

Empiric Antibiotic Therapy for Sepsis Patients: Monotherapy With β -Lactam or β -Lactam Plus an Aminoglycoside?

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SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician(s) knowledgeable in the subject area.

The source for this systematic review abstract is Paul M, Silibiger I, Grozinsky S, Soares-Weiser K, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev*. 2006;(1):CD003344.

The *Annals'* EBEM editors assisted in the preparation of the abstract of this Cochrane systematic review, as well as the Evidence-Based Medicine Teaching Points.

OBJECTIVE

The objective of this review is to examine the efficacy of monotherapy with β -lactam antibiotics versus the standard β -lactam-aminoglycoside antibiotic combination in treatment of sepsis, with regard to all-cause mortality and an estimation of the rate of adverse effects with each treatment.

DATA SOURCES

The authors searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 3, 2004), MEDLINE (1966 to July 2004), EMBASE (1980 to March 2003), LILACS (1982 to July 2004), and conference proceedings of the Interscience Conference of Antimicrobial Agents and Chemotherapy (1995 to 2003). The reviewers examined citations of the identified studies and contacted corresponding authors of each study. Researchers active in the field were also contacted.

STUDY SELECTION

The authors included only randomized and quasirandomized trials comparing any β -lactam monotherapy to any combination of 1 β -lactam with 1 aminoglycoside for the treatment of sepsis. Studies included septic patients from both community-acquired

and nosocomial sources. Sepsis was defined as a clinically evident infection with a systemic response. Trials with neonates and preterm babies were excluded, as well as studies in which more than 15% of the patients were neutropenic.

Interventions included intravenous β -lactams: penicillins with and without a β -lactamase inhibitor; cephalosporins and carbapenems; and aminoglycosides: gentamicin, tobramycin, amikacin, netilmicin, streptomycin, and isepamicin.

The primary outcome was all-cause mortality measured at the conclusion of the study follow-up. Secondary outcomes included clinical failures, hospital length of stay, dropouts, superinfection, bacterial resistance to antibiotics, and adverse effects, such as nephrotoxicity, pseudomembranous colitis, and allergic reactions.

DATA EXTRACTION AND ANALYSIS

One author inspected the study abstracts from the electronic search. When relevant articles were identified, the article was obtained and inspected by 2 authors. Two authors independently (blinding not stated) assessed the quality of each trial.

Two reviewers extracted data from the trials. In case of disagreement between the reviewers, a third reviewer extracted the data. A third also extracted data from 10% of the studies that were randomly selected. Outcome measures were collected on an intention-to-treat basis whenever possible.

The data were analyzed, comparing the trial characteristics, including patients, infections, interventions, and outcome measures. Separate meta-analyses were conducted for trials in which the same β -lactam was compared with and without an aminoglycoside and in which a different β -lactam was used in each group. For the primary outcome variable, all-cause mortality, data were reported as relative risk (RR) of death with 95% confidence intervals (CIs). The authors performed a sensitivity analysis based on the quality assessment.

RESULTS

Fatality and Clinical Failures

The reviewers' search strategy identified 43 trials including 5,527 patients. The majority of these studies compared a

Table. Fatality and clinical failure: monotherapy versus combination therapy.

Outcomes	Type of Infections	Comparison to Same Beta-Lactam	Comparison to Different Beta-Lactams
Fatality	All Causes	1.01 [0.75,1.35]	0.85 [0.71,1.01]
	Gram Negative Infections	0.56 [0.08,4.07]	1.25 [0.80,1.95]
	Gram Negative Bacteremia	1.62 [0.30,8.75]	1.31 [0.63,2.70]
	Non-Urinary Tract Infections	0.88 [0.53,1.47]	0.70 [0.52,0.95]
Clinical Failure	All Causes	1.11 [0.95,1.29]	0.77 [0.69,0.86]
	Gram Negative Infections	1.23 [0.90,1.68]	0.85 [0.66,1.09]
	Gram Negative Bacteremia	1.07 [0.45,2.56]	0.75 [0.38,1.48]
	Pseudomonas aeruginosa	1.02 [0.68,1.51]	1.24 [0.77,1.98]
	Bacteremia	1.43 [0.77,2.66]	0.64 [0.46,0.89]
	Urinary Tract Infections	1.12 [0.59,2.13]	1.23 [0.80,1.88]
	Non-Urinary Tract Infections	1.18 [0.99,1.42]	0.70 [0.61,0.81]

different β -lactam in the monotherapy than in the β -lactam plus aminoglycoside group. Twelve of these trials with 1,381 patients compared monotherapy with combination therapy using the same β -lactam in both groups. The Table summarizes the meta-analyses of both the same and different β -lactams trials comparing fatality and clinical failure between the monotherapy and combination therapy groups. The majority of these studies compared a different, usually newer and broader-spectrum β -lactam in the monotherapy than in the β -lactam plus aminoglycoside group. An RR of less than 1.0 favors monotherapy; greater than 1.0 favors combination therapy.

From the Table, combining an aminoglycoside with a β -lactam antibiotic compared to monotherapy failed to improve mortality rates from all causes, including in the subgroup of patients with Gram-negative infections and bacteremia. In fact monotherapy (different β -lactams) compared to combination therapy significantly improved fatality from non-urinary tract infections. Clinical failures were less common from all causes with monotherapy (different β -lactams) than combination therapy, secondary to favorable outcomes in treating bacteremia and non-urinary tract infections.

For Gram-positive infections, in vitro studies showing a benefit in adding an aminoglycoside to a β -lactam were not borne out by clinical meta-analyses. Combination therapy did not significantly improve all-cause mortality (RR=0.44; 95% CI 0.12 to 1.58) or the risk of clinical failure (RR=0.69; 95% CI 0.40 to 1.19).

In comparing outcomes by site of infection, combination therapy provided no significant improvement in mortality in sepsis at the same site (RR=1.25; 95% CI 1.01 to 1.55) or different site (RR=0.83; 95% CI 0.69 to 0.99), abdominal same site (RR=0.91; 95% CI 0.54 to 1.55) or different site (RR=1.09; 95% CI 0.56 to 2.15), or urinary tract infection different site (RR=1.33; 95% CI 0.34 to 5.21). Clinical failures by infection site also found no significant benefit to combination therapy in sepsis at the same site (RR=1.25; 95% CI 1.01 to 1.55) or different site (RR=0.75; 95% CI 0.66 to 0.84), abdominal same site (RR=1.03; 95% CI 0.80 to 1.32) or different site (RR=0.82; 95% CI 0.59 to 1.13), or urinary tract infection same site (RR=0.98; 95% CI 0.46 to 2.09) or different site (RR=1.12; 95% CI 0.65 to 1.91).

Resistance Development and Adverse Events

The largest comparison included 27 studies with 3,085 patients. The reviewers detected no significant difference between the rates of bacterial or fungal or bacterial superinfections in the combination group. Colonization was nonsignificantly more frequent with combination therapies (RR=0.78; 95% CI 0.60 to 1.01). Only a few studies monitored resistance among initially isolated pathogens, and the reviewers noted no difference between monotherapy and combination therapy.

The addition of an aminoglycoside in the combination therapy group resulted in a significant increase in the risk (RR=0.34; 95% CI 0.23 to 0.39) of nephrotoxicity. This increase in nephrotoxicity was observed in both the once-daily dosing of aminoglycosides and multiday regimens.

CONCLUSIONS

The authors concluded that in sepsis patients there is no difference in overall mortality between monotherapy or combination therapy. The addition of an aminoglycoside only increased the risk of nephrotoxicity. The authors concluded that a broad-spectrum antibiotic β -lactam required less modification than a narrow-spectrum β -lactam with aminoglycoside combination. No specific infection or disease was identified in which the addition of an aminoglycoside to a broad-spectrum β -lactam antibiotic therapy provided an advantage.

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COMMENTARY: CLINICAL IMPLICATIONS

The majority of the approximately 750,000 US citizens with sepsis will first present to an emergency department (ED).¹ Emergency physicians are on the front line of treating a disease with a 20% to 50% mortality rate.² Early goal-directed therapy

for sepsis appears effective in reducing mortality rates, but at the cost of significant time and personnel resources.³

Yet, identification of the offending organism and its antibiotic resistance patterns are certainly outside of the purview of most emergency physicians, which results in empiric selection of antibiotic regimen(s) for patients with sepsis as part of the early goal-directed therapy approach. The choice of antibiotic(s) must represent a balance between a sufficiently broad bacterial coverage for critically ill patients and the concerns for complications, adverse reactions, emerging bacterial resistance, and finally cost.

The trials reviewed in this Cochrane review provide considerable high-quality evidence on which to select empiric antibiotic therapy for ED patients with sepsis. Using a comprehensive search strategy to reduce publication bias and methods to eliminate selection bias, these authors have identified the best available evidence comparing β -lactam monotherapy to combination therapy with β -lactams and aminoglycosides. Meta-analyses of 43 studies comparing a β -lactam with and without an aminoglycoside convincingly show that monotherapy is safe and as effective as combination therapy, but without the additional risk of nephrotoxicity.

The results of this meta-analysis appear counterintuitive to our ingrained approach to sepsis patients of empirically providing a broad range of antibiotics with coverage for both Gram-negative and Gram-positive bacterium, consistent with current treatment guidelines such as the Surviving Sepsis Campaign.⁴ Limitations of the meta-analysis are primarily related to the overall quality of included trials in this Cochrane review, which were rated as poor. For example, concealment of allocation was deemed adequate in only 30% of the studies. The majority of the trials were unblinded, and intention to treat was evidenced in only 44%. Finally, follow-up was specified in only 67% of the studies.

Methodologic limitations of this meta-analysis include the fact that the majority of the trials compared one β -lactam (broader spectrum) with a different β -lactam (narrower spectrum) and aminoglycoside combination. The “apples to oranges limitation” is somewhat ameliorated by the large number of trials reviewed, which showed similar results even with different β -lactams.

The greatest fear emergency physicians have of empirically selecting β -lactam monotherapy is that their antibiotic selection in a sepsis patient may not address the issue of resistant bacteria. Although some studies have identified higher mortality rates with antibiotic-resistance mismatch,^{5,6} recent evidence comparing bacteremic ICU patients who received appropriate versus inappropriate empiric antibiotics failed to find a difference in mortality rates (multivariable adjusted odds ratio = 1.71; 95% CI 0.66 to 4.7).⁷ This study was limited by a small number of patients having abdominal or respiratory sources of infection in the inadequately treated group (12% versus 33%; $P = .01$), which highlights the importance of source identification in septic patients in the ED. Besides respiratory

infections, which may benefit from a broader spectrum of empiric antibiotics, endocarditis guidelines strongly suggest empiric combination therapy with an aminoglycoside.⁸

TAKE-HOME MESSAGE

Sepsis in the ED can safely be treated empirically with a broad-spectrum β -lactam antibiotic alone. For most patients, the empiric addition of an aminoglycoside will not significantly improve outcome but will increase the risk of nephrotoxicity. Local and regional ED early goal-directed therapy guidelines should be revised to indicate this.

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EBEM TEACHING POINT

The substance of this meta-analysis as a Cochrane review was first published as a review article in a paper journal, the *British Medical Journal*.⁹ Although the 2 reviews present similar methods, results, and conclusions, why did the authors republish this material? In general, Cochrane reviews have been criticized for being unwieldy for the practicing clinician because of the sheer size and language used. In addition, some clinicians do not have access to the products of the Cochrane. Consequently, for a variety of reasons, publications of condensed versions of the reviews have been appealing from both the perspective of the journal, as well as the authors.

Journals

Traditionally, Cochrane reviews have been considered methodologically more rigorous than paper-based reviews. The rigor is ensured through meticulous attention to avoiding biases, multiple levels of peer review, and revisions that permit reviews to improve over subsequent updates. For journals, publishing a Cochrane review would represent a high-impact article that may be frequently cited.

Authors

Authors of Cochrane reviews who submit articles to paper journals could be accused of duplicate publications; however, most authors would disagree. For example, the reviews are often difficult to condense into a paper review. In addition, the impact factor for Cochrane reviews is unknown, and although it is estimated to rival the best general medical journals such as *Lancet*, many institutions do not recognize this resource in considerations for evaluation and promotion.

Readers must be careful to ensure they are reading the most current review and make efforts to identify the most recent version for the purposes of decisionmaking.

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