Antimicrobial Therapy of Sepsis and Septic Shock—When Are Two Drugs Better Than One?

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KEYWORDS

- Sepsis • Pneumonia • Bacteremia
- Combination anti-infective therapy

Sepsis affects approximately 750,000 individuals in the United States each year, accounting for 2.1% to 4.3% of hospitalizations, and 11% of all admissions to the ICU.[1] From 1979 to 2000, there was an annual increase in the incidence of sepsis of 8.7%, from 164,000 cases (82.7 per 100,000 population) to nearly 660,000 (240.4 per 100,000 population).[2] Sepsis exacts a high mortality, killing 20% to 50% of severely affected patients[3] and is the 10th leading cause of death overall in the United States.[4]

Management of sepsis is complex, and includes aggressive efforts at resuscitation and fluid replacement, supportive therapies, and use of empiric antimicrobial therapy. Optimal use of antibiotic therapy is a critical determinant of survival in sepsis and septic shock. Inappropriate antibiotic choices and doses in critically ill patients can markedly increase mortality and morbidity.[5–7] In a small randomized controlled trial, for example, where patients were stratified according to disease severity, and randomized to either pharmacokinetic-based dose adjustment or traditional physician-directed dosing, the investigators found that use of the correct pharmacokinetic

The authors have no conflicts to disclose (N.S. and C.L.A.).

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Crit Care Clin 27 (2011) e1–e27
doi:10.1016/j.ccc.2010.12.001 **criticalcare.theclinics.com**
0749-0704/11/$ – see front matter

dose of the appropriate antimicrobial significantly reduced mortality rates in critically ill patients.[7]

Two meta-analyses have failed to demonstrate evidence of improvement of outcome with combination therapy in immunocompetent patients with sepsis and/or gram-negative bacteremia.[8,9] Of note, these meta-analyses did not undertake analyses in the subgroup of patients with septic shock. The most accepted rationale for combination chemotherapy is the generation of an increased spectrum of coverage, to increase the likelihood that the infecting pathogen is susceptible to at least one of the agents in the combination. The utility of this approach has been supported by several studies[10] and forms the rationale for the initial use of combination therapy in several clinical guidelines on management of sepsis.[11] In this setting, the antibiotics may be tailored quickly once antimicrobial susceptibility results become available. Other proposed advantages of combination over monotherapy include antibacterial synergism and the prevention of the development of resistance.[12–17] Although some animal models[18–20] and clinical studies of infection, including endocarditis, gram-negative bacteremia, and neutropenic infections,[21–23] support combination therapy for purposes of synergistic effect, the potential clinical benefit in other severe infections that can potentially be associated with sepsis and septic shock has been questioned. In clinical practice, physicians frequently use combination therapy despite the conflicting evidence for its effectiveness.[24] The results of recent studies have contributed to our understanding of this important issue.[25] In this article, we examine the evidence for, or against, the use of combination drug therapy compared with monotherapy in the management of serious infections, sepsis, and septic shock.

DEFINING SEPSIS AND SEPSIS SYNDROMES

The definitions of sepsis and sepsis syndromes have evolved over time, even as advances in the understanding and pathophysiology of sepsis have occurred. The modern clinical definition of sepsis originated in the proposal by Bone and colleagues[26] in 1989 to define sepsis syndrome as "hypothermia (T <35.5C) or hyperthermia (T >38.3C), tachycardia (>90beats/min), tachypnea (>20breaths/min), clinical evidence of an infection site, and at least one end-organ demonstrating inadequate perfusion or dysfunction expressed as poor or altered cerebral function, hypoxemia (PaO2 <75 torr), elevated plasma lactate, or oliguria (urine output <30 ml/h or 0.5 ml/kg body weight/h without corrective therapy)." The American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened a consensus conference in 1991 to create a standardized set of definitions for patients with sepsis.[27] Sepsis was further defined as "the presence of systemic inflammatory response syndrome (SIRS) with a confirmed infectious process," with SIRS defined as the presence of at least 2 of the following 4 clinical criteria: (1) body temperature greater than 38°C or less than 36°C, (2) heart rate greater than 90 beats per minute, (3) respiratory rate greater than 20 breaths per minute or hyperventilation with a PaCO2 less than 32 mm Hg, and (4) white blood cell count greater than 12,000/mm^3, less than 4000/mm^3, or with greater than 10% immature neutrophils. "Severe sepsis" was defined as sepsis with evidence of organ failure (similar to the earlier term, "sepsis syndrome").

Almost a decade later, with further advances in the understanding of sepsis, and concern regarding the validity of the SIRS criteria[28] as laid out in the ACCP/SCCM definitions, an international sepsis definition conference was held under the sponsorship of several societies, including the SCCM, ACCP, the European Society of Intensive Care Medicine (ESICM), and Surgical Infection Societies (SIS).[29] The participants

agreed that an expanded list of signs and symptoms of sepsis might better reflect the clinical response to infection. Currently, sepsis is now defined as the presence of several clinical, hematologic, biochemical, and immunologic variables associated with an infection (**Fig. 1**). Septic shock is a subset of sepsis with acute circulatory failure.

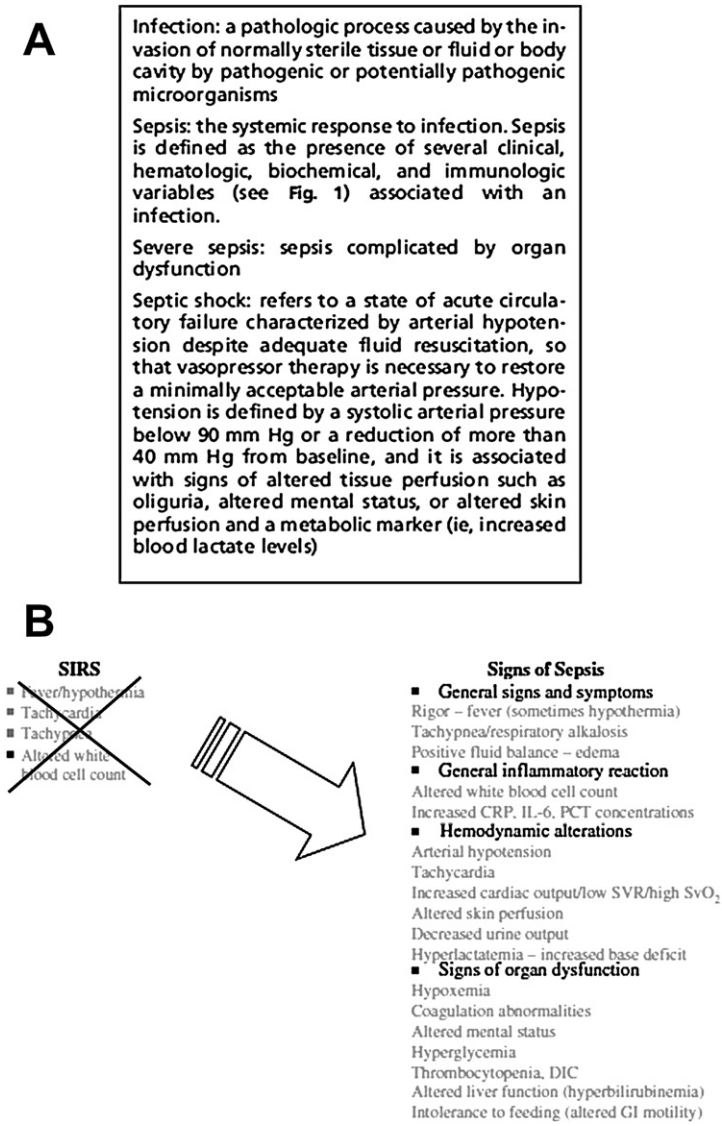

Fig. 1. (*A*) Currently proposed definitions of infection and sepsis. (*Data from* Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250–6.) (*B*) The Sepsis Definitions Conference suggested that the systemic inflammatory response syndrome criteria be replaced by a longer list of possible signs and symptoms of sepsis. Although none of these is specific of sepsis, the unexplained presence of several in combination should raise suspicion of sepsis. (*Adapted from* Vincent JL, Korkut HA. Defining sepsis. Clin Chest Med 2008;29(4):585–90, vii; with permission.)

SOURCES OF INFECTION AND MICROBIOLOGY OF SEPSIS

In a recent meta-analysis and review, Bochud and colleagues[30] identified the predominant sources of infection in patients with severe sepsis and septic shock by decreasing order of frequency, as the lungs, the bloodstream (without another identifiable source), the abdomen, the urinary tract, and soft tissues. This is corroborated by a multicenter prospective cohort study by Sands and colleagues,[31] where, in 866 cases of sepsis syndrome, respiratory infections were the most common, accounting for 42.4% of all infections. This was followed by bloodstream infections of undetermined origin (12.0%). Similarly, in a multicenter prospective study in French public hospitals, the primary source of infection was likewise pleuro-pulmonary, with almost half (41%) accounting for total episodes of documented severe sepsis.[32] However, in this cohort, intra-abdominal infections accounted for 32% of episodes of sepsis where a unique source of sepsis was identified, whereas primary bacteremia was identified in only 4% of cases. Kumar and colleagues[33,34] similarly found that pleuro-pulmonary, intra-abdominal, and urinary tract source infection were, in order, the largest contributors to a large (n = 5715) multi-institutional cohort of septic shock cases.

The microbiology of sepsis has changed over the past 3 decades. In the late 1970s through the 1980s, gram-negative bacteria were the predominant organisms causing sepsis. Subsequently thereafter, gram-positive organisms outnumbered gram-negative organisms, with a notable increase by an average of 26% per year.[2] In the 1997 study by Sands and colleagues,[31] gram-positive organisms were responsible for 39.5% of bloodstream infections, as opposed to the 35.0% accounted for by gram-negative organisms. Inclusive of all infections, however, gram-negative organisms outnumbered gram-positive organisms by 8.8%. Sepsis syndromes caused by gram-positive organisms are mainly from *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, and streptococci. In contrast, gram-negative sepsis is commonly caused by members of the family Enterobacteriaceae, especially *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*.[30] In 2000, among organisms reported to have caused sepsis, gram-positive bacteria accounted for 52.1% of cases, with gram-negative bacteria accounting for 37.6%, polymicrobial infection for 4.7%, anaerobes for 1.0%, and fungi 4.6%. Interestingly, there was a 207% increase in the number of cases of sepsis caused by fungal organisms, from 5231 cases in 1979 to 16,042 in 2000.[2] Most causes of fungal sepsis are caused by *Candida* species, which are the fourth most common cause of bloodstream infection and are associated with high mortality.[35,36]

RATIONALE FOR APPROPRIATE ANTI-INFECTIVE THERAPY IN SEPSIS

Antimicrobial therapy has long been recognized as a cornerstone in the treatment of critically ill patients with sepsis and/or septic shock.[3,37] Although the initial antimicrobial choices for therapy are usually empiric, a considered approach to antimicrobial selection is crucial, given data showing poor outcomes with inadequate or inappropriate initial therapy. McCabe and Jackson[38] were among the first to observe this in their landmark study of a cohort of 173 patients with gram-negative bacteremia, where it was observed that appropriate initial antibiotic therapy reduced mortality from 48% to 22%. Since that time, multiple other studies have been published, which have found similar results.[39–46] More recently, Kollef and colleagues[47] reported that inadequate treatment of infections among patients requiring ICU admission was an important determinant of hospital mortality. The investigators found that inadequate antimicrobial treatment of infection was found to be the most important independent determinant of hospital mortality for the entire patient cohort (adjusted odds ration

[OR], 4.27; 95% confidence interval [CI], 3.35 to 5.44; $P<.001$). Similarly, Garnacho-Montero and colleagues[48] established that the risk of in-hospital mortality was 8 times greater in medical patients receiving inadequate antimicrobial therapy within the first 24 hours than in those medical patients who received adequate empirical antibiotic therapy. Kumar and colleagues[33] found a remarkable fivefold increase (52.0% vs 10.3%) in survival when 5715 patients with septic shock received appropriate rather than inappropriate initial empiric therapy (OR, 9.45; 95% CI, 7.74 to 11.54; $P<.0001$).

RATIONALE FOR COMBINATION ANTI-INFECTIVE THERAPY

There are 3 major potential advantages to using combination anti-infective therapy for serious, life-threatening infections[49]: (1) an increased likelihood that the infective pathogen will be susceptible to at least one of the components of the dual regimen, thereby allowing appropriate initial therapy; (2) prevention of emergence of resistance during therapy; and (3) additive or synergistic effect of the antimicrobials,[13,14,50] which translates into improved patient outcomes, such as reduction in mortality. In contrast, the disadvantages of using a combination of drugs include a greater likelihood of adverse effects, increased cost, possible antagonism between specific drug combinations,[51] and the propagation of antimicrobial resistance.[52,53]

Although several studies have attempted to address the issue of whether or not 2 anti-infectives improve outcomes in sepsis compared with a single agent, the question has not been definitively answered. There are several reasons for this. Many studies are observational in nature. In these studies, factors such as selection bias and confounding by indication are difficult to avoid, especially with the use of relatively subjective criteria such as clinical response,[49] rather than mortality. Another difficulty is that most randomized studies are designed to assess noninferiority. These studies are explicitly designed with a structural bias in favor of showing equivalence between a newer, more pharmacodynamically potent drug and a combination of 2 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) to allow robust subgroup analyses, and as such, synergy and emergence of resistance cannot be rigorously assessed. Meta-analyses that have combined the results of individual studies allow for critical assessment of the literature, identification of important gaps and limitations, and generation of hypotheses for future trials, but may also suffer from the heterogeneity and intrinsic weaknesses/deficits of the included studies.[54]

MAJOR SEPSIS SYNDROMES

Pneumonia

Health care–associated pneumonia

Most health care–associated pneumonia is ventilator-associated pneumonia (VAP), which is the most common nosocomial infection acquired in the intensive care unit (ICU). VAP develops in 10% to 20% of patients who undergo mechanical ventilation for longer than 24 hours[55–57] and is associated with longer ICU stays, increased costs,[58] and increased mortality.[59–62]

According to the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) treatment guidelines for health care–associated pneumonia, recommendations for empirical treatment of early VAP are single-agent ceftriaxone, ampicillin/sulbactam, or a fluorquinolone. In contrast, regimens for late VAP, which is more commonly caused by multiresistant organisms such as *Pseudomonas* spp, *Acinetobacter*, or methicillin-resistant *S aureus*, include a carbapenem with or without

vancomycin, or combination therapy composed of an aminoglycoside or quinolone with an anti-pseudomonal penicillin, a β-lactam/β-lactamase inhibitor combination, ceftazidime, or cefepime.[63] Combination therapy for VAP is commonly used as definitive treatment, presumably to promote synergy and improve clinical outcomes.

In a recent meta-analysis of suspected VAP by Aarts and colleagues,[64] comprising 1805 patients, a total of 11 trials compared monotherapy with combination therapy. Eight of the 11 trials, composed of a total of 1459 patients, reported mortality (**Fig. 2**). In a pooled analysis, there was no mortality difference for patients receiving monotherapy in comparison with combination therapy (relative risk [RR] 0.94, 0.76–1.16). Similarly, outcomes did not change in a sensitivity analysis of treatment failure (RR 0.92, 0.72–1.17), or in the 5 trials exclusively enrolling ventilated patients (mortality RR 0.95, 0.68–1.32). The investigators concluded that it did not appear likely that combination therapy was clinically superior to monotherapy.

It appears that the only reason to use combination therapy for VAP that is currently supported by evidence is the increased likelihood of appropriate initial anti-infective therapy. Once the organism is identified, then de-escalation to a single drug should be used, if permitted by the susceptibility testing. Agents identified as effective monotherapy in patients with health care–associated pneumonia not attributable to drug-resistant pathogens include ciprofloxacin, levofloxacin, meropenem, cefepime, and pipercillin-tazobactam.[65–70]

Community-acquired pneumonia

Community-acquired pneumonia (CAP) is a common infection that continues to carry a high risk of morbidity despite recent advances in the use, spectrum, and potency of antibiotics as well as resuscitative technologies. In fact, mortality attributable to severe CAP has shown little improvement in the past 3 decades, remaining between 20% and 25% in patients admitted to the ICU.[71–75] Although CAP is typically caused by mixed and atypical pathogens, *Streptococcus pneumoniae* remains the most prevalent pathogen, as well as one of the most lethal ones.[76] The 2 most frequently recommended initial antibiotic regimens for hospitalized patients with CAP, which have activity against its major causes, include (1) an extended spectrum β-lactam with a macrolide, or (2) an anti-pneumococcal quinolone. Despite similar spectra of activity, emerging evidence from mostly retrospective studies suggests the superiority of dual therapy over monotherapy for certain populations, particularly patients with severe CAP, or bacteremic pneumococcal pneumonia[77–80] (**Table 1**). More recently, 2 other studies have looked at the mortality benefit of using combination anti-infective therapy in patients with severe CAP.[81,82]

In the study by Rodriguez and colleagues,[81] a secondary analysis of a prospective observational cohort was undertaken for patients with CAP who developed shock. Among the 529 patients recruited for the original study, 51% or 270 patients required vasoactive support, and were characterized as having shock. Among these patients with shock, combination antibiotic therapy was associated with a significantly higher 28-day adjusted in-ICU survival (hazard ratio [HR] 1.69, 1.09–2.6, $P = .01$). In addition, even when monotherapy was appropriate in vitro, it still provided a lower 28-day adjusted ICU survival than an adequate antibiotic combination (HR 1.64, 1.01–2.64, $P = .04$). Notably, combination regimens were further examined to determine whether the difference seen in survival rate with combination or monotherapy was secondary to a specific antibiotic or combination thereof. When compared with monotherapy, survival rates were higher for antibiotic combinations, including β-lactam plus macrolide (HR 1.73, 1.08–2.76, $P = .02$) and β-lactam plus fluoroquinolones (HR 1.77, 1.01–3.15 $P = .05$).

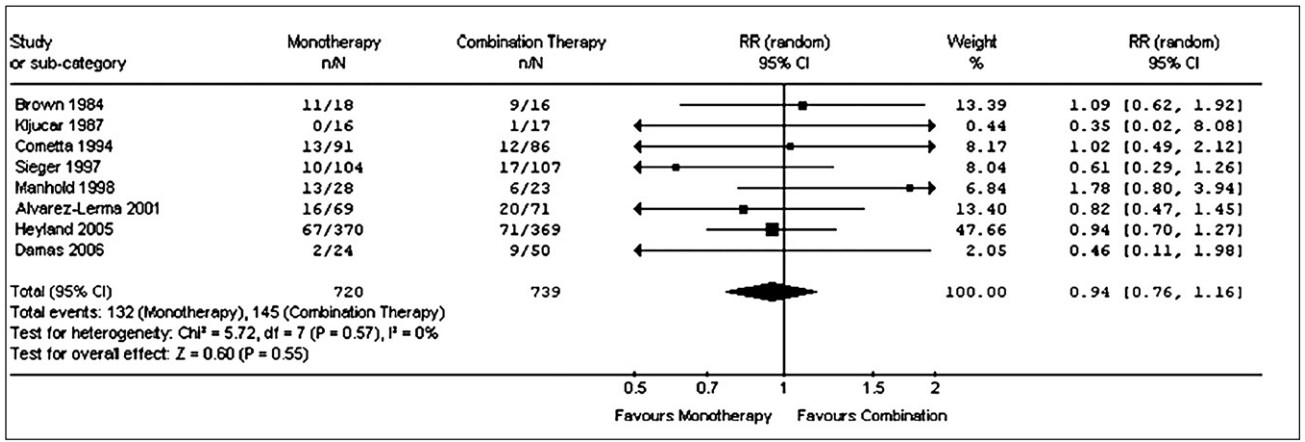

Fig. 2. Mortality in pooled trials comparing monotherapy to combination therapy. There is no evidence that combination therapy improves survival when compared with monotherapy. RR, relative risk; CI, confidence interval. (*Data from* Aarts MA, Hancock JN, Heyland D, et al. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. Crit Care Med 2008;36:108–17.)

Table 1
Studies indicating benefit of combination antibiotic therapy in patients with bacteremic pneumococcal infection

Authors	Year Published	No. Patients	Study Type
Murfson and Stanck[78]	1999	Various	Retrospective review
Waterer et al[79]	2001	225	Retrospective review
Baddour et al[77]	2004	844	Prospective, observational
Weiss et al[80]	2004	95	Retrospective review

Data from Feldman C, Anderson R. Therapy for pneumococcal bacteremia: monotherapy or combination therapy? Curr Opin Infect Dis 2009;22:137–42.

In a study of 845 patients of which 515 received combination therapy with a β-lactam plus macrolide, and the remainder fluoroquinolone monotherapy, Lodise and colleagues[82] found no differences in 14-day and 30-day mortality rates between groups. However, among patients with severe pneumonia (pneumonia severity index [PSI] category V), the 14-day mortality rate was significantly lower for those receiving combination therapy than for those receiving single-drug therapy (8.2% vs 26.8%, $P = .02$). No differences in the 14-day and 30-day mortality rates were observed for the lower PSI categories.

In a recent retrospective study of patients with pneumococcal bacteremia,[83] 108 patients were included, of whom 42 (39%) received empiric monotherapy, and 66 (61%) received combination therapy. Patients with bacteremic pneumococcal pneumonia treated with combination therapy had no significant difference in mortality compared with patients who received monotherapy (OR 1.25; 0.25–6.8). When restricted to subjects who had severe pneumonia (PSI class IV/V), there was still no difference in mortality between the 2 arms ($P = .6$), although the study had limited power to address this question. Interestingly, patients who received dual therapy had increased length of stay after adjusting for severity of illness ($P = .02$). According to the investigators, potential explanations for this include difficulty in transitioning combination therapy to an oral formulation, differences in severity of illness that were not fully adjusted for, or antagonism between bacteriostatic and bactericidal antibiotics.

Based on the evidence provided previously, it appears that the benefits of combination therapy for CAP may be limited to those with severe CAP (PSI Class IV/V), and those with pneumococcal bacteremia and septic shock. Possible explanations for the apparent beneficial effects of combination therapy in CAP, which have been comprehensively covered in a recent review, include coverage for atypical pathogens, polymicrobial infections, resistant pathogens, synergistic effects, and the anti-inflammatory immunomodulatory effects of the macrolides.[84]

That macrolide antibiotics are unique in that they not only inhibit the production of pneumolysin and other pneumococcal virulence factors, but possess neutrophil-directed anti-inflammatory properties, may account for the advantage of using them as part of combination therapy for severe CAP. These properties include decreased neutrophil chemotaxis and infiltration into the respiratory epithelium, inhibition of transcription factors leading to decreased proinflammatory cytokine production, downregulation of adhesion molecule expression, inhibition of microbial virulence factors including biofilm formation, reduced generation of oxygen-free radicals, enhanced neutrophil apoptosis, and decreased mucus hypersecretion with improved mucociliary clearance. This effective control of neutrophil-mediated inflammation may explain the efficacy of these agents in the pharmacotherapy of various chronic respiratory diseases in which the neutrophil is believed to be the primary offender.[85,86]

Bloodstream Infections

Blood stream infections (BSIs) are a major cause of morbidity and mortality. These infections are the 10th leading cause of death in the United States, and the age-adjusted death rate has risen by 78% over the past 2 decades.[87] Based on a study of nosocomial bloodstream infections in US hospitals, it appears that the proportion of nosocomial BSIs attributable to antibiotic-resistant organisms is increasing. Among 24,179 cases of BSIs over a 7-year period, 65% were caused by gram-positive organisms and 25% by gram-negative organisms. The most common gram-positive organisms causing BSIs were coagulase-negative staphylococcus (30%), *Staphylococcus aureus* (21%), and *Enterococcus* sp (9%), and the most common gram-negative organisms were *E coli* sp and *Klebsiella* sp.[88]

Gram-negative bacteremia

Multidrug-resistant gram-negative bacteria have reemerged as a major threat to critically ill patients in the ICU. The continuing increase in antimicrobial resistance in US hospitals remains a concern. There was a nearly 50% increase in nonsusceptible *Klebsiella pneumoniae* isolates to third generation cephalosporins between 2002 and 2003. Also concerning is the decreasing susceptibility of *Pseudomonas aeruginosa* to multiple drugs, with increasing resistance to third-generation cephalosporins, quinolones, and carbapenems by 20%, 15%, and 9% respectively, between 1998–2002 to 2003.[89] Because many species of gram-negative bacilli have frequent intrinsic and acquired resistance, which causes serious infections and high mortality,[90] empiric combination antimicrobial therapy has been advocated for gram-negative bacteremia.[91,92]

In 2004, Safdar and colleagues[9] published a meta-analysis to determine whether or not a combination of 2 or more drugs would reduce mortality in patients with gram-negative bacteria. Their study included 17 studies, of which 5 were prospective cohorts, 2 were randomized controlled trials, and the rest were retrospective. Most studies used beta-lactams or aminoglycosides alone and in combination. Overall, they did not observe a mortality benefit with combination therapy (OR 0.96, 0.7–1.32). Several subgroup analyses were also performed to determine whether the findings would differ if trials were separated according to date of publication (ie, before or after 1990, when more potent antimicrobials were made available) or study design (ie, retrospective vs prospective). Regardless of subset analyses, there remained no added benefit to combination therapy. However, in an analysis restricted to 5 studies of *P aeruginosa* bacteremia, the summary OR was 0.5 (0.32–0.79, $P = .007$), suggesting a 50% relative reduction in mortality with the use of combination therapy (**Fig. 3**). The investigators noted, however, that 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.

In the review mentioned earlier, Paul and colleagues[8] performed a subgroup analysis of 4 trials (193 patients) restricted to sepsis from gram-negative bacteremia, and they found no mortality benefit with combination therapy (RR 1.40, 0.72 to 2.71). Similarly, no fatality benefit was observed when subanalysis was restricted to infections caused by *P aeruginosa* (RR 1.50, 0.07 to 32.84).

Gram-positive bacteremia

Staphylococcus aureus is the second most common bloodstream isolate, both in hospital and community-acquired bacteremias in all age groups. Bacteremia from *S aureus* still confers remarkably high mortality, ranging up to 60% in some studies, although antistaphylococcal antibiotics have been available for more than

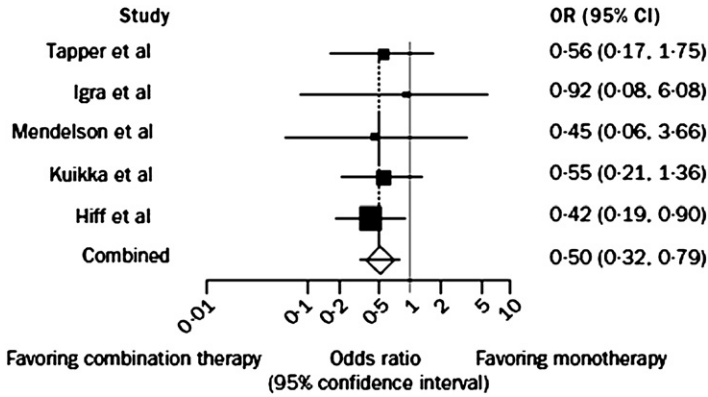

Fig. 3. Analysis of studies comparing combination anti-infective therapy with monotherapy for reducing mortality of *Pseudomonas* spp bacteremia. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary odds ratio is 0.50 (95% CI 0.32–0.79), indicating a mortality benefit with combination antimicrobial therapy. (*Data from* Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in gram-negative bacteraemia? A meta-analysis. Lancet Infect Dis 2004;4: 519–27.)

40 years.[93–96] Similarly, bacteremia from *Enterococcus* sp continues to be very difficult to treat, given the inherent resistance of enterococci to β-lactam antibiotics.[97]

Remarkably, there are few clinical trials that focus on the use of combination therapy for gram-positive bacteremia and sepsis. In fact, the use of initial low-dose gentamicin in the management of suspected *S aureus* endocarditis is based on in vitro data demonstrating that synergistic doses of aminoglycosides, in combination with antistaphylococcal penicillins or vancomycin, result in more rapid bactericidal activity against *S aureus,* and on in vivo data from a rabbit model of endocarditis showing more rapid eradication of *S aureus* from cardiac vegetations.[98,99] In the same manner, the use of combination therapy for *Enterococcus* sp is based on a study that showed bactericidal synergism between penicillin G and streptomycin, demonstrated by in vitro time-kill techniques.[100]

In the review by Paul and colleagues,[8] a small subset of randomized trials that assessed the value of addition of an aminoglycoside in gram-positive infections was included. Three studies assessed staphylococcal endocarditis,[101–103] 1 study assessed any staphylococcal infection,[104] and 1 study assessed streptococcal endocarditis.[105] Although the use of β-lactam-aminoglycoside treatment is standard practice with these infections,[106] the results in the meta-analysis did not point to a clinical benefit with combination therapy. To our knowledge, there are no randomized controlled trials comparing monotherapy with combination therapy for enterococcal bacteremia. In fact, the data for combination therapy is mostly from retrospective analyses and reviews (**Table 2**).[97,100,107–111]

Recently, Schrenzel and colleagues[112] looked at the use of combination therapy for deep-seated or bacteremic staphylococcal infections. In their multicenter randomized controlled trial, 127 patients were included in the intention-to-treat analysis, with 58 patients randomized to fleroxacin-rifampicin, and 45 in the standard parenteral group (eg, flucloxacillin or vancomycin). Primary outcome was clinical or microbiologic cure, and mortality was only a secondary outcome variable. Nevertheless, there was no overall mortality benefit observed with combination therapy versus standard therapy

Table 2
Results of combined cell wall–active antibiotic and aminoglycoside treatment of enterococcal endocarditis

References, Author	Year of Study	No. of Episodes	Cure, %[a]	Antibiotic Therapy in Cured Episodes, Median Days	
				Cell Wall Active[b]	Aminoglycoside[c]
Geraci and Martin[100]	1954	14	50	38	38
Vogler et al[110]	1962	13	77	—	—
Mandell et al[107]	1970	36	83	42[d]	42[d]
Moellering et al[108]	1974	14	57	36	24
Wilson et al[111]	1984	56	88	28[d]	28[d]
Rice et al[109]	1991[e]	40	73	39[d]	35[d]
Present study	2002	93	81	42	15

Dashes mean not reported.
[a] Cure implies no death during treatment and no relapse at followup.
[b] Cell wall active agents include penicillin, ampicillin or vancomycin.
[c] Aminoglycoside includes streptomycin, gentamicin, tobramycin or netilmicin.
[d] Mean.
[e] Antibiotic therapy includes all treated patients.
Data from Olaison L, Schadewitz K. Enterococcal endocarditis in Sweden, 1995–1999: can shorter therapy with aminoglycosides be used? Clin Infect Dis 2002;34:159–66.

(RR 0.7, 0.3–1.8, $P = .48$). Likewise, in those patients who were clinically evaluated, there was no difference in cure rates between the 2 arms among the patients with catheter-related bacteremia, (RR 0.8, 0.4–1.3, $P = .63$) or those who had primary bacteremia (RR 1.4, 0.3–5.9, $P = .54$).

With the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA), a few trials have challenged the use of β-lactam-aminoglycoside combination therapy with new, alternative agents. In a randomized controlled study by Fowler and colleagues,[86] 124 patients with *S aureus* bacteremia with or without endocarditis were randomized to receive daptomycin, and 122 to receive a combination of low-dose gentamicin plus either an antistaphylococcal penicillin or vancomycin. Daptomycin was found to be noninferior to the standard regimen (absolute risk reduction [ARR] 2.4, –10.2–15.1), and mortality rates were not significantly different between the 2 treatment arms. Interestingly, however, compared with patients who received daptomycin, significantly more patients who received standard therapy had renal impairment as an adverse event (18.1% vs 6.7%, $P = .009$) or had worsening of creatinine clearance (46.8% vs 19.8%, $P<.001$). The incidence of renal impairment was similar among patients who received gentamicin and vancomycin (20.4%) and patients who received gentamicin and an antistaphylococcal penicillin (18.6%). Renal impairment resulted in the discontinuation of treatment in 5 (4.3%) of 116 patients in the standard-therapy group and in 1 (0.8%) of 120 patients in the daptomycin group.

Thereafter, Rehm and colleagues[113] performed a subset analysis of patients infected with MRSA who were included in the previous study. They found that 20 (44.4%) of the 45 patients treated with daptomycin and 14 (32.6%) of the 43 patients who used vancomycin/gentamicin were successfully treated (ARR 11.9%, 28.3 to 32.1). The overall death rate among patients in the daptomycin group did not differ significantly: 12 (27%) of 45, compared with 8 (19%) of 43 for the vancomycin/gentamicin group ($P = .45$). Again, however, there was significantly more renal dysfunction in the combination arm that was evident by 28 days ($P<.05$). Cosgrove and colleagues[114] performed a safety analysis of

the same population of patients, and found that a total of 22% of patients who received initial low-dose gentamicin versus 8% of patients who did not receive initial low-dose gentamicin experienced decreased creatinine clearance ($P = .005$). They went on to recommend against routine use of initial low-dose gentamicin in the management of most cases of *S aureus* bacteremia and native valve endocarditis, on the basis of evidence of potential harm and the lack of evidence for clinically significant benefit.

Currently, there is no strong evidence that supports the use of combination therapy for staphylococcal bacteremia. Surprisingly, despite many years of standard combination therapy for endocarditis, there is a dearth of literature in this field, and much of the data are based on in vitro studies. Certainly, further controlled trials are needed to examine this issue.

Intra-abdominal Infections

Intra-abdominal infections (IAI) represent a group of diseases that are commonly encountered in surgical practice. In most uncomplicated IAIs, definitive management is surgical, and antibiotics are not warranted beyond surgical prophylaxis.[115] In contrast, complicated IAIs extend beyond the source organ and into the peritoneal cavity through a perforated viscus, thereby stimulating a systemic inflammatory response, and necessitating both source control and broad-spectrum anti-infective therapy. In cases of severe sepsis or septic shock secondary to IAI, defined as abdominal sepsis, mortality is approximately 25% to 35%,[116,117] but may exceed 70%.[118,119]

Most IAIs are polymicrobial and most commonly involve enteric gram-negative bacilli. Health care–associated IAIs, compared with community-acquired IAIs, are significantly more likely to involve resistant pathogens.[120–123] In vitro susceptibility of organisms isolated from IAIs is documented by the Study for Monitoring Antimicrobial Resistance Trends (SMART), which is a surveillance program that monitors resistance patterns. The SMART report for 2008 showed that against members of the family Enterobacteriaceae, the most active agents ($\geq$90% susceptible) were carbapenems, amikacin, cefepime, and piperacillin-tazobactam. *E coli* and *Klebsiella pneumoniae* were the most common organisms isolated, and extended-spectrum β-lactamase (ESBL) production was detected in 4.7% and 17.5% of them, respectively. Among the ESBL-producing bacteria, the carbapenems retained their activity better than other antimicrobials.[124]

Once adequate source control is obtained, appropriate initial antimicrobial therapy heavily influences outcome in complicated IAIs, as with other severe infections.[123,125–128] In addition, increased mortality associated with inappropriate empiric antibiotic therapy cannot be reversed by subsequent modifications.[126] Evidence-based guidelines regarding selection of antimicrobial therapy for IAIs, were formulated by the Surgical Infection Society, the Infectious Diseases Society of America, the American Society for Microbiology, and the Society of Infectious Disease Pharmacists.[127,129] In the guidelines, the use of either single-drug regimens or combination therapy is recommended. Although it is stated in the guidelines that "antibiotic therapy for such (healthcare-associated) infections … may require the use of multi-drug regimens (eg, an aminoglycoside or quinolone or a carbapenem and vancomycin),"[127] no specific recommendations are made regarding the use of combination therapy.

The specific combination regimens indicated for treatment of IAIs in the guidelines are either aminoglycoside based,[130–133] cephalosporin based,[117,132,134–137] or quinolone based.[138,139] Even though the recommendation to use these combinations comes from randomized prospective, controlled trials, some, but not all the trials included patients in severe sepsis or septic shock. The review by Bochud and colleagues included 5 trials that evaluated the use of combination therapy versus

monotherapy for the empiric treatment of abdominal sepsis.[30] In all 5 trials, there was no significant mortality difference between the 2 treatment arms (**Table 3**).

Since then, to our knowledge, there have been 2 new randomized controlled trials that have examined the use of combination therapy in abdominal infections.[128,144] Yellin and colleagues[128] found that success rates of ertapenem compared with combination therapy using ceftriaxone and metronidazole were similar at 83% (22/29) and 77% (24/31) in the ertapenem and comparator groups, respectively. Solomkin and colleagues[144] compared moxifloxacin monotherapy to ceftriaxone plus metronidazole in patients with complicated community-origin intra-abdominal infection. Moxifloxacin was noninferior to ceftriaxone plus metronidazole in terms of clinical response at test-of-cure in the per protocol population (clinical cure, 90.2% for moxifloxacin vs 96.5% for ceftriaxone/metronidazole; 95% CI of the difference –11.7 to –1.7). However, the patients included in these trials were not critically ill: in the study by Yellin and colleagues,[128] 94% of patients in each treatment arm had APACHE scores of 14 or lower, and in the study by Solomkin and colleagues,[144] all patients had community-acquired abdominal infections, none of whom were in severe sepsis or shock.

Based on limited data, the use of combination therapy in abdominal sepsis does not appear to be more advantageous compared with single-drug therapy, for as long as the initial antimicrobial drug is appropriate.

SEPSIS AND SEPTIC SHOCK

With regard to sepsis, Paul and colleagues[8] performed a review and meta-analysis comparing β-lactam-aminoglycoside combination therapy with β-lactam monotherapy for severe infections in non–immune-compromised patients with sepsis. In this analysis, a total of 64 randomized and quasi-randomized trials were included, comprising 7568 patients, of which approximately 1000 had pneumonia.[24] Paul and colleagues[24] concluded there was no difference in all-cause fatality (RR 0.90; 95% CI, 0.77 to 1.06) and that empirical evidence did not show the synergy effect when

Table 3
Comparison of randomized controlled trials of monotherapy versus combination therapy for abdominal sepsis

Author, Year	Total # pts, N	Experimental Therapy	Control Therapy	Mortality (%)	RR (CI)	*P* Value
Schentag 1983[142]	98	Moxalactam	Clindamycin + tobramycin	7/49 (14) v 6/49 (12)	1.17	1
Poenaru 1990[133]	104	Imipenem	Clindamycin/ metronidazole + tobramycin	4/52(8) v 9/52 (17)	.47	.235
Solomkin 1990[143]	162	Imipenem	Clindamycin + tobramycin	11/81(14) v 14/81 (17)	.82	.664
Fink 1991[141]	40	Ticarcillin-clavulanate	Clindamycin + gentamicin	3/20(15) v 5/25(20)	.75	.716
Dupont 2000[140]	204	Pipercillin-tazobactam	Pipercillin-tazobactam + amikacin	19/99 (19) v 22/105 (21)	0.9	.862

Data from Bochud PY, Bonten M, Marchetti O, et al. Antimicrobial therapy for patients with severe sepsis and septic shock: an evidence-based review. Crit Care Med 2004;32:S495–512.

adding an aminoglycoside to a β-lactam in the clinical setting. They cited that specific growth conditions in vitro that may induce synergism may be unattainable in vivo. Pharmacokinetic and pharmacodynamic properties involving specific antibiotics, sites of infection, timing, and intervals of administration may prevent synergism in vivo as well. Adverse events related directly to the aminoglycoside, or to the combination, may also interfere with an in vivo benefit, amounting altogether to no benefit. In addition, in this analysis, adverse events occurred more frequently with combination therapy. Specifically, nephrotoxicity occurred more often in the combination treatment arm (RR 0.3, 023–0.39).

Meta-regression studies have found that efficacy of some medical therapies, including immunomodulatory therapy of sepsis, can be contingent on the underlying severity of illness and risk of death. A potential survival benefit with combination antimicrobial therapy may be similarly restricted to high-risk groups. A benefit in the most severely ill patients may be diluted or offset by less severely ill patients in whom no benefit exists or adverse effects of combination therapy dominate. Kumar and colleagues[25] hypothesized that any beneficial effect of combination (ie, 2 antibiotics of different antimicrobial classes active for the isolated pathogen) antimicrobial therapy on mortality of life-threatening infection is restricted to patients with septic shock or otherwise high risk of death. This hypothesis was tested in a meta-regression study of 50 studies from which 62 evaluable datasets of varying monotherapy mortality were derived. Notably, Kumar and colleagues[25] found the same absence of a significant benefit of combination therapy overall as did Paul and colleagues.[24] However, stratification of the dataset by monotherapy mortality/clinical failure rate found that the pooled OR for mortality when the monotherapy mortality/clinical failure rate was less than 15% significantly favored monotherapy (OR, 1.53; 95% CI, 1.16 –2.03; $P = .003$; I^2 8.2%). The pooled OR for monotherapy mortality/clinical failure rate of 15% to 25% indicated no difference in efficacy of monotherapy or combination therapy (OR, 1.05; 95% CI, 0.81–1.34; $P = .7657$; I2 _ 30.7%). However, combination therapy demonstrated a significant advantage over monotherapy when the rate of death/clinical failure exceeded 25% (pooled OR, 0.54; 95% CI, 0.45–0.66; $P<.0001$; $I^2 = 0\%$). Stratification of datasets resulted in a marked decrease in heterogeneity in all stratified groups, suggesting that variations in mortality clinical failure risk represented a substantial portion of the heterogeneity in the aggregate meta-analysis (**Fig. 4**). Twelve studies were split into 2 mutually exclusive groups of higher and lower mortality risk (septic shock or critically ill vs non–septic shock or non–critically ill). Meta-analysis of each group showed a significant benefit of a combination therapy strategy in only the septic shock/critically ill group (OR 0.49; 95% confidence interval, 0.35–0.70; $P<.0001$; I2_0%) (**Fig. 5**). Meta-regression indicated that the benefit of combination therapy with respect to outcome was dependent only on the risk of death in the monotherapy group. A similar result was found when datasets were restricted to randomized controlled trials only.

The reason for the divergent results between the 2 studies should be examined. It is notable that both studies failed to demonstrate evidence of benefit in the overall dataset. However, the underlying hypothesis of the article by Kumar and colleagues[25] specifically postulated that any benefit would be restricted to only the most critically ill subset, particularly those with septic shock. The power of the study to detect a difference in outcome among the most severely ill subset was enhanced by (1) splitting studies into mutually exclusive groups of septic shock/critically ill and non–septic shock/non–critically ill where possible (2) and (3) excluding studies where a structural bias would favor an equivalence outcome (ie, a highly potent β-lactam vs a less potent β-lactam and a second agent). The fact that clinical failure with combination therapy

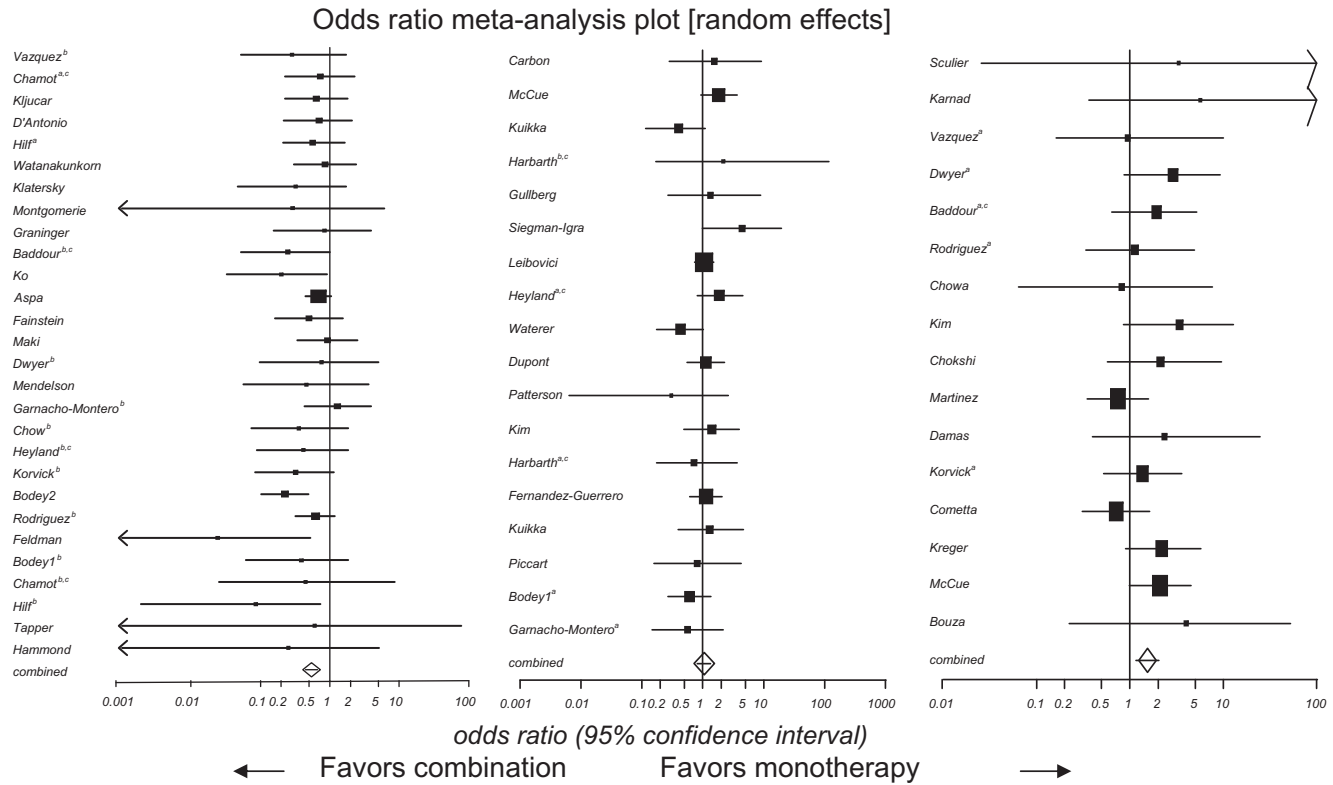

Fig. 4. Analysis of studies comparing combination antibiotic therapy with monotherapy for reducing mortality of life-threatening infections associated with sepsis. Note the gradual shift of the odds ratio from the right to the left as monotherapy mortality increases. The size of the squares is proportional to the reciprocal of the variance of the studies.

[a] Nonshock or noncritically ill stratified dataset; [b] Shock or critically ill stratified dataset; [c] Modified dataset provided by study authors. (*Data from* Kumar A, Safdar N, Kethireddy S, et al. A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-analytic/meta-regression study. Crit Care Med 2010;38:1651–64.)

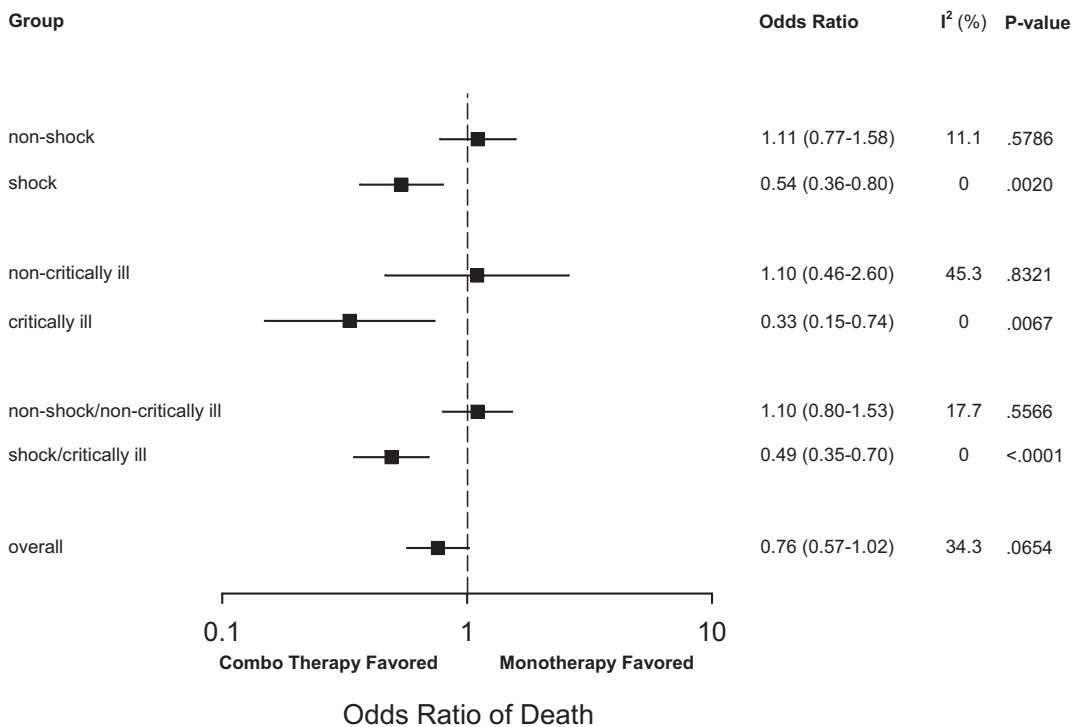

Fig. 5. Subset analysis comparing combination antibiotic therapy with monotherapy for reducing mortality of life-threatening infections associated with sepsis in shock/critically ill and nonshock/noncritically ill patient datasets (derived from 12 studies in which groups could be separated). (*Data from* Kumar A, Safdar N, Kethireddy S, et al. A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-analytic/meta-regression study. Crit Care Med 2010;38:1651–64.)

was more common only among those studies with a structural bias (ie, comparing different β-lactams) in the meta-analysis by Paul and colleagues[24] points out the difficulties of using such studies (even randomized studies) to assess this issue.

The meta-regression findings by Kumar and colleagues[145] are consistent with the results of a recent retrospective, propensity matched, multicenter, cohort study by the same primary author, in ICUs of 28 academic and community hospitals in 3 countries between 1996 and 2007. A total of 4662 eligible cases of culture-positive, bacterial septic shock treated with combination or monotherapy (2 or more vs 1 antibiotic with in vitro activity for isolated pathogen) from which 1223 propensity-matched pairs were generated. The primary outcome of study was 28-day mortality. Using a Cox proportional hazards model, combination therapy was associated with decreased 28-day mortality (444 [36.3%] of 1223 vs 355 [29.0%] of 1223; HR, 0.77; 95% CI, 0.67–0.88; $P = .0002$). The beneficial impact of combination therapy applied to both gram-positive and gram-negative infections but was restricted to patients treated with beta-lactams in combination with aminoglycosides, fluoroquinolones, or macrolides/clindamycin (**Fig. 6**).

Notably, the most potent β-lactams including carbapenems failed to exhibit evidence of combination therapy benefit (**Fig. 7**). This may be because the cidality of such drugs is near maximal for the vast majority of human bacterial pathogens causing septic shock. In this circumstance, the addition of a second drug may have little incremental benefit. This may be an important observation in view of the

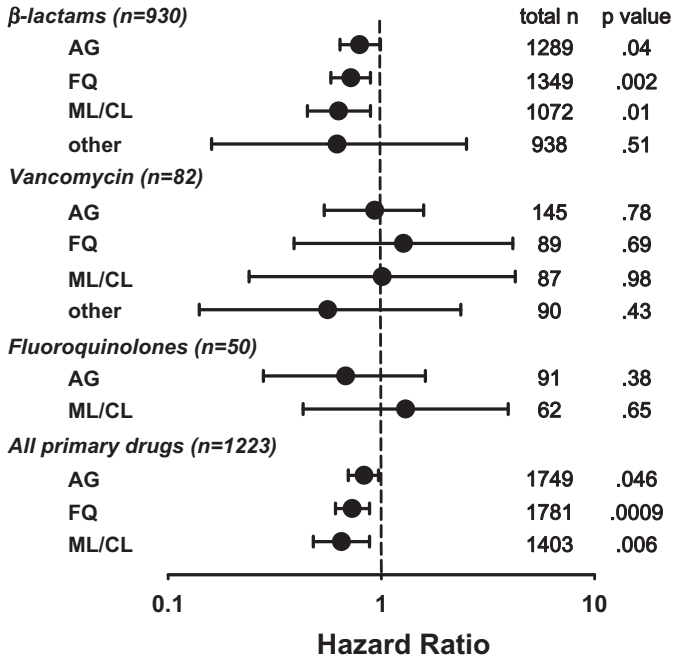

Fig. 6. Supplemental antibiotic and outcome. The use of aminoglycoside (AG), fluoroquinolone (FQ), or a macrolide/clindamycin (ML/CL) in addition to a beta-lactam was associated with a reduced hazard ratio for death compared to beta-lactam alone. (*Data from* Kumar A, Zarychanski R, Light B, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity matched analysis. Crit Care Med 2010;38:1773–85.)

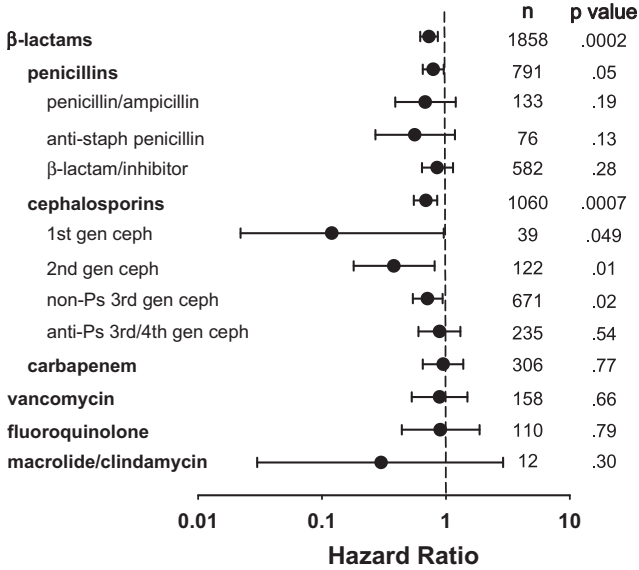

Fig. 7. Primary antibiotic and outcome. The use of β-lactams as part of combination therapy was associated with reduced hazard ratio of death. A significant association with survival was seen with use of most penicillins and cephalosporins in such therapy. The benefit did not extend to antipseudomonal beta-lactamase inhibitors, cephalosporins, and carbapenems. Combinations in which an antibiotic other than a beta-lactam was the primary agent also did not show evidence of benefit. Monotherapy represents the reference group. CT, combination therapy; ceph, cephalosporin; gen, generation; MT, monotherapy; Ps, pseudomonalstaph; staph, Staphylococcus. (*Data from* Kumar A, Zarychanski R, Light B, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity matched analysis. Crit Care Med 2010;38:1773–85.)

anticipated publication of the upcoming MAXSEP trial, a randomized comparison of meropenem versus meropenem and moxifloxacin therapy of severe sepsis and septic shock.[146]

Combination therapy was also associated with significant reductions in ICU (437 [35.7%] of 1223 vs 352 [28.8%] of 1223; OR, 0.75; 95% CI, 0.63–0.92; $P = .0006$) and hospital mortality (584 [47.8%] of 1223 vs 457 [37.4%] of 1223; OR, 0.69; 95% CI, 0.59–0.81; $P<.0001$). The use of combination therapy was associated with increased ventilator (median and [interquartile range], 10 [0–25] vs 17 [0–26]; $P = .008$) and pressor/inotrope-free days (median and [interquartile range], 23 [0–28] vs 25 [0–28]; $P = .007$) up to 30 days.

For patients in septic shock who have a high baseline risk of mortality, combination empiric antibiotic therapy for several days with 2 drugs of different mechanisms of action and with likely activity for the putative pathogen is appropriate. Monotherapy is recommended for patients who are not critically ill and at high risk of death.

SUMMARY

Anti-infective therapy is the cornerstone of treatment for critically ill patients with sepsis, and the use of initial appropriate antimicrobial therapy is crucial in determining positive outcomes. In the current era of increasing antimicrobial resistance, empiric

combination therapy in critically ill patients with a high baseline risk of death and those with septic shock is recommended to ensure appropriate coverage. However, even if a single agent would be expected to cover the likely pathogen with a high degree of certainty, current data suggest a potential advantage with combination therapy in this patient group. For serious infections without shock, monotherapy is sufficient. If empiric combination therapy is initiated for serious infections without shock, continued use of combination therapy as definitive treatment once susceptibility supports de-escalation to a single drug is not supported by current evidence. In fact, in some cases, combination therapy may increase the risk of adverse events such as renal toxicity. Although data are lacking, we also recommend only a limited period of several days of combination therapy for patients with septic shock who show evidence of clinical response to antimicrobial therapy.

The data reviewed suggest that the question of whether combination therapy is beneficial or not may be outdated. The appropriate question may be to ask under what circumstances combination therapy is beneficial. With the emergence of multiple drug-resistant organisms, and the lack of new antimicrobials, there remains an urgent need to devote research to identify the optimal treatment regimens for the critically ill population of patients with sepsis, particularly septic shock.

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