

Early Antimicrobial Therapy

Although there are several approaches that may yield accelerated pathogen clearance, the simplest approach involves ensuring that effective antimicrobial therapy is initiated as quickly as possible, particularly once septic shock has developed. In the context of septic shock, early, potent antimicrobial therapy will rapidly reduce the microbial load driving organ injury/dysfunction and hypotension reducing the risk of irreversible shock and death (**Fig. 6**).

In one of the earliest enunciations of this principle as it relates to all serious infections, Paul Ehrlich, in his address to the 17th International Congress of Medicine, 1913 said "Frapper fort et frapper vite" i.e., "hit hard and hit fast" with antimicrobials.[52] In the modern context, his advice as it pertains to rapid therapy embodies three distinct elements. First, it is clearly necessary that initial empiric antimicrobial therapy be microbially appropriate (i.e., with in vivo antimicrobial activity for the presumed pathogen). Second, this appropriate empiric therapy must be administered as quickly as possible. Third, therapeutic levels in blood and at the target site should be achieved as quickly as possible following the first antimicrobial dose.

Appropriateness of Antimicrobial Therapy

Although data in sepsis without shock is inconsistent,[53-57] most studies suggest that failure to initiate antimicrobial therapy to which the pathogen is sensitive is associated with marked increases in mortality especially in septic shock.[3,58-68] For that reason, empiric antibiotic regimens should approach 100% coverage of pathogens for the suspected source of infection. Initiation of inadequate antimicrobial therapy may occur as frequently as 17.1% in community-acquired and 34.3% in nosocomial bacteremia admitted to the ICU.[69] Similarly, 18.8% and 28.4% of septic shock cases were initially treated with inadequate antimicrobial therapy in another large study.[62]

Retrospective studies have shown that the risk of death increases from 30–60% in ICU bacteremia[3,70] to 70–100% in gram-negative shock[3] when the initial empiric regimen fails to cover the inciting pathogen. More recent data suggests that the initiation of inappropriate empiric antimicrobial therapy (i.e., failing to cover the pathogen) is associated with a reduction in survival of approximately 5-fold (range 2.5- to 10-fold in selected subgroups) from 55% to about 11%.[62] These findings of sharply increased mortality risk with initial inadequate antimicrobial therapy apply to serious infections caused by gram-negative and gram-positive bacteria as well as *Candida* species.[3,58-65] Similar findings have been documented with a variety of other serious infections associated with septic shock including community-acquired pneumonia, hospital- and ventilator-associated pneumonia, and bacterial peritonitis (for review, see refs. 66 and 67).

As a consequence of the high mortality associated with inappropriate initial therapy, empiric regimens should err on the side of over-inclusiveness. The most common cause of initiation of inappropriate antimicrobial therapy is a failure of the clinician to appreciate the risk of infection with antibiotic-resistant organisms (either otherwise uncommon organisms with increased native resistance or antibiotic-resistant isolates of common organisms). Selection of an optimal antimicrobial regimen requires knowledge of the probable anatomic site of infection; the patient's immune status, risk factors, and physical environment; and the local microbiologic flora and organism resistance patterns. Risk factors for infection with resistant organisms include prolonged hospital stay, recent antimicrobial use, prior hospitalization, and prior colonization or infection with multiresistant organisms. Increased severity of illness is associated with risk of inadequate therapy;[69] this may imply that the probability of resistant organisms is increased in patients progressing to higher levels of disease severity (i.e., septic shock).

Superior empiric coverage can be obtained through the use of a local and unit-specific antibiograms[71,72] or infectious diseases consultation.[73-75] Some data suggests improved clinical outcomes with such consultation.[76] Although not routinely required,

extended spectrum gram-negative regimens, vancomycin, and/or antifungal therapy may be appropriate in specific, high risk cases with severe sepsis. In addition, given that 90–95% of patients with septic shock have co-morbidities or other factors that make them high risk for resistant organisms, it may be appropriate to initially treat all patients with septic shock using a combination of antimicrobials that result in a broadly expanded spectrum of coverage for the first few days. This approach should ensure that high risk patients are not inappropriately categorized as low risk, thereby improving the likelihood of initial adequacy of antimicrobial coverage.

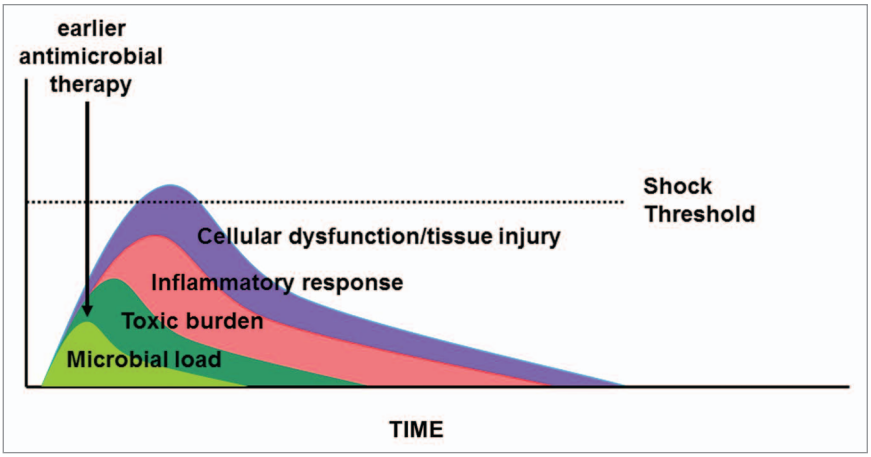

Figure 6. Impact of earlier antimicrobial therapy in sepsis and septic shock. See text for explanation.

In order to avoid institutional problems with antimicrobial resistance in the long-term, empiric antimicrobial therapy must be adjusted to a narrower regimen within 48–72 h if a plausible pathogen is identified or if the patient stabilizes clinically (i.e., resolution of shock). While several retrospective studies have demonstrated that inappropriate therapy of severe sepsis and septic shock yields increased mortality,[3,58-65,70] none have suggested that early narrowing of therapy is detrimental if the organism is identified or if the patient is responding well clinically. To the contrary, some studies have suggested that de-escalation of antimicrobial therapy is associated with improved outcomes.[77-80] This approach will maximize appropriate antibiotic coverage of inciting pathogens in septic shock while minimizing selection pressure toward resistant organisms. Although it is tempting to continue a broad spectrum regimen in the 15–20% of patients who are improving but culture negative for a potential pathogen, intensivists must recognize that a strategy of broad spectrum initial antimicrobial therapy will only be sustainable if overuse of these agents can be avoided. Aggressive de-escalation of antimicrobial therapy within 48–72 h after initiation is required.

Antimicrobial Delay

Although available studies indicate that delays in initiation of appropriate antimicrobial therapy of bacteremia/candidemia and sepsis without shock are only inconsistently associated with outcome,[64,81-88] such delays appear to have a substantial role in determining the mortality of high-risk infections with a strong association with septic shock.[63,89-111] The central role of such delays in septic shock is apparent in the major upward inflection in mortality of antibiotic-treated murine septic shock coincident with the onset of hypotension and lactic acidosis.[38] Other animal studies have similarly shown a very rapid inflection in mortality in experimental severe infections absent appropriate antimicrobial therapy.[112,113]

Human studies pertaining to the impact of delays of antimicrobial therapy on serious infections date back at least to the work of Bodey and colleagues[114] who demonstrated increasing mortality risk when appropriate antimicrobials were delayed more than a day following documentation of *Pseudomonas* bacteremia. Meehan et al. has shown that delays in initial antimicrobial administration greater than 8 h after admission to the emergency room for community acquired pneumonia is associated with increased mortality in a large cohort of Medicare patients.[97] Houck has pushed this boundary lower by demonstrating increased mortality in Medicare patients with community-acquired pneumonia who were treated with antimicrobials more than 4 h following ICU admission.[102]

One major retrospective analysis of septic shock has suggested that the delay to initial administration of effective antimicrobial therapy is the single strongest predictor of survival with significant decreases in projected survival for every hour delay.[115] Initiation of effective antimicrobial therapy within the first hour following onset of septic shock-related hypotension was associated with 79.9% survival to hospital discharge. For every additional hour to effective antimicrobial initiation in the first 6 h post-hypotension onset, survival dropped an average of 7.6%. The adjusted odds ratio of death was already significantly increased by the second hour post-hypotension onset and the ratio continued to climb with longer delays. An unpublished analysis of an expanded data set demonstrates that significant decreases in projected survival occur with delays greater than 30 min. Despite these findings, the median time to delivery of effective antimicrobial therapy following initial onset of recurrent/persistent hypotension in septic shock was 6 h.[115] Substantial delays before initiation of effective therapy have been shown in several studies of serious infections.[97,102,116-119] Additional retrospective studies of human bacteremia, candidemia, septic shock, community-acquired pneumonia, hospital-acquired pneumonia, surgical infections, meningitis with sepsis, and sepsis in solid organ transplants have confirmed that the mortality in these septic conditions is increased with significant delays in antimicrobial administration.[61,63,90,93-98,100,101,103-106,109-111,117,120-125]

Several studies have now assessed the impact of speed of appropriate empiric antimicrobial therapy on outcome in relationship to other elements of therapy. In our own study of

human septic shock,[115] we found that 28% of the variance in outcome of septic shock could potentially be explained by variations in speed of delivery of effective antimicrobials while variations in fluid resuscitation could explain <2%. This suggested that greater remediable deficiencies (and greater potential for improvement in care) may lie with the former therapy than with the latter. A recent propensity analysis by Ferrer and colleagues[126] of approximately 2800 patients with severe sepsis and septic shock suggested that only rapid antimicrobial therapy (<1 h compared with >6 h of severe sepsis diagnosis) and use of drotrecogin-alfa (activated) among elements of an internationally recommended "sepsis bundle"[127] were independently associated with survival. Similarly, Varpula and colleagues[128] have shown that only early initiation of antimicrobials (<3 vs >3 h of emergency room admission) among elements of a "sepsis bundle" was associated with improved survival in 92 patients with community-acquired septic shock using logistic regression analysis. Another analysis of the impact of various elements of the bundle demonstrated that only administration of antibiotics within 2 h and obtaining blood cultures before antibiotic administration were associated with improved survival in 316 consecutive patients with severe sepsis or septic shock.[129] Likewise, Subramanian and colleagues have shown that only rapid initiation of antimicrobial therapy (<1 h following ICU admission or <3 h following admission to the emergency department) and early restoration of global perfusion indices were independently associated with survival in 95 consecutive patients with septic shock.[130] Delays in appropriate antimicrobial therapy have also been associated with development of acute lung injury,[131] acute renal failure,[132] and worsening of organ failure[133] and higher inflammatory cytokines and other inflammatory markers.[133,134] Further support for the importance of time to appropriate antimicrobial therapy comes from studies of the impact of bundles of hospital-based interventions which have consistently shown improvement in outcome of sepsis and septic shock.[126,135-143] The most consistent element of therapy improved with such bundled quality assurance approaches is timeliness and appropriateness of antimicrobial therapy.[144]

In view of these data, intravenous administration of broad spectrum antimicrobial should be initiated immediately (preferably <30 min) following the clinical diagnosis of septic shock. Patients with other serious infections are similarly well served with maximally rapid initiation of antimicrobial therapy. Appropriate, intravenous, broad spectrum empiric therapy should be initiated as rapidly as possible in response to clinical suspicion of infection in the presence of persistent hypotension, i.e., presumptive septic shock. An assumption that persistent or recurrent hypotension is caused by anything other than sepsis in the setting of documented or suspected infection should be avoided in the absence of very strong clinical evidence indicating a specific alternate etiology.

Laboratory tests congruent with sepsis or septic shock should be considered supportive of the diagnosis but obtaining such tests should never delay antimicrobial therapy. For septic shock, the presumptive diagnosis should be made on clinical criteria. A potential survival advantage may exist if a pathogenic organism can be isolated in severe infections including septic shock.[62,145] Every effort should be made to obtain appropriate site-specific cultures in order to allow identification and susceptibility testing of the pathogenic organism; however, as with other laboratory testing, such efforts should not delay antimicrobial therapy.

Loading Doses

Although administration of early appropriate antimicrobial therapy is the central element in management of septic shock, clearance of pathogens will not begin until therapeutic levels of the antimicrobials in the circulation are achieved. The pharmacokinetic principles underlying drug absorption and distribution for optimization of antimicrobial dosing in non-critically ill patients are well established. However, an equivalent broad understanding of dosing issues in critically ill patients has lagged.

Patients with critical illness are known to have major alternations in antimicrobial pharmacokinetics. In particular, many antimicrobials exhibit markedly increased volume of distribution (Vd) especially those agents that are primarily distributed in the extracellular space. Included in this group are β-lactams, aminoglycosides, vancomycin, teicoplanin, and colistin.[146-148] This increased Vd can result in inadequate levels of these antimicrobials during the initial treatment phase.[149-152] Failure to achieve therapeutic levels early after initiation of antimicrobials may result in suboptimal organism clearance and inferior clinical results.

Therapeutic serum levels of a variety of antimicrobials fail to be consistently achieved using standard dosing regimens in critically ill patients with sepsis and septic shock. β-lactams represent a particularly important example of the problem given their frequency of use in the ICU. In septic shock patients, inadequate serum concentrations for coverage of *Pseudomonas* during the first dosing interval have been shown for piperacillin–tazobactam, ceftazidime, cefepime, and meropenem using standard intermittent dosing.[150] Similarly, initial serum levels of aminoglycosides in septic patients are often inadequate resulting in inferior clinical outcomes.[153,154] Comparable finding have been reported for fluoroquinolones,[155,156] vancomycin,[152,157] teicoplanin,[158] and colistin.[149,159]

An emerging body of literature suggests that loading doses of some antimicrobials can potentially yield improved clinical outcomes.[149-151,154,157-162] Supportive data exists in severely ill patients including those with septic shock for aminoglycosides,[162] fluoroquinolones,[161] vancomycin,[152,157] teicoplanin,[158] and colistin.[149,159] Loading doses may be particularly important when β-lactams are administered as continuous or extended infusions (see later section on this subject). In this circumstance, failure to use a loading dose can substantially delay achievement of therapeutic levels and may be responsible for less than optimal clinical responses in some studies of extended/continuous infusion of β-lactams in critically ill patients.[163] Loading doses are also recommended for a broad range of other antimicrobials including tigecycline, fluconazole, anidulafungin, and caspofungin.

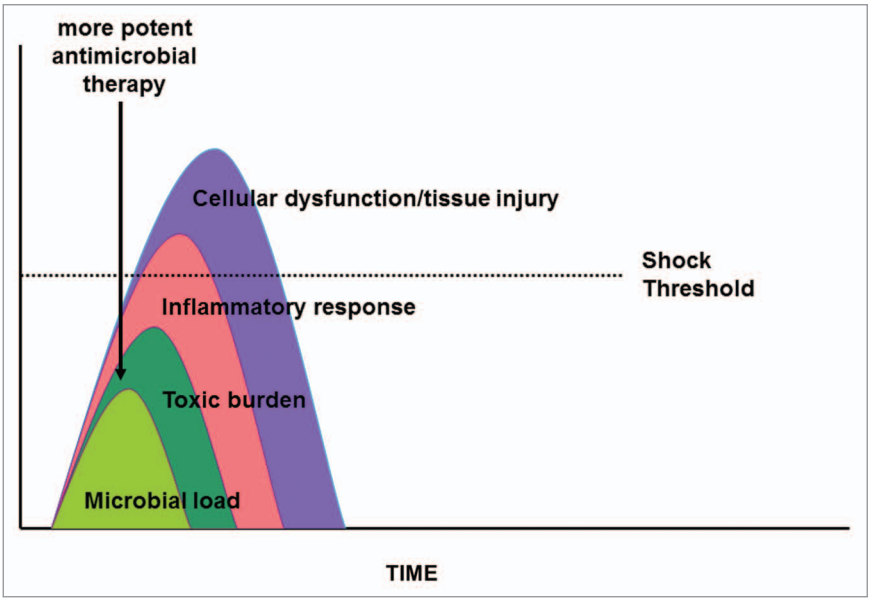

Figure 7. Impact of more potent antimicrobial therapy in sepsis and septic shock. See text for explanation.

Potency of Antimicrobial Therapy

According to Ehrlich's dictate on optimizing therapy of serious infections, the first principle was to "hit hard".[52] In the simplest terms, this can be understood to mean that, all other things being equal, highly potent antimicrobial regimens providing the most rapid clearance of pathogens are preferred (**Fig. 7**). This principle has many implications in regards to antimicrobial strategy. It would suggest that cidal therapy may be preferred over static since the terms "static" and "cidal" intrinsically define the rate of pathogen clearance. This principle also suggests that pharmacokinetic optimization of antimicrobial dosing is a requisite element of ideal therapy since "optimization" refers to dosing regimens that clear pathogens more effectively. Further, to the extent that combination therapy has been shown to accelerate pathogen clearance in some models of infection,[164] this principle implies that improved survival should result.

Rapid pathogen clearance should, in theory, lead to improved clinical response in those infections where a persistent organism burden leads to a time-dependent risk of irreversible and irreplaceable organ injury. The classic example is bacterial meningitis where persistence of organism after initiation of therapy is associated with poor outcome.[165,166] In the case of septic shock, more rapid pathogen clearance can similarly be expected to lead to less release of endogenous mediators, more rapid resolution of hemodynamic instability, and improved survival.

Cidal vs. Static Therapy

Although cidal therapy, by definition, should provide more rapid clearance of pathogens, clinical studies generally suggest a lack of clinical superiority over static therapy in most infections.[167-169] However, there is a paucity of data on this issue in conditions with time-dependent risk particularly septic shock.

The best known study that has addressed the issue of the importance of cidality in life-threatening infections is the classic study of bacterial meningitis by Lepper and colleagues.[170] Meningitis, like septic shock is a condition where the speed of pathogen clearance would be expected to be associated with outcome given that delays of therapy can be expected to result in a progressively increasing risk of irreversible organ (brain) injury and, therefore, death. Lepper's 1951 study demonstrated that the addition of tetracycline, a bacteriostatic antibiotic, to penicillin (a bactericidal drug dependent on active bacterial replication for killing activity) for therapy of pneumococcal meningitis was associated with worse survival compared with penicillin alone. The basis of this outcome has been thought to be potential antagonism of penicillin-driven bacterial clearance by tetracycline. Similar results have been described when β-lactams are combined with chloramphenicol for treatment of pediatric gram-negative (excluding *Haemophilus influenzae*) meningitis.[171-174] Chloramphenicol, though a cidal drug for most meningeal pathogens is static for gram-negatives (other than *H. influenzae*). Supportive data in experimental rabbit meningitis suggests a similar need for cidal therapy.[175]

In recent years, relatively few studies have compared the efficacy of well-established cidal vs static agents in serious infections that may be associated with sepsis and septic shock. One randomized controlled study of anidulafungin (a cidal antifungal echinocandin[176]) demonstrated superiority over a static triazole, fluconazole in invasive candida infections.[26] As with bacterial endocarditis[177-179] and osteomyelitis,[180] higher cidal activity of antibiotic regimens is associated with better clinical cure rates in neutropenic gram-negative bacteremia.[181]

With respect to specific bacteriostatic antibiotics, at least one study has suggested inferior microbiological clearance of pathogens in association with a trend to inferior clinical response in clinically evaluable subset in patients with skin and soft tissue infection treated with tigecycline (a static drug) compared with a combination of aztreonam and vancomycin[182] though other studies have failed to show similar results.[183,184] A metaanalysis of tigecycline non-inferiority trials has shown evidence of increased mortality in the tigecycline arm.[185] The use of chloramphenicol for intra-abdominal infections yielded similar initial clinical outcomes compared with penicillin with gentamicin for community-acquired pneumonia in third-world children.[186] However, its use was associated with a significantly higher relapse rate at one month suggesting suboptimal microbiologic cure.

Although nominally a cidal agent, vancomycin has relatively weak bacterial killing activity relative to anti-staphylococcal penicillins for methicillin-sensitive *S. aureus* (MSSA) in time kill studies.[187] Accordingly, retrospective studies have shown

that vancomycin yields inferior clinical responses and/or survival than anti-staphylococcal β-lactams in patients with MSSA bacteremic infections including pneumonia.[92,187-191] Notably, the bacteriostatic agents quinipristin/dalfopristin (a streptogramin) and linezolid (an oxazolidinone) appear to be no more effective than vancomycin for therapy of serious *S. aureus* infections.[192-194] The cidal lipopeptide daptomycin in contrast tends to be superior to vancomycin and comparable to β-lactams in the treatment of bacteremic *S. aureus* infections.[195,196]

Overall, the available evidence supports the potential superiority of cidal therapy in life-threatening infections where a time-dependent risk of irreversible and irreplaceable organ injury exists. However, additional studies will be required to definitively address this question in septic shock where the difference should be most profound.

Pharmacokinetic Optimization

A substantial body of literature suggests that optimization of dosing strategies can improve pathogen clearance and clinical responses in infection. However, to date, data on the impact of pharmacokinetic (PK) optimization on mortality in serious infections, particularly septic shock, remains sparse. This review will focus on the two groups of agents used commonly as monotherapy. However, similar principles regarding PK optimization and ideal antimicrobial therapy apply to other agents.

Time-dependent killing agents

For β-lactam antibiotics, the key PK parameter for optimization of pathogen clearance is the fractional time above the minimal inhibitory concentration (fT > MIC) of the pathogen. This refers to the amount of time (relative to the dosing interval) that the concentration of free antibiotic in the plasma exceeds the minimal inhibitory concentration (MIC) of the organism. Experimental studies including murine neutropenic thigh infection and pneumonia models suggests that a fT > MIC of >40–70% (depending on the class of β-lactam) during the course of therapy yields maximal rate of pathogen clearance and clinical response/cure rate.[197] There are relatively few studies that examine the role of fT > MIC in serious human infections.

In one study, the rate of clearance of gram-negative bacteria from a total of 32 cases of nosocomial pneumonia among the critically ill was correlated with the fractional time above the dynamic response concentration (similar to fT > MIC) of the pathogen to the treatment antibiotic, cefmenoxime.[198] Higher values were also associated with decreased durations of therapy. More recently, the same group has shown that a fT > MIC of 100% in 76 patients enrolled in comparative RCTs of ceftazidime and cefepime for sepsis with bacteremia, lower respiratory tract infection, or complicated urinary tract infection was associated with better bacterial eradication and clinical cure rate than patients with an fT > MIC < 100%.[199] In another retrospective study of non-urinary tract infections caused by *P. aeruginosa*, achievement of cefepime exposures of > 60% fT > MIC minimized the possibility of a poor microbiological response.[200] In another study, continuous infusion (which generates 100% fT > MIC for sensitive pathogens) rather than intermittent cefmandole (both with intermittent carbenicillin) was resulted in improved clinical cure in the neutropenic (ANC < 100) and cefmandole sensitive pathogen groups of a group of 235 randomized patients.[201] The use of continuous infusion as opposed to intermittent administration of piperacillin has also been shown to be associated with a more rapid decrease in APACHE II score at days 2–4 of the ICU stay in another randomized trial of 40 septic critically ill patients with serious infections.[202] Continuous infusion of meropenem has further been shown to be superior to intermittent dosing with respect to microbiologic cure in a randomized, open label study in severe infections admitted to ICU (with a trend favoring improved clinical cure) compared with standard intermittent dosing.[203]

Among the sickest of the approximately 200 patients (with an APACHE II score of ≥17), extended infusion of piperacillin/tazobactam (4 h rather than a standard 30 min bolus which also increases fT > MIC) for serious Pseudomonas infections has been found to be associated with a shorter hospitalization and lower 14 d mortality.[204] This finding is particularly noteworthy in that a mortality effect was noted in only the most critically ill patients; presumably, a large proportion of these would have had septic shock. Similarly, others have shown that continuous infusion of meropenem, piperacillin/tazobactam, and ceftazidime are each associated with a higher rate of clinical cures in high risk gram-negative ventilator-associated pneumonia than is intermittent dosing.[205-207] This applied particularly to organisms with higher MIC values including *Pseudomonas*. A recent double-blind, randomized controlled study of severe sepsis has shown that continuous infusion of β-lactams yields a higher clinical cure rate than does intermittent infusion of the same dose of the antibiotic.[208]

At least two metaanalyses of continuous infusion of β-lactams in human infection have been published.[209,210] Neither showed an overall beneficial effect of continuous infusion; however, both yielded intriguing insights. Each study commented on the trend toward greater beneficial effects in those studies with high baseline mortality risk, an observation that is congruent with our underlying hypothesis that the benefit of pharmacokinetic optimization of dosing strategies on mortality should exist primarily in septic shock and other conditions where a time-dependent risk of irreversible and irreplaceable organ failure exists. In totality, these data support the use of high-end daily dosing at short intervals, extended infusions if necessary and continuous infusions where possible. These data also suggest the need for studies of continuous infusion β-lactam therapy in the highest risk septic shock patients who are most likely to benefit.

Concentration-dependent killing agents

For fluoroquinolones and aminoglycoside antibiotics, the key PK parameter for optimization of pathogen clearance is the area under the curve divided by the MIC relative to the dosing interval and normalized to 24 h (AUC_{24}/MIC) although peak/maximum concentration divided by the MIC of the pathogen (Cmax/MIC) is a closely related value.[211-215] These refer again to free drug values. Experimental animal models and human studies suggest that a AUC_{24}/MIC of >87–125 (depending on the individual drug and clinical syndrome) during the course of therapy yields optimal pathogen clearance and clinical cure.[197,211-215]

In one study of ciprofloxacin therapy of serious infections in 74 critically ill patients, an AUC_{24}/MIC of >125 (total drug) was associated with a significantly better clinical response and bacterial clearance than values below that cut-off.[215] Time to bacterial eradication sequentially fell with AUC_{24}/MIC values of <125 (32 d), 125–250 (6.6 d), and >250 (2.0 d). Another study found that clinical cure rates in excess of 90% could be achieved in cases of *Pseudomonas* bacteremia with AUC_{24}/MIC values of >123 and Cmax/MIC values >8 for ciprofloxacin and/or aminoglycoside therapy.[213] The same authors found cure rates of >90% above and <30% below a threshold AUC_{24}/MIC of 250.[216] Similarly, levofloxacin Cmax/MIC of >12.2 was found to be associated with a favorable clinical response and pathogen eradication in a prospective open-label study of hospitalized infections requiring at least 3 d of intravenous therapy.[217] Other have found that patients with VAP experienced more consistent eradication of the pathogen when the AUC_{24}/MIC was ≥87.[218] Similarly, others have shown more effective elimination of *P. aeruginosa* when levofloxacin AUC_{24}/MIC was ≥88 (90% vs 43% if <88).[219] Unfortunately, no human data linking fluoroquinolone PK indices to survival or mortality surrogates and no studies of septic shock have yet been reported.

Nonetheless, given that several studies have shown that inadequate plasma concentrations of fluoroquinolones can be anticipated in critically ill patients, an approach that maximizes the dose within a non-toxic range (e.g., 600 every 12 h for ciprofloxacin or 750 mg daily for levofloxacin assuming preserved renal function) is likely to provide maximally rapid pathogen clearance.[156,212,216] Such a high dose approach is prudent particularly for critically ill patients with severe sepsis and/or septic shock where rapid clearance of pathogen would be expected to improve survival.

Vancomycin is another antibiotic whose efficacy is most closely related to concentration-dependent pharmacokinetic indices. One retrospective study of methicillin-resistant *S. aureus* bacteremia reported fewer vancomycin treatment failures in those who had AUC_{24}/MIC values ≥421.[220] In another retrospective study in patients with MRSA pneumonia, better microbiological and clinical outcomes in patients who had vancomycin AUC_{24}/MIC values ≥400.[221] The author has recently demonstrated that AUC_{24}/MIC is independently associated with survival in a retrospective study of MRSA septic shock.[222]

Antimicrobial pharmacokinetic indices have been linked clinical and microbiologic response in a variety of studies but studies showing an association with survival are more limited. To the extent that such studies exist, they tend to show a survival advantage in critically ill patients, particularly those with septic shock.

Combination vs. Monotherapy

Assuming that a pathogen is sensitive to one antibiotic in a regimen, the incremental contribution of a second antibiotic to which the pathogen is sensitive is uncertain. Combination therapy using antibiotics of different classes can generate an additive or even synergistic antimicrobial killing effect leading to more rapid pathogen clearance.[164,223-226] Antimicrobial synergy with increased bacterial clearance appears to be best established for β-lactam/aminoglycoside combinations.[227-230] However, similar data on synergistic activity has emerged for combinations of a β-lactam and fluoroquinolone.[231-237] There is even some data suggesting additive effects[238] or even potential synergism[239-242] for β-lactam/macrolides combinations in certain circumstances.

Despite animal models[164,243,244] and clinical studies of infection including endocarditis, gram negative bacteremia, cryptococcal meningitis, and neutropenic sepsis[225,245-247] suggesting a potential therapeutic role of combination therapy, the clinical benefit with respect to outcome of severe infections associated with sepsis has been uncertain. One metaanalysis of randomized controlled trials failed to demonstrate a benefit of β-lactam/aminoglycoside combination therapy in a wide variety of infections.[248] Two separate metaanalyses have also failed to demonstrate evidence of benefit with combination therapy in immunocompetent patients with sepsis and/or gram-negative bacteremia.[249,250] Other metaanalyses of neutropenic sepsis have similarly suggested little incremental benefit of combination therapy of a β-lactam ± an aminoglycoside.[251]

A few studies have suggested the possibility that a mortality benefit of combination therapy may exist in sicker patients, particularly those with severe pneumococcal pneumonia/bacteremia[252-255] and gram-negative bacteremia.[256-258] Based on these data and the view that increased bacterial clearance would be beneficial in septic shock, we performed a stratified metaanalysis/metaregression of 60 sepsis data sets. This analysis showed that combination therapy using 2 drugs (primarily β-lactams with a second agent) yielded a consistent benefit in terms of clinical cure and survival only in patient groups with septic shock or otherwise at high baseline (monotherapy) risk of death.[259] Although a pooled odds ratio indicated no overall mortality/clinical response benefit in sepsis (including both sepsis without shock and septic shock) with combination therapy (odds ratio 0.856, 95% confidence interval 0.71–1.03, $P = 0.0943$, $I^2 = 45.1\%$), stratification of data sets by monotherapy mortality risk demonstrated substantial benefit in the most severely ill subset (monotherapy risk of death >25%, OR 0.51, 95% CI 0.41–0.64, $I^2 = 8.6\%$). Of those 24 data sets that could be stratified by the presence or absence of shock/critical illness, the more severely ill group with shock consistently demonstrated increased efficacy of a combination therapy strategy (OR 0.49 95% CI 0.35–0.70, $P < 0.0001$, $I^2 = 0\%$). Metaregression indicated that efficacy of combination therapy was dependent only on the risk of death in the monotherapy group. A consistent benefit of combination therapy was found in groups with a baseline (monotherapy) mortality risk of >25% and/or characterized by the presence of septic shock. Of note, these findings held even when the analysis was restricted to only randomized controlled trials.

Our recent study of 2446 propensity-matched septic shock patients has expanded this observation.[260] We found that combination therapy using two antibiotics of different antimicrobial classes (i.e., a β-lactam with a fluoroquinolone, aminoglycoside, or in the case of sensitive gram-positives, macrolide/clindamycin) to which the pathogen was sensitive in vitro resulted in an improved 28 d (63.7% vs 71%, hazard ratio, 0.77; 95%

confidence interval, 0.67–0.88; $P = 0.0002$) and hospital survival (52.2% vs 62.6%, odds ratio, 0.69; 95% confidence interval, 0.59–0.81; $P < 0.0001$). This beneficial effect was independent of organism group and clinical syndrome and was restricted to β-lactams in combination with fluoroquinolones, aminoglycosides, or a macrolide/clindamycin. Interestingly, the most potent β-lactams, β-lactamase inhibitor combinations, and carbapenems (which have 100% $t >$ MIC and therefore maximal cidality for most pathogens) failed to demonstrate evidence of benefit with combination therapy. As predicted by our model of the pathogenesis of septic shock, duration of hypotension was also significantly shorter with combination therapy.

While a randomized controlled trial of therapy of severe sepsis using meropenem ± moxifloxacin failed to demonstrate similar benefit,[261] this outcome was predicted by the failure in our propensity study[260] for carbapenem combinations to yield a survival advantage for the reason noted above. Several additional recent retrospective studies have similarly shown a benefit of combination therapy using antibiotics with different mechanisms of action in septic shock and related conditions.[262-264]

Although highly suggestive, these recent retrospective analyses cannot be considered definitive. However, pending the publication of appropriate randomized trials, a strategy of several days of combination therapy for cases of septic shock may be advisable. If our model of microbial load-driven pathogenesis of septic shock accurately reflects the pathophysiology of septic shock, only a few days of combination therapy (until hemodynamic stabilization) is required since at that point, the organism burden has been reduced to a level which no longer drives septic shock and significant ongoing organ injury.

Conclusion

There has been little improvement in the mortality of septic shock since the advent of modern antimicrobial therapy over 60 years ago. The development of ever more broad-spectrum and potent antimicrobials has predictably resulted in evolutionary pressure on microbial pathogens resulting in selection toward resistant organisms. One consequence of this phenomenon may be the lack of progress in efficacy of antimicrobial therapy of septic shock over the ensuing decades.

This review presents a novel model of septic shock pathogenesis that integrates microbiologic, immunologic, and physiologic aspects of the disorder. This alternate paradigm of septic shock pathogenesis differentiates between the pathophysiologic processes that underlie sepsis without shock and septic shock. The model can be used to understand and predict key determinants of antimicrobial therapy response in septic shock. In particular, this model implies that improved outcomes in severe infections with septic shock may be easily achieved through better use of the antimicrobials already in our armamentarium.

In the past, resuscitative elements have taken priority in the management of septic shock. Optimal use of antimicrobial therapy has not been emphasized. However, the reviewed data suggest that empiric, broad spectrum antimicrobial administration should be considered an intrinsic component of initial resuscitation of septic shock. In addition, early optimization of pathogen clearance using highly cidal agents, optimization of antimicrobial pharmacokinetics, and use of appropriate combination therapy appears to increase survival. Available evidence suggests that an approach that combines rapid and potent therapy (i.e., hitting "fast and hard") should result in significant reductions of septic shock mortality.

Disclosure of Potential Conflicts of Interest

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