

# Optimizing Antimicrobial Therapy of Sepsis and Septic Shock: Focus on Antibiotic Combination Therapy

Gloria Vazquez-Grande, MD<sup>1</sup> Anand Kumar, MD<sup>2</sup>

<sup>1</sup> Section of Critical Care Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

<sup>2</sup> Section of Critical Care Medicine and Section of Infectious Diseases, Department of Medicine, Medical Microbiology and Pharmacology/Therapeutics, University of Manitoba, Winnipeg, Manitoba, Canada

Address for correspondence Anand Kumar, MD, Section of Critical Care Medicine and Section of Infectious Diseases, Department of Medicine, Medical Microbiology and Pharmacology/Therapeutics, University of Manitoba, Winnipeg, Manitoba, Canada (e-mail: akumar61@yahoo.com).

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## Abstract

There has been little improvement in septic shock mortality in the past 70 years, despite ever more broad-spectrum and potent antimicrobials. In the past, resuscitative elements have been the primary area of clinical septic shock management and research. The question of the optimal use of antimicrobial therapy was relatively ignored in recent decades. This review explores the pathophysiology of sepsis in an attempt to produce a better understanding and define key determinants of antimicrobial therapy response in septic shock. Optimizing existing antimicrobials delivery can drive significant improvements in the outcome of sepsis and septic shock. Inappropriate antimicrobial selection and dosing or delays in the administration substantially increase mortality and morbidity in life-threatening infections. Definitive combination therapy (where a pathogen known to be susceptible to a given agent is additionally covered by another agent) remains controversial. Although some in vitro studies, animal models, and clinical studies of infection including endocarditis, gram-negative bacteremia, and neutropenic infections have supported combination therapy, the potential clinical benefit in other severe infections has been questioned. Several meta-analyses have failed to demonstrate improvement of outcome with combination therapy in immunocompetent patients with sepsis and/or gram-negative bacteremia. These meta-analyses did not undertake subgroup analyses of the septic shock population. This article reviews the existing evidence supporting combination therapy for severe infections, sepsis, and septic shock.

## Keywords

- ▶ septic shock
- ▶ life-threatening infection
- ▶ antibiotic
- ▶ combination therapy
- ▶ survival

Severe sepsis and septic shock with sepsis-associated multiple organ failure represent the major causes of infection-associated mortality and remain the most common cause of death in intensive care units (ICUs) of developed countries. They account for 10 to 15% of all ICU admissions and ~25% of sepsis cases<sup>1</sup>; up to 50 to 75% of severe sepsis cases progress to septic shock.<sup>2</sup> Septic shock alone represents 5 to 8% of all ICU admissions.<sup>3</sup>

Historically, the mortality associated with sepsis and septic shock has been ~50 to 75%.<sup>4–6</sup> This decreased after the

development of modern antimicrobial therapies, starting with penicillin in the early 1940s. Since then sepsis-associated mortality has fallen to the 30 to 50% range.<sup>4,5</sup>

Since the development of modern antimicrobials, bacterial pathogens have continuously evolved under their selective pressure. There has also been a gradual increase in the incidence of sepsis over the intervening decades.<sup>7</sup> Current estimates suggest a doubling of total cases of severe sepsis in United States by 2050 (from the actual 800,000 cases per year

to 1.6 million cases), with a less than proportionate increase in population of only 33% during the same period.<sup>8</sup>

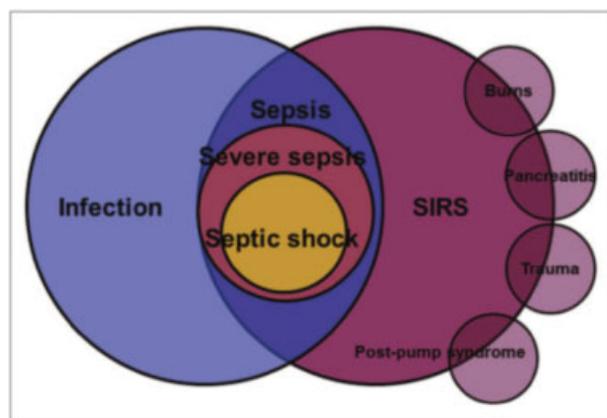
Despite major advances in technology and a constant improvement and refinement of our understanding of sepsis pathophysiology, numerous clinical trials have failed to produce any new drugs with consistent beneficial effects on this patient population.<sup>9,10</sup> Part of the reason for the failure to develop effective novel therapies may be a fundamental misunderstanding of the pathophysiology of septic shock.<sup>11</sup>

## The Immunologic Model

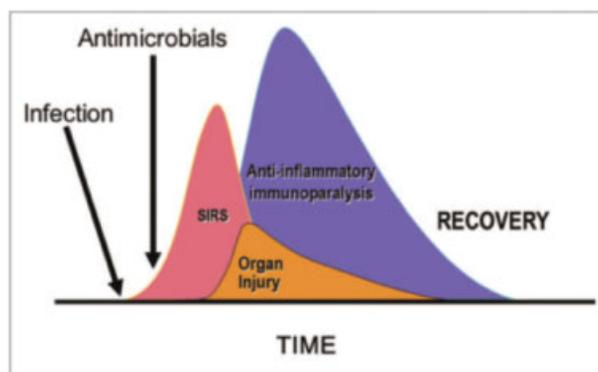
The currently accepted immunologic paradigm of sepsis suggests that this disorder is present when the activation of the systemic inflammatory pathways is triggered by infection.<sup>12,13</sup> The infection initiates an immunologic response (inflammatory cytokine and eicosanoid/coagulation cascade) that propagates independently of the underlying infectious trigger.<sup>14,15</sup> This view of sepsis is reflected in the classic figure by Bone and colleagues (→ Fig. 1).<sup>12</sup> The figure indicates that sepsis is defined by the co-occurrence of infection and systemic inflammatory response syndrome (SIRS), a syndrome that is only indirectly related to the underlying infection. There is no clear suggestion (in the figure) that uncontrolled infection drives the development of SIRS.

This model suggests that progression of sepsis occurs as a consequence of inflammatory cellular signaling and a counter-inflammatory (immunoparalytic) response,<sup>16,17</sup> despite the rapid elimination of the pathogen through administration of cidal antimicrobial therapy<sup>14</sup> (→ Fig. 2). In this view, sepsis, severe sepsis, and septic shock are related disorders of increasing severity, sharing an underlying pathophysiology involving direct endogenous mediator-driven cellular dysfunction and injury.

Under this model, septic shock is considered to be a consequence of the underlying cellular injury induced by the inflammatory mediators rather than by a clinical entity with different and distinct pathogenesis and pathophysiology. If this view of sepsis is wrong or incomplete, this may



**Fig. 1** SIRS, sepsis, severe sepsis, and septic shock. SIRS, systemic inflammatory response. Adapted with permission from Bone et al.<sup>12</sup> See text for explanation.



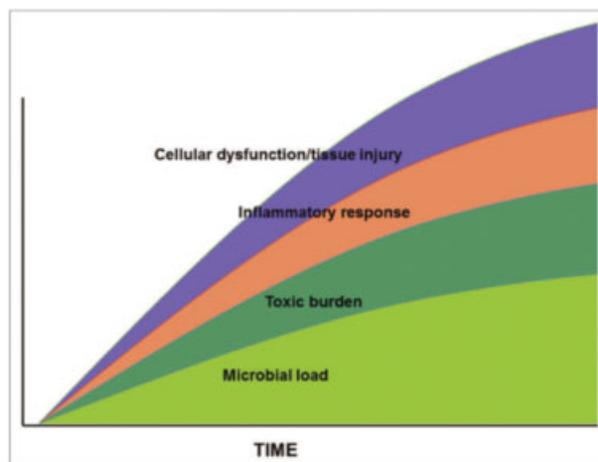
**Fig. 2** Immunologic view of sepsis and septic shock. SIRS, systemic inflammatory response. Adapted with permission from van der Poll and van Deventer.<sup>14</sup> See text for explanation.

explain the reason why immunomodulatory therapies that were developed based on this model failed to improve outcomes in clinical trials.<sup>18</sup>

A key deficiency of this immunologic paradigm of sepsis is that most pathogens cannot be eliminated quickly from the patient, despite the use of cidal antimicrobial therapy.<sup>19–23</sup> Pathogens likely persist over time, maintaining an inflammatory potential. If immunomodulatory therapies (most of which are immunosuppressive) are initiated, clearance of the pathogen burden may even be slowed down despite use of cidal antimicrobials.

## The Classic Paradigm: Microbiologic Primacy

Another view of septic shock derives from the classic model where the infection is the key driving element of sepsis (→ Fig. 3).<sup>11</sup> The septic process starts with a focus of infection, where the organism replicates, increasing the microbial load over time. The pathogens release endo- and exotoxins (toxic burden), which stimulate the production of the endogenous mediators of the inflammatory cascade. The central aspect of the microbiologic paradigm is that the microbial load drives



**Fig. 3** Microbiologic view of sepsis and septic shock. Reproduced with permission from Kumar.<sup>11</sup> See text for explanation.

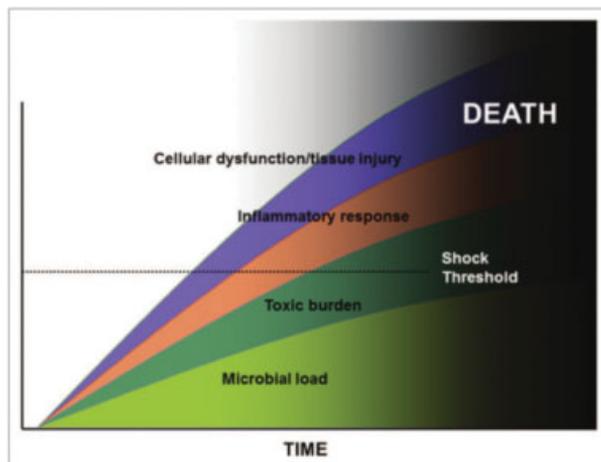
the downstream responses. Thus, the elimination of the underlying infection should terminate the inflammatory cascade and limit tissue injury and organ dysfunction. This model forms the basis of standard antimicrobial therapy in sepsis and septic shock.

However, this model has a key deficiency in that it fails to recognize a key element of septic injury progression, the occurrence of irreversible shock, as originally described by Wiggers in 1950.<sup>24</sup> The concept of irreversible shock suggests that shock can only be tolerated for a limited time regardless of the etiology. If the condition driving shock is not directly addressed within a short period of time, shock will become irreversible, with inevitable progression to death. This is directly associated with the idea of the “golden hour,” first demonstrated in the context of hemorrhagic shock in trauma, but applicable to other shock states. A corollary of this concept suggests that mortality will not be improved without early definitive elimination of the underlying source of hemodynamic instability (e.g., thrombolysis,<sup>25</sup> angioplasty,<sup>26</sup> or definitive repair/control of a bleeding lesion causing hypovolemic shock<sup>27</sup>). With respect to mortality reduction, it is not sufficient to provide only supportive care.

### A Composite Model: Integrating Infection and Shock

If we consider septic shock under an alternative composite perspective, the presence of shock becomes the key driver in the genesis of irreversible organ injury. In this paradigm of septic shock, the underlying source of shock is the microbial load. Thus, the faster you reduce the microbial load to a subcritical threshold, after the onset of persistent or recurrent hypotension, the higher the survival.

This model construct is similar to the microbial paradigm, with two additions (→ Fig. 4).<sup>11</sup> The shock threshold line is the point at which inflammatory mediator-associated cellular dysfunction manifests as septic shock (which is highly variable between individuals). Once that point has been passed, persistent/recurrent hypotension sets the patient on the path to irreversible organ injury and death.<sup>11</sup>



**Fig. 4** Composite view of sepsis and septic shock. Reproduced with permission from Kumar.<sup>11</sup> See text for explanation.

The optimal therapy in this paradigm of septic shock is to rapidly reduce the microbial load to minimize the time that inflammatory stress is sufficient to sustain shock (→ Fig. 5).<sup>11</sup> This should limit the risk of reaching the individually indeterminate pathophysiologic point at which recovery is no longer possible.

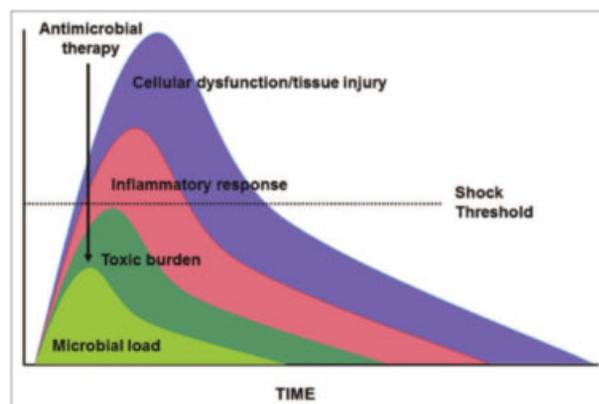
This composite model has two major pathophysiologic implications. First, septic shock and sepsis without shock are different diseases rather than the same syndrome with differing severity. The evidence for this proposal lay in stark clinical features (hypotension, lactic acidosis, substantial exhaustion of compensatory physiologic responses) and high (>50%) mortality in septic shock, in contrast to the milder clinical features and lower mortality (~15%) of sepsis or severe sepsis,<sup>28</sup> the different profiles of inflammatory mediators in these conditions<sup>29,30</sup> and evidence of immune dysfunction in septic shock compared with sepsis without shock.<sup>31</sup>

The second major implication is that delays in initiation of appropriate antimicrobial therapy is associated with a higher microbial load,<sup>32-34</sup> and that organism burden is associated with increased morbidity and mortality in serious infections.<sup>6,35-41</sup> Hence, early appropriate antimicrobial therapy with acceleration of the speed of bacterial clearance should be associated with both improved morbidity and mortality.<sup>42</sup>

### Optimizing Pathogen Clearance

As central corollary of this composite/integrative model of septic shock is that the key determinant of outcome in septic shock is accelerated pathogen clearance. → Table 1 lists the antimicrobial determinants of pathogen clearance in serious infections including septic shock.<sup>11</sup> Each factor has a potential impact on speed of pathogen clearance in the clinical context.

This review will focus on antimicrobial optimization principles that underlay rapid reduction in the pathogen burden, particularly combination therapy as it relates to septic shock. Supplemental antimicrobial therapies (source control), anti-toxin/immunomodulatory strategies and supportive measures will not be discussed in this review.



**Fig. 5** Impact of appropriate antimicrobial therapy in sepsis and septic shock. Reproduced with permission from Kumar.<sup>11</sup> See text for explanation.

**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 cidalty
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

Source: Reproduced with permission from Kumar.<sup>11</sup>

### Early Antimicrobial Therapy

Appropriateness of the initial empiric antimicrobial therapy, early administration without delays, and achievement of therapeutic levels as soon as possible (ideally after the first dose) are the three pillars of effective antimicrobial therapy. Application of these three principles will reduce the microbial burden, decreasing the risk of irreversible shock and death.

This approach is based on Paul Ehrlich's famous dictate: "Frappier fort et frapper vite" (i.e., "hit hard and hit fast"), stated in the 17th International Congress of Medicine in 1913.<sup>43</sup>

### Appropriate Empiric Antimicrobial Therapy

Although data in sepsis without shock are inconsistent,<sup>44–48</sup> empiric antibiotics should cover every reasonably likely pathogen, as failure to initiate antimicrobial therapy to which the pathogen is sensitive is associated with marked increases in mortality, especially in septic shock.<sup>49–55</sup> Inadequate antimicrobial therapy is started frequently<sup>49,56</sup> (15–35%), increasing mortality risk. Recent data suggest that inappropriate empiric antimicrobial treatment reduces survival fivefold in serious infections with septic shock.<sup>49</sup>

To broaden the spectrum of coverage of the empiric antimicrobial therapy, combination strategies should be used for the first few days, at least in patients with septic shock. However, empiric combination therapy must be adjusted to a narrower regimen in the first 72 hours if possible, to minimize selection pressure toward resistant organisms. There are no studies that have suggested that early narrowing of therapy is detrimental if the organism is identified or if the patient is responding well clinically. On the contrary, some studies have pointed to de-escalation of antimicrobial therapy associated with improved outcomes.<sup>57–60</sup>

### Antimicrobial Delay

Delay in the initiation of appropriate antimicrobial therapy has a substantial role in determining mortality in high-risk infections with a particularly strong association with septic shock.<sup>52,61–66</sup> Delays are only inconsistently associated with mortality in bacteremia/candidemia and sepsis without shock.<sup>67–71</sup>

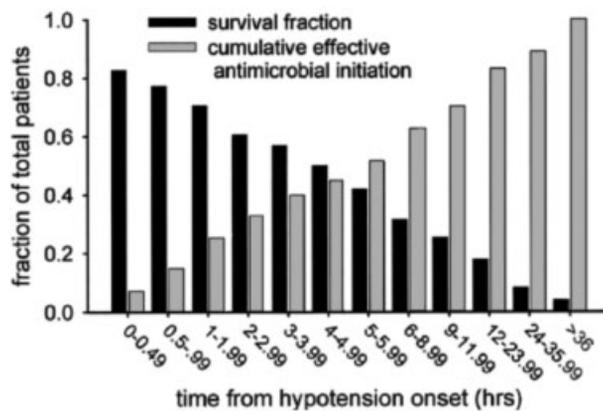
One major retrospective analysis of septic shock suggested that the delay in initial administration of effective antimicrobial therapy is the single strongest predictor of survival.<sup>72</sup> Every hour of delay in appropriate antimicrobial administration, in the first 6 hours after hypotension is documented, decreases survival by 7.6%. Despite this findings, the median time to deliver appropriate antimicrobial therapy in septic shock was 6 hours (although these data are now several years outdated) (► Fig. 6).<sup>72</sup>

Additional retrospective studies of human bacteremia, candidemia, septic shock, community-acquired pneumonia, hospital-acquired pneumonia, surgical infections, and meningitis with sepsis have confirmed that the mortality in these septic conditions is increased with significant delays in antimicrobial administration.<sup>52,63,64,66,73–76</sup> The impact on outcome of speed of appropriate empiric antimicrobial administration in relationship with other therapies such as fluid resuscitation suggests that greater remediable deficiencies (and greater potential for improvement in care) may lie with the appropriate early antibiotic administration.<sup>72,77,78</sup>

In view of these data, intravenous administration of broad-spectrum antimicrobials should be initiated as rapidly as possible in response to clinical suspicion of infection in the presence of persistent hypotension. Obtaining laboratory test or cultures should never delay antimicrobial therapy.

### Loading Doses

Early appropriate antimicrobial therapy is the central element in management of septic shock, but clearance of



**Fig. 6** Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. The x-axis represents time (hour) following first documentation of septic shock-associated hypotension. Black bars represent the fraction of patients surviving to hospital discharge for effective therapy initiated within the given time interval. The gray bars represent the cumulative fraction of patients having received effective antimicrobials at any given time point. Reproduced with permission from Kumar et al.<sup>72</sup>

pathogens will not begin until therapeutic levels of the antimicrobials in the circulation are achieved.

The markedly increased volume of distribution that many antimicrobials exhibit (i.e.,  $\beta$ -lactams, aminoglycosides, vancomycin, teicoplanin, and colistin) can result in failure to achieve therapeutic levels initially with standard dosing approaches.<sup>79–82</sup> An emerging body of literature suggests that loading doses of some antimicrobials can potentially yield improved clinical outcomes.<sup>79,80,83</sup>

### Potency of Antimicrobial Therapy

According to Ehrlich's dictate on optimizing therapy of serious infections, the first principle was to "hit it hard." This principle has many implications in regard to antimicrobial strategy. It suggests that highly potent antimicrobial regimens that provide the most rapid clearance of pathogens are preferred (► Fig. 7).<sup>11</sup> It also suggests that pharmacokinetic optimization of antimicrobial dosing is a requirement for ideal therapy. Further to the extent that combination therapy has been shown to accelerate pathogen clearance in some models of infection,<sup>84</sup> this principle implies that improved survival should result. In the case of septic shock, more rapid pathogen clearance is expected to lead to less release of endogenous mediators, more rapid resolution of hemodynamic instability, and improved survival.

### Cidal versus 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.<sup>85,86</sup> There are a paucity of data in this issue regarding septic shock. The best known study that has addressed the issue of the importance of cidal therapy in life-threatening infections is the classic study of bacterial meningitis by Lepper and colleagues in 1951.<sup>87</sup> This study showed inferior outcomes with chlortetracycline which is bacteriostatic compared with penicillin, a cidal drug. In recent years, few studies have compared the efficacy of well-established

cidal versus static agents in serious infections that may be associated with sepsis and septic shock.

One randomized controlled study of anidulafungin, a cidal antifungal echinocandin, demonstrated superiority over fluconazole, a static triazole, in invasive candida infections.<sup>22</sup> Other studies showed that higher cidal activity of antibiotic regimens are associated with better clinical cure rates in bacterial endocarditis,<sup>88,89</sup> osteomyelitis,<sup>90</sup> and in neutropenic gram-negative bacteremia.<sup>91</sup>

Although nominally a cidal agent, vancomycin has relatively weak bacterial killing activity relative to antistaphylococcal penicillins for methicillin-sensitive *S. aureus* (MSSA) in time kill studies.<sup>92</sup> Accordingly, retrospective studies have shown that vancomycin yields inferior clinical responses and/or survival than anti-staphylococcal  $\beta$ -lactams in patients with MSSA bacteremic infections including pneumonia.<sup>92–94</sup> Notably, the bacteriostatic agents, quinupristin/dalfopristin (a streptogramin) and linezolid (an oxazolidinone), appear to be no more effective than vancomycin for therapy of serious *S. aureus* infections.<sup>95,96</sup> The cidal lipopeptide, daptomycin, in contrast, tends to be superior to vancomycin and comparable to  $\beta$ -lactams in the treatment of bacteremic *S. aureus* infections.<sup>97</sup>

Overall, the available evidence supports the potential superiority of cidal therapy in life-threatening infections. However, additional studies will be required to definitively address this question in septic shock where the difference should be most profound.

### Pharmacokinetic Optimization

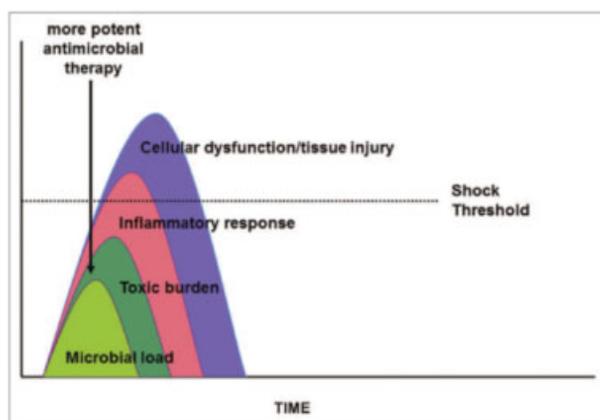
A substantial body of literature suggests that optimization of dosing strategies can improve pathogen clearance and clinical responses in infection. However, to date, data on the impact of pharmacokinetic (PK) optimization on mortality in serious infections, particularly septic shock, remain sparse.

### Time-Dependent Killing Agents

For  $\beta$ -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. There are relatively few studies that examine the role of high  $fT > MIC$  (>60–100%) is associated with better bacterial eradication and clinical cure.<sup>98,99</sup>

Continuous infusion of certain antibiotics, which generates 100%  $fT > MIC$  for sensitive pathogens, compared with intermittent administration (i.e., piperacillin-tazobactam, meropenem, ceftazidime), resulted in improved clinical cure,<sup>100–103</sup> shorter hospitalization, and lower mortality<sup>104</sup> in the subset of the most critically ill patients, many of whom would have had septic shock.

At least two meta-analyses of continuous infusion of  $\beta$ -lactams in human infection have been published.<sup>105,106</sup> 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



**Fig. 7** Impact of more potent antimicrobial therapy in sepsis and septic shock. Reproduced with permission from Kumar.<sup>11</sup> See text for explanation.

observation that is congruent with our underlying hypothesis that the benefit of PK optimization of dosing strategies on mortality should exist primarily in septic shock.

As a whole, these data support the use of high-end daily dosing at short intervals or extended infusions and continuous infusions where possible. These data also suggest the need for studies of continuous infusion  $\beta$ -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 of the pathogen normalized to 24 hours ( $AUC_{24}/MIC$ ), although peak/maximum concentration divided by the MIC ( $C_{max}/MIC$ ) is a closely related value.<sup>107–109</sup>

Experimental animal models and human studies suggest that an  $AUC_{24}/MIC$  of  $>87$  to 125 for fluoroquinolones (depending on the individual drug and clinical syndrome) during the course of therapy yields optimal pathogen clearance and clinical cure.<sup>107–109</sup> Unfortunately, there are no human data linking fluoroquinolone PK indices to survival or mortality and no studies of septic shock have yet been reported. Similarly, peak/MIC ratios of  $>10$  to 12 have been shown to be associated with improved clinical and microbiologic cure rates with aminoglycosides.<sup>110–112</sup>

Vancomycin is another antibiotic whose efficacy is most closely related to concentration-dependent pharmacokinetic indices. Retrospective studies of methicillin-resistant *S. aureus* (MRSA) bacteremia and pneumonia reported better microbiological and clinical outcomes in patients who had vancomycin  $AUC_{24}/MIC$  of 400.<sup>113,114</sup> This has been shown to be independently associated with survival in a retrospective study of MRSA septic shock.<sup>115</sup>

Antimicrobial pharmacokinetic indices have been linked to clinical and microbiologic response in a variety of studies, but the ones 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 in those with septic shock.

### Combination Therapy

There are three major potential advantages of using combination anti-infective therapy for serious life-threatening infections.<sup>116</sup> The most accepted one is that combination therapy increases the spectrum of coverage, allowing a higher probability of appropriate initial therapy, reducing mortality.<sup>78,117</sup> This is the primary reason why initial empiric combination therapy is broadly utilized and specifically recommended in sepsis and septic shock clinical guidelines.<sup>78</sup>

Another potential advantage of combination therapy when compared with monotherapy is reduced risk for emerging of resistance during therapy.<sup>118–120</sup> Similarly, potential additive or synergistic effect<sup>118,119</sup> leading to more rapid pathogen clearance<sup>84,119,121,122</sup> may translate into improved patient outcome and may be the most directly clinically relevant advantage of combination therapy.

Antimicrobial synergy, with increased bacterial clearance, has been best established for  $\beta$ -lactam/aminoglycoside combinations.<sup>123</sup> It has also been described in  $\beta$ -lactam/fluoroquinolone combinations,<sup>124,125</sup> and there are some data that suggest additive effects or even synergism for  $\beta$ -lactam/macrolides combination.<sup>126</sup> There are also potential disadvantages related to combination therapy, such as increased risk for toxicity, higher costs, possible antagonism between specific drug combinations, and selection of resistant strains.<sup>127</sup>

Despite efforts to address the issue of whether two antimicrobials improve outcome in sepsis and septic shock compared with a single agent, the results of published clinical studies and meta-analyses on combination therapy for gram-negative bacteremia and/or sepsis are contradictory. The question has not been definitively answered.

In the meta-analysis of gram-negative bacteremia performed by Safdar and colleagues in 2004,<sup>128</sup> an overall mortality benefit with combination therapy (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.7–1.32) was not found in the overall dataset. Several subgroup analyses were also performed to determine whether the findings would differ if trials were separated according to date of publication (i.e., before or after 1990, when more potent antimicrobials were made available) or study design (i.e., retrospective vs. prospective). Regardless of subset analyses, there remained no added benefit to combination therapy except in an analysis restricted to the five studies of *Pseudomonas aeruginosa* bacteremia. In that group, the summary OR was 0.5 (95% CI, 0.32–0.79;  $p = 0.007$ ), suggesting a 50% relative reduction in mortality with the use of combination therapy. The authors noted, however, that the underlying populations in these studies varied considerably, and a sizeable proportion of patients were immune-compromised, making it difficult to apply the results to the general population.

The systematic review of randomized controlled trials performed by Marcus et al in 2011 also failed to demonstrate a benefit of combination therapy with  $\beta$ -lactam/aminoglycoside in a wide variety of infections.<sup>129</sup> The meta-analysis performed by Paul and colleagues in 2004<sup>130</sup> and the two Cochrane reviews performed by the same group in 2006<sup>131</sup> and 2014,<sup>132</sup> have also failed to demonstrate evidence of improvement of outcome with combination therapy in immunocompetent patients with sepsis. Further, the addition of an aminoglycoside to a broad-spectrum  $\beta$ -lactam did not only fail to reduce the overall mortality in patients with gram-negative sepsis but was also associated with an increased risk for adverse events.<sup>132</sup> Similarly, in 2003, the same group published a meta-analysis in neutropenic sepsis that suggested little incremental benefit of combination therapy of  $\beta$ -lactam and an aminoglycoside in this setting.<sup>133</sup> Of note, none of these studies undertook an analysis in the subgroup of septic shock patients. Moreover, in the Cochrane review of 2006, a lack of benefit with combination therapy was more common among those studies with a structural bias (i.e., comparing a more potent  $\beta$ -lactam with a weaker  $\beta$ -lactam and a second agent).

Several studies have found that the efficacy of some antimicrobial therapies can be restricted to severely ill patients at high risk of death, particularly in severe pneumococcal pneumonia/

bacteremia<sup>134–136</sup> and gram-negative bacteremia.<sup>137,138</sup> In the study by Rodríguez and colleagues in 2007, a secondary analysis of a prospective observational cohort of community-acquired pneumonia who developed shock, concluded that combination therapy was associated with a significantly higher survival.<sup>136</sup> Korvic et al and Hilf et al found similar results in gram-negative bacteremia with shock.<sup>137,138</sup> These data suggest the possibility that the benefit in outcome of combination therapy in sepsis may only exist in severely ill patients, particularly those with septic shock.

The conflicting results addressing the question of the usefulness of combination therapy in sepsis might be explained by the heterogenic nature of the different studies, structural bias, and variations between patient characteristics, severity of infections, infection sites, causative bacteria, and antibiotic treatment. Many of these studies were observational (where selection bias and confounding by indication are difficult to avoid, especially with the use of relatively subjective criteria such as clinical response, rather than mortality). Another difficulty is that most randomized studies are designed to assess noninferiority (which means they have a structural bias in favor of showing equivalence between monotherapy and combination therapy). Moreover, those studies often do not compare the same antibiotic in monotherapy and in combination with a second agent. Usually, a more pharmacodynamically potent agent in monotherapy is compared to a combination of two weaker agents. In addition, randomized controlled trials often do not have sufficient numbers of a particular type of microorganism or a particular patient population (such as septic shock, a population that is often excluded) to allow robust subgroup analyses. Thus, synergy is difficult to rigorously assess in many individual studies.

Based on the possibility that any benefit in survival with combination therapy may be restricted to only the most critically ill subset of patients, we tested this hypothesis performing a stratified meta-analysis/meta-regression of 60 sepsis datasets (derived from 48 individual studies).<sup>139</sup> The quality of the study was enhanced by splitting data from 12 studies into mutually exclusive groups of septic shock/critically ill and non-septic shock/non-critically ill and by excluding studies where a structural bias would favor an equivalence outcome (i.e., a highly potent  $\beta$ -lactam vs. a less potent  $\beta$ -lactam and a second agent). Studies of neutropenic sepsis were also excluded. Notably, the pathogen was required to be sensitive to both agents in the combination therapy group.

Although we found the same absence of significant benefit of combination therapy overall, stratification of the datasets by baseline (monotherapy) mortality risk showed a consistent substantial benefit in terms of clinical cure and survival with combination therapy in the most severely ill subset of patients (monotherapy risk of death >25%; OR, 0.51; 95% CI, 0.41–0.64;  $I^2 = 8.6\%$ ) (–Fig. 8<sup>139,140</sup>). Of the 24 datasets derived from 12 studies that could be stratified by the presence of shock or critical illness, the septic shock/critically ill group demonstrated consistently better outcomes with combination therapy (OR, 0.49; 95% CI, 0.35–0.70;

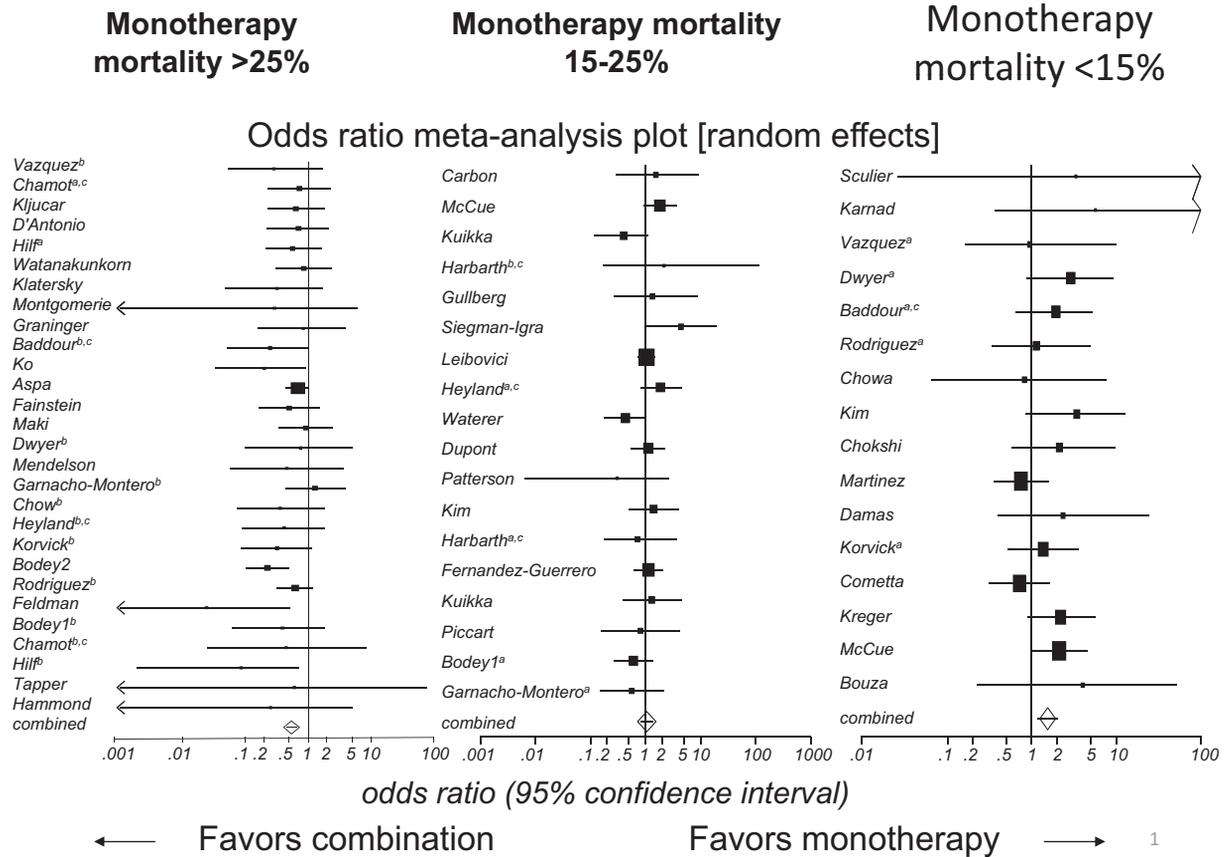
$p < 0.0001$ ;  $I^2 = 0\%$ ) (–Fig. 9<sup>139</sup>). This meta-regression indicated that the benefit found with combination therapy was only dependent on the risk of death in the monotherapy group (i.e., the severity of illness). This finding held when datasets were restricted to randomized controlled trials. These results also held in subgroups stratified by a variety of factors including organism, organism grouping (gram positive or negative), clinical syndrome, and supplemental antibiotic agent.

This study was followed by a large retrospective propensity-matched multicenter cohort study by our group,<sup>53</sup> evaluating the therapeutic benefit of early combination therapy with at least two antibiotics with confirmed activity against the pathogen isolated in septic shock patients. Significant beneficial effects were observed in outcome, finding an improved 28-day survival (444 of 1,223 [36.6%] vs. 355 of 1,223 [29%]; hazard ratio 0.77; 95% CI, 0.67–0.88;  $p = 0.0002$ ) (–Fig. 10<sup>53</sup>). Combination therapy was also associated with significant reductions in ICU (437 of 1,223 [35.7%] vs. 352 of 1,223 [28.8%]; OR, 0.75; 95% CI, 0.63–0.92;  $p = 0.0006$ ) and hospital mortality (584 of 1,223 [47.8%] vs. 457 of 1,223 [37.4%]; OR, 0.69; 95% CI, 0.59–0.81;  $p < 0.0001$ ). The beneficial impact of combination therapy applied to both gram-positive and gram-negative infections but was restricted to  $\beta$ -lactam antibiotics in combination with aminoglycosides, fluoroquinolones, or macrolides. Notably, the most potent  $\beta$ -lactams (i.e., carbapenems, anti-pseudomonal third- and fourth-generation cephalosporins,  $\beta$ -lactamase inhibitor combinations) failed to demonstrate a benefit in outcome with combination therapy.<sup>53,141</sup> This may be explained by their high cidal activity, as it is near maximal for most pathogens ( $ft > MIC \sim 100\%$ ). In this circumstance, the addition of a second drug may have little incremental benefit. Several additional recent retrospective studies show a benefit in survival of patients in septic shock and related critical conditions with combination therapy using antibiotics with different mechanisms of action.<sup>52,142</sup>

Although highly suggestive, these retrospective analyses cannot be considered definitive. While waiting for appropriately designed randomized controlled trials, combination of empiric antibiotic therapy for several days with two drugs of different mechanisms of action is appropriate for patients in septic shock. Monotherapy is reasonable for patients who are not critically ill and not at high risk of death.

## Conclusion

Anti-infective therapy is the cornerstone of treatment for critically ill patients with sepsis and septic shock. The choice of initial empiric antimicrobial therapy is crucial in determining positive outcomes. The optimal selection of antibiotics depends on the local resistance epidemiology as well as individual risk factors for resistance, including recent antibiotic use, hospitalization, and previous colonization or infection with resistant strains. The speed with which appropriate antimicrobials are initiated is now well recognized as a crucial element in providing effective care of patients with all life-threatening infections including septic shock. In addition,

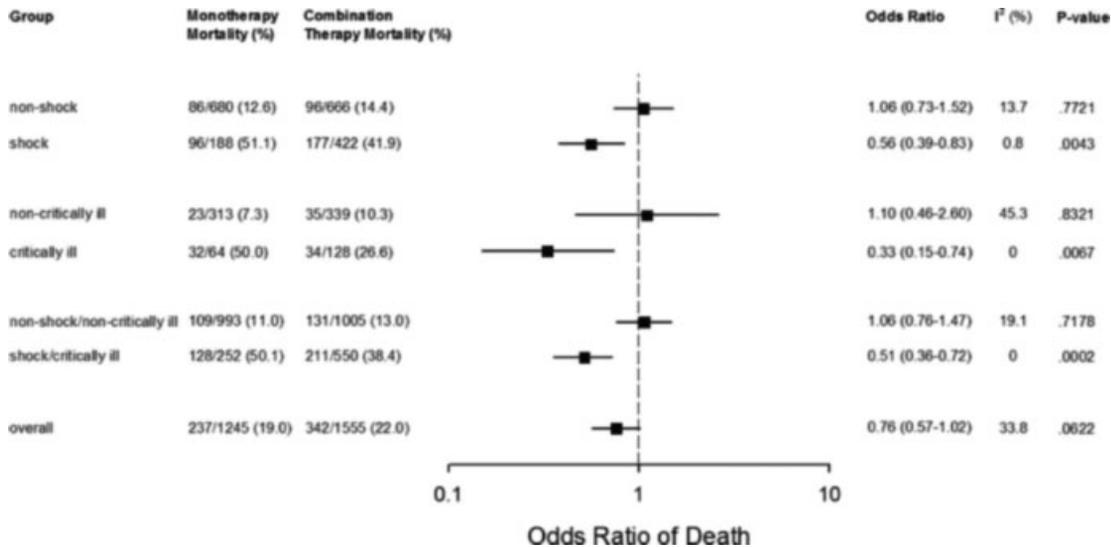


**Fig. 8** Analysis of studies comparing combination antibiotic therapy with monotherapy for reducing mortality of life-threatening infections associated with sepsis. Note the gradual shift of the odds ratio from the right to the left as monotherapy mortality increases. The size of the squares is proportional to the reciprocal of the variance of the studies. <sup>a</sup>Nonshock or noncritically ill stratified dataset. <sup>b</sup>Shock or critically ill stratified dataset. <sup>c</sup>Modified dataset provided by study authors. Adapted and reproduced with permission from Kumar et al<sup>139</sup> (originally cited in Abad et al<sup>140</sup>).

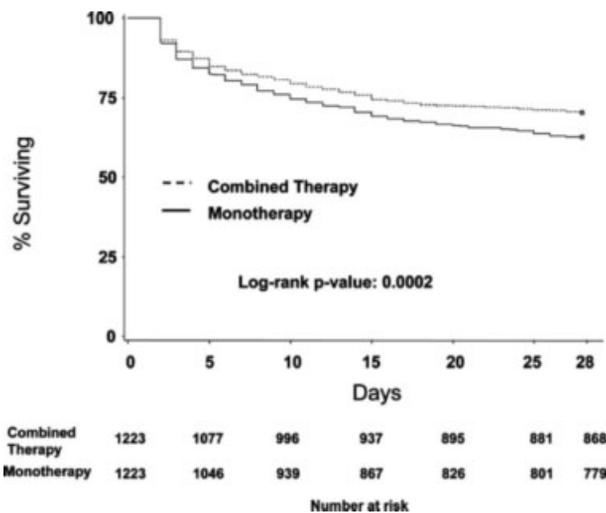
maximization of cidalty through pharmacokinetic optimization and combination therapy can be useful.

Several studies have attempted to answer the question of whether combination therapy improves outcomes in septic

patients when compared with monotherapy. The data reviewed suggest that the question of whether combination therapy is beneficial may be outdated. The appropriate question may be under what circumstances combination therapy is beneficial.



**Fig. 9** Subset analysis comparing combination antibiotic therapy with monotherapy for reducing mortality of life-threatening infections associated with sepsis in shock/critically ill and nonshock/noncritically ill patient datasets (derived from 12 studies in which groups could be separated). Reproduced with permission from Kumar et al.<sup>139</sup>



**Fig. 10** Adjusted Cox proportional hazards of mortality associated with combination antibiotic therapy of septic shock. Reproduced with permission from Kumar et al.<sup>53</sup>

Combination therapy is useful under certain circumstances. For example, many experts would support the use of combination therapy for serious pseudomonal infections and for neutropenic sepsis. In addition, in situations where there is a significant level of bacterial multidrug resistance, the use of combination therapy may be warranted to ensure that likely pathogens are sensitive to at least one antibiotic.

If our composite model of septic shock with a microbial load-driven pathogenesis accurately reflects the pathophysiology of disease progression, only a few days of combination therapy (to hemodynamic stabilization and usually to organism identification) is required. Once hemodynamic stabilization is achieved, the microbial burden has been reduced to a subcritical threshold that should no longer leave the patient at risk for irreversible injury. Pending the publication of appropriate randomized trials, a strategy of several days of combination therapy for septic shock cases may be advisable.

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