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Early Antimicrobial Therapy in Severe Sepsis and Septic Shock

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Abstract The advent of modern antimicrobial therapy following the discovery of penicillin during the 1940s yielded remarkable improvements in the case fatality rates of serious infections, including septic shock. Since then, pathogens have continuously evolved under selective antimicrobial pressure, resulting in a lack of additional significant improvement in clinical effectiveness of antimicrobial therapy of septic shock despite ever more broad-spectrum and potent drugs. In addition, although substantial effort and money were expended on the development of novel nonantimicrobial therapies of sepsis in the past 30 years, clinical progress in this regard has been limited. This article explores the possibility that the key to significant improvement in the outcome of septic shock may lie, in great part, with improvements in delivery of existing antimicrobials. Recognizing the role of delays in administration of antimicrobial therapy in the poor outcomes of septic shock is central to this effort.

Keywords Antibiotic · Antimicrobial · Antifungal · Sepsis · Septic shock · Infection · ICU · Critical care · Treatment · Therapy · Delay

Introduction

Septic shock and sepsis-associated multiple-organ failure remain the most common cause of death in intensive care units (ICUs) of the medically advanced nations. Historically, the mortality associated with sepsis and septic shock has been about 50% to 75% [1–3]. The primary advance in the therapy of septic shock was the development of antibiotic therapy 50 years ago, which resulted in a reduction in sepsis-associated mortality to the 30% to 50% range [1, 2]. However, the past 40 years saw 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 US cases of severe sepsis to 1.6 million by 2050 with an increase in population of only 33% [5]. Currently, cases of severe sepsis and septic shock account for about 10% to 15% of all ICU admissions, with about 25% of cases of sepsis [6] and 50% to 75% of cases of severe sepsis progressing 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, until recently, numerous clinical trials have failed to produce any new drugs with consistent beneficial effects on this patient population. Even the efficacy of activated protein C —the only novel nonantimicrobial pharmacotherapy of sepsis and septic shock approved since the advent of modern antimicrobials—was recently questioned [10, 11].

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 of this disorder suggests that sepsis is present when infection-driven systemic activation of inflammatory pathways occurs [12, 13]. In this paradigm, the syndrome progresses as a consequence of inflammatory cellular signaling despite the rapid elimination of the pathogen through administration of cidal antimicrobial therapy [14, 15]. Sepsis, severe sepsis (ie, sepsis with organ failure), and septic shock (ie, sepsis with cardiovascular failure) are considered to be related disorders of

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increasing severity but sharing a similar basic underlying pathology, one of direct inflammatory 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 a very 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. A variety of immunomodulatory therapies based on this paradigm of sepsis have been developed but failed to improve outcomes in clinical trials [16]. One key deficiency of this model may be that most pathogens cannot be eliminated quickly despite cidal antimicrobial therapy and likely persist during the period that immunomodulatory therapies (most of which are immunosuppressive) might be initiated.

Another view of septic shock derives from the classic microbiologic paradigm of life-threatening infection and sepsis. In this model, infection is the key driving element of sepsis and septic shock. The process begins with a nidus of infection (eg, peritonitis, pneumonia). Within that focus, the organism replicates and, untreated, the microbial infectious load increases over time. The microbial pathogens release a variety of endotoxins and exotoxins, which have antigenic properties and stimulate an overlay of endogenous mediators, including inflammatory cytokines (eg, tumor necrosis factor, interleukin-1) and eicosanoids (prostaglandin E_2, prostacyclin, thromboxanes, leukotrienes). The result is tissue dysfunction, which can be manifested as cellular and, ultimately, organ dysfunction, including septic shock. The central element 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.

However, this model fails to recognize a key element in mortality of septic states: the concept of irreversible shock, as originally described by Wiggers [17]. This concept suggests that regardless of the cause, shock can only be tolerated for a limited time. Once present, shock will become irreversible and inevitably progress to death if the condition is not reversed within a short period. This concept is directly associated with the idea of the "golden hour," which was first demonstrated in the context of hemorrhagic/traumatic shock but is applicable to various forms of critical injury, particularly other shock states. Many studies have shown that early definitive intervention (ie, 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 with nondefinitive support modalities (eg, blood products for hemorrhagic shock, intra-aortic balloon pump for myocardial infarction-associated cardiogenic shock, pressors for all forms of shock). However, mortality will not be improved without definitive elimination of the underlying source of hemodynamic instability: for example, thrombolysis [18], angioplasty [19], or bypass for cardiogenic shock due to myocardial infarction; embolectomy or thrombolysis of massive pulmonary embolism causing obstructive shock [20]; or definitive repair/control of a bleeding lesion causing hypovolemic shock [21].

Septic shock can be viewed through a similar prism. In this circumstance, the underlying source of shock is the total microbial load. This proposed paradigm predicts that the speed with which the inciting infection is reduced to a subcritical threshold after the onset of persistent or recurrent hypotension will be of paramount importance in surviving septic shock. Rather than being an incidental epiphenomenon, shock becomes a central driver in the genesis of irreversible organ injury. 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 used to predict key aspects of pathogenesis of septic shock and to develop novel approaches to effective therapy. This construct is similar to the infectious diseases model of septic shock, with two major additions. First, a physiologic point exists at which inflammatory mediator-associated cellular dysfunction and tissue injury manifest as septic shock. This threshold is 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 novel element 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 hypotension onset (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. The implied maximally effective approach to therapy is to rapidly reduce the infectious load so that the period of time in shock (irrespective of whether vasopressors are able to maintain blood pressure) before reduction of the microbial load to a subcritical threshold is held to an absolute minimum (ie, minimizing the period

that sufficient organisms are present to generate shock). Based on the model, this approach should minimize the risk that the indeterminate pathophysiologic point at which recovery is no longer possible in septic shock is passed.

Such a model of injury in septic shock has two major pathophysiologic implications. 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 simplest line of evidence for this proposition is the commonality of the stark clinical features (eg, hypotension, lactic acidosis, substantial exhaustion of compensatory physiologic responses) and high (>50%) mortality of septic shock and other shock syndromes of any etiology, in contrast to the relatively milder clinical features and lower (~15%) mortality of sepsis or severe sepsis [22]. 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 [23].

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, evidence exists to support this contention. We have shown that the onset of shock in a rodent model of *Escherichia coli* peritonitis/septic shock consistently occurs at a defined microbial organism load in blood [24]. Even as varying numbers of organisms 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 organisms. However, meningococci have remarkably consistent growth characteristics. Several studies have demonstrated that earlier antimicrobial therapy is critical in the outcome of severe meningococcal disease. One study 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 lipopolysaccharide in plasma of patients with meningococcal disease [25]. In another study, logistic regression analysis demonstrated that blood bacterial load predicted outcome of meningococcal shock [26]. Delays in antimicrobial therapy were associated with outcome only in univariate analysis, and all deaths were associated with bacterial loads greater than 10^5 CFU/mL. Other studies similarly demonstrated that the increasing organism burden is associated with increased morbidity and mortality in serious infections [27]. For example, the risk of septic shock and death in serious pneumococcal infections increases with organism burden [28•], and mortality of *Staphylococcus aureus* septic shock increases with shorter times to blood culture positivity (a surrogate marker of higher bacterial blood counts) [29].

One of the central testable hypotheses derived from this paradigm is that the rapid clearance of pathogens will be the central determinant of outcome in any infection with a time-dependent risk of irreversible and irreplaceable organ injury. Such conditions may include meningitis, rapidly progressive necrotizing soft-tissue infections, and, in particular, septic shock. 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 medically advanced nations. Although several approaches may yield benefit, 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 antimicrobial therapy will reduce the microbial load driving organ injury/dysfunction and hypotension, thus reducing the risk of irreversible shock and death.

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 in 1913, said “Frapper fort et frapper vite”—hit hard and hit fast with antimicrobials. In the modern context, his advice as it pertains to rapid therapy embodies two distinct elements. First, it is clearly necessary that initial empiric antimicrobial therapy be appropriate. Second, this appropriate empiric therapy must be administered as quickly as possible.

Appropriateness of Antimicrobial Therapy

Failure to initiate antimicrobial therapy that covers the pathogen is associated with marked increases in mortality, especially in septic shock. For that reason, empiric antibiotic regimens should approach 100% coverage of pathogens for the suspected source of infection. The initiation of inadequate antimicrobial therapy may occur as frequently as 17.1% in patients with community-acquired and 34.3% in patients with nosocomial bacteremia admitted to the ICU [30]. Similarly, 18.8% and 28.4% of patients with septic shock were initially treated with inadequate antimicrobial therapy in another large study [31•]. Retrospective studies have shown that the risk of death increases from 30% to 60% in ICU bacteremia [3, 32] to 70% to 100% in gram-negative shock [3] when the initial empiric regimen fails to cover the inciting pathogen. More recent data suggest that the initiation of inappropriate

empiric antimicrobial therapy (ie, failing to cover the pathogen) is associated with a reduction in survival of about fivefold (range 2.5- to 10-fold in selected subgroups) from 55% to about 11% [31•] (Fig. 1). 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* spp [3, 31•, 33–36]. Similar findings were documented with a variety of serious infections, including community-acquired pneumonia, hospital- and ventilator-associated pneumonia, and bacterial peritonitis [37, 38].

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 the clinician's failure 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, prior hospitalization, and prior colonization or infection with multiresistant organisms.

Superior empiric coverage can be obtained through the use of a local antibiogram or infectious diseases consultation [39, 40•]. Although not routinely required, extended-spectrum gram-negative regimens, vancomycin, and/or antifungal therapy may be appropriate in specific, high-risk patients with severe sepsis (Table 1). In addition, given that 90% to 95% of patients with septic shock have comorbidities or other factors that put them at high risk for resistant organisms, it may be appropriate to initially treat all patients with septic shock using a combination of antimicrobials, resulting in a broadly expanded spectrum of coverage for the first few days. This approach should yield improved initial adequacy of antimicrobial coverage, and ensure that high-risk patients are not inappropriately categorized as low-risk.

It is critically important to adjust empiric antimicrobial therapy to a narrower regimen within 48 to 72 h if a plausible pathogen is identified or if the patient stabilizes clinically (ie, resolution of shock). Although several retrospective studies have demonstrated that inappropriate therapy of bacteremic septic shock yields increased mortality [3, 32–36], none have suggested that early narrowing of therapy is detrimental if the organism is identified or if the patient is

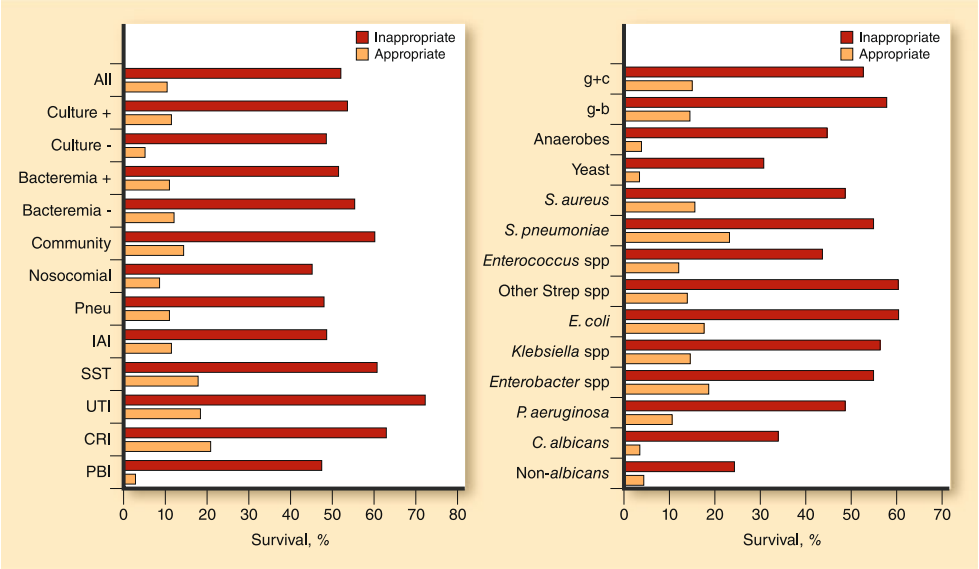

Fig. 1 Antimicrobial appropriateness and survival in septic shock subgroups. Bacteremia$^-$—nonbacteremic infections; bacteremia$^+$—bacteremic infections; community—community-acquired infections; CRI—catheter-related infections, including central venous, dialysis, pulmonary artery, and arterial catheters; culture$^-$—culture-negative infections; culture$^+$—culture-positive infections; g-b—infections caused by gram-negative bacilli; g+c—infections caused by gram-positive cocci; IAI—all intra-abdominal infections, including peritonitis, cholangitis, cholecystitis, intra-abdominal abscess, ischemic bowel, and so on, but excluding infections of the abdominal wall; nosocomial—nosocomial infections; PBI—primary blood stream infections; pneu—all infections of the respiratory tract including pneumonia and empyema; spp—species; SST—skin and soft-tissue infections, including fascial or skeletal muscle but excluding surgical wound infections; UTI—all infections of the urinary tract, including pyelonephritis (with or without obstruction) and perinephric abscesses, but exclusive of infections of the reproductive tract; yeast—*Candida* and other yeast infections, excluding blastomycosis and filamentous fungi such as *Aspergillus*. (*Adapted from* Kumar A et al. [31•].)

Table 1 Indications for extended empiric antibiotic therapy of severe sepsis/septic shock

Increased gram-negative coverage	Nosocomial infection
	Neutropenic or immunosuppressed
	Immunocompromised because of chronic organ failure (eg, liver, renal, lung, heart)
Increased gram-positive coverage (eg, vancomycin, daptomycin)	High-level endemic MRSA (community or nosocomial)
	Neutropenic patient
	Intravascular catheter infection
	Nosocomial pneumonia
Fungal/yeast coverage (triazole, echinocandin, amphotericin B)	Neutropenic fever or other immunosuppressed patient unresponsive to standard antibiotic therapy
	Prolonged broad-spectrum antibiotic therapy
	Positive relevant fungal cultures
	Consider empiric therapy if high-risk patient with severe shock

MRSA methicillin-resistant *Staphylococcus aureus*

responding well clinically. To the contrary, some studies have suggested that narrowing of antimicrobial therapy is associated with improved outcomes [41, 42]. 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% of improving patients who are 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 48 to 72 h after initiation is required.

Antimicrobial Delay

Delays in initiation of appropriate antimicrobial therapy have a substantial role in determining the mortality of septic shock. The central role of such delays is apparent in the major upward inflection in mortality of antibiotic-treated murine septic shock coincident with the onset of hypotension and lactic acidosis [24]. Other animal studies have similarly shown a very rapid inflection in mortality in experimental severe infections, absent appropriate antimicrobial therapy [43, 44]. Human studies pertaining to the impact of delays of antimicrobial therapy on serious infections date back at least to the work of Bodey et al. [45], who demonstrated increasing mortality risk when appropriate antimicrobials were delayed more than a day following documentation of *Pseudomonas bacteremia*. Meehan et al. [46] showed that delays in initial antimicrobial administration greater than 8 h after admission to the emergency department for community-acquired pneumonia are associated with increased mortality in a large cohort of Medicare patients. Houck et al. [47] pushed this boundary lower by demonstrating increased mortality in Medicare patients with community-acquired pneumonia whose antimicrobial treatment was delayed more than 4 h following ICU admission.

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 of delay [48••]. 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 (Fig. 2). For every additional hour to effective antimicrobial initiation in the first 6 h after hypotension onset, survival dropped an average of 7.6%. With effective antimicrobial initiation between the first and second hour after hypotension onset, survival had already dropped to 70.5%. With effective antimicrobial therapy delay of 5 to 6 h after hypotension onset, survival was just 42.0%, and by 9 to 12 h, survival was 25.4%. The adjusted odds ratio of death was already significantly increased by the second hour after hypotension onset, and the ratio continued to climb with longer delays. An unpublished analysis of an expanded dataset 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 [48••]. Substantial delays before initiation of effective therapy have been shown in several studies of serious infections [46, 47, 49, 50]. Additional retrospective studies of human bacteremia, candidemia, septic shock, community-acquired pneumonia, hospital-acquired pneumonia, and meningitis with sepsis have confirmed that the mortality in these septic conditions is increased with significant delays in antimicrobial administration [36, 46, 50–52, 53•, 54–57, 58•, 59–63, 64••].

Several studies have now assessed the impact of speed of appropriate empiric antimicrobial therapy on outcome in

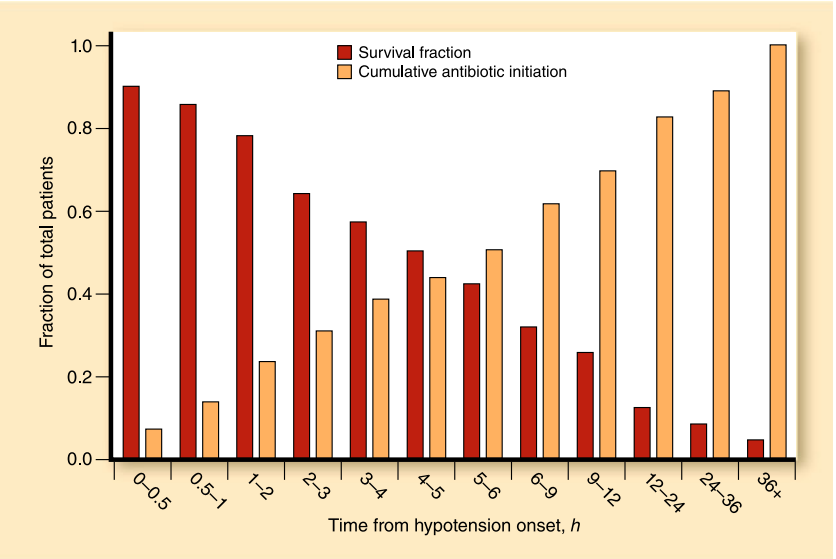

Fig. 2 Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. The x-axis represents time (hours) following first documentation of septic shock-associated hypotension. The *dark bars* represent the fraction of patients surviving to hospital discharge, and the *light bars* represent the cumulative fraction of patients having received effective antimicrobials at any given time point. (*From* Kumar A et al. [48••], with permission.)

relationship to other elements of therapy. In our study of human septic shock, 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, whereas variations in fluid resuscitation could explain less than 2% [48••]. 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 et al. [65••] of about 2,800 patients with severe sepsis and septic shock suggested that only rapid antimicrobial therapy (<1 h vs >6 h of severe sepsis diagnosis) and use of drotrecogin-α (activated) among elements of an internationally recommended "sepsis bundle" were independently associated with survival [66]. Similarly, Varpula et al. [67], using logistic regression analysis, showed that only early initiation of antimicrobials (<3 vs >3 h of emergency department admission) among elements of a "sepsis bundle" was associated with improved survival in 92 patients with community-acquired septic shock. 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 [68]. Likewise, Subramanian et al. [69] showed that only rapid initiation of antimicrobial therapy (<1 h following ICU admission or

Table 2 Causes of delays in administration of antimicrobials in severe infection

1) Failure to recognize that hypotension represents septic shock
2) Effect of inappropriate antimicrobial initiation (delays administration of appropriate antimicrobials)
3) Failure to appreciate risk of resistant organisms in certain scenarios (eg, immunocompromised vs immunosuppressed; antecedent antimicrobial use) leading to inappropriate initial antimicrobials
4) Wait for blood or site-specific cultures and gram stains before giving antibiotic
5) Requirement for two nurses to check for potential drug sensitivity before administration of antimicrobials
6) For community-acquired septic shock, transfer from emergency department before ordered antibiotics given
7) Failure to use "stat" orders
8) Failure to recognize that administration of inappropriate antimicrobials is equivalent to absent antimicrobial therapy when responding to clinical failure (ie, should not delay appropriate antimicrobials because inappropriate drugs recently given)
9) No specified order with multiple drug regimens so that key drug (usually most expensive and hardest to access) may be given last
10) Administrative/logistic delays (nursing/pharmacy/ward clerk)

Table 3 Potential approaches to minimize delays in initiation of empiric antimicrobial therapy

1) The presence of hypotension in a patient with known or suspected infection should be considered as septic shock in the absence of a definitive alternate explanation
2) No transfer from emergency department before ordered antibiotics given
3) All initial orders for any intravenous antibiotic automatically "stat"
4) Syndrome-based, algorithm-driven guidelines similar to meningitis and neutropenic sepsis with designated broad-spectrum antimicrobial regimen at each center
5) Antimicrobial order to include sequence and time limit (eg, within 30 min of order)
6) First intravenous dose of most broad-spectrum agents (ie, β-lactam/carbapenems) "push" by physician
7) Nursing and physician education

<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. Delays in appropriate antimicrobial therapy have also been associated with development of acute lung injury [70] and acute renal failure [71]; worsening of organ failure [72]; and higher levels of inflammatory cytokines and other inflammatory markers [72, 73]. 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 [74–76]. The most consistent element of therapy improved with such bundled quality assurance approaches is timeliness and appropriateness of antimicrobial therapy [77].

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 (ie, 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 [31•, 78]. Every effort should be made to obtain appropriate site-specific cultures to allow identification and susceptibility testing of the pathogenic organism; however, as with other laboratory testing, such efforts should not delay antimicrobial therapy. Common causes for delays in antimicrobial therapy and potential solutions are reviewed in Tables 2 and 3.

Conclusions

Little improvement has occurred in the mortality of septic shock since the advent of modern antimicrobial therapy more than 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 suggests that improved outcomes in severe infections and septic shock may be more 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. Timely administration of effective antimicrobial therapy has not been emphasized in the management of these major infections. However, the reviewed data suggest that empiric, broad-spectrum antimicrobial administration should be considered an intrinsic component of initial resuscitation of septic shock. Available evidence suggests that this approach should result in significant reductions of septic shock mortality.

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- •• Of major importance

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