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A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics.

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OBJECTIVE: The clinical benefits of extended infusion or continuous infusion of beta-lactam antibiotics remain controversial. We systematically reviewed the literature to determine whether any clinical benefits exist for administration of beta-lactam antibiotics by extended or continuous infusion. DATA SOURCE: PubMed (January 1950 to November 2007), EMBASE (1966 to November 2007), and the Cochrane Controlled Trial Register were searched (updated November 2007). STUDY SELECTIONS: Randomized controlled trials (RCTs) were meta-analyzed, and observational studies were described by two unblinded reviewers. DATA EXTRACTION: A total of 846 patients from eligible prospective randomized controlled studies were included in the meta-analysis. Two observational studies were deemed appropriate for description. DATA SYNTHESIS: A meta-analysis of prospective RCTs was undertaken using Review Manager. Among a total of 59 potentially relevant studies, 14 RCTs involving a total of 846 patients from nine countries were deemed appropriate for meta-analysis. The use of continuous infusion of a beta-lactam antibiotic was not associated with an improvement in clinical cure (n = 755 patients; odds ratio: 1.04, 95% confidence interval: 0.74-1.46, p = 0.83, I = 0%) or mortality (n = 541 patients; odds ratio: 1.00, 95% confidence interval: 0.48-2.06, p = 1.00, I = 14.8%). All RCTs except one used a higher antibiotic dose in the bolus administration group. Two observational studies, not pooled because they did not meet the a priori criteria for meta-analysis, showed that beta-lactam administration by extended or continuous infusion was associated with an improvement in clinical cure. The difference in the results between the meta-analysis results and the observational studies could be explained by the bias created by a higher dose of antibiotic in the bolus group in the RCTs and because many of the RCTs only recruited patients with a low acuity of illness. CONCLUSIONS: The limited data available suggest that continuous infusion of beta-lactam antibiotics leads to the same clinical results as higher dosed bolus administration in hospitalized patients.

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Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America.

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The Infectious Diseases Society of America (IDSA) continues to view with concern the lean pipeline for novel therapeutics to treat drug-resistant infections, especially those caused by gram-negative pathogens. Infections now occur that are resistant to all current antibacterial options. Although the IDSA is encouraged by the prospect of success for some agents currently in preclinical development, there is an urgent, immediate need for new agents with activity against these panresistant organisms. There is no evidence that this need will be met in the foreseeable future. Furthermore, we remain concerned that the infrastructure for discovering and developing new antibacterials continues to stagnate, thereby risking the future pipeline of antibacterial drugs. The IDSA proposed solutions in its 2004 policy report, "Bad Bugs, No Drugs: As Antibiotic R&D Stagnates, a Public Health Crisis Brews," and recently issued a "Call to Action" to provide an update on the scope of the problem and the proposed solutions. A primary objective of these periodic reports is to encourage a community and legislative response to establish greater financial parity between the antimicrobial development and the development of other drugs. Although recent actions of the Food and Drug Administration and the 110th US Congress present a glimmer of hope, significant uncertainly remains. Now, more than ever, it is essential to create a robust and sustainable antibacterial research and development infrastructure--one that can respond to current antibacterial resistance now and anticipate evolving resistance. This challenge requires that industry, academia, the National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control and Prevention, the US Department of Defense, and the new Biomedical Advanced Research and Development Authority at the Department of Health and Human Services work productively together. This report provides an update on potentially effective antibacterial drugs in the late-stage development pipeline, in the hope of encouraging such collaborative action.

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Cefepime Therapy and All-Cause Mortality.

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The findings of increased all-cause mortality associated with cefepime therapy reported in a 2007 meta-analysis by Yahav and colleagues in The Lancet Infectious Disease prompted an early communication by the Food Drug Administration (FDA). The FDA stated that it would review more safety data to further evaluate the risk of death to patients treated with cefepime. The meta-analysis' conclusion and the FDA early communication have stirred up debates in many institutions about how to properly adjust their antibiotic practice. Our review of the method of the meta-analyis (e.g., the method of data collection) raises questions about its conclusion; we call for additional review of the clinical data before any effort is made to limit or eliminate cefepime from the current practice guidelines. We make a number of recommendations on the appropriate use of cefepime therapy while awaiting further FDA advice.

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Combination antimicrobial treatment versus monotherapy: the contribution of meta-analyses.

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Systematic reviews and meta-analyses have put into perspective the clinical implications of in vitro synergy (Box 1). Randomized, controlled trials are the cornerstone of evidence-based medicine. The trials included in the meta-analyses described in this article are the building blocks of evidence. Individual trials, however, were individually underpowered to address the broader clinical question and relevant patient-related outcomes. On the question of combination therapy, meta-analyses have shaped the complete picture. The interactions observed in vitro have not been shown to improve patient-related outcomes. Authors of systematic reviews have the privilege of considering and selecting the clinical outcomes most relevant for the individual patient. Thus, all-cause mortality, rather than treatment failure with antibiotic modifications or infection-related mortality, has been selected for the assessment of patients who had severe gram-negative infections and febrile neutropenia. Mortality and relapse were assessed for patients who had endocarditis, and clinical and lung function scores were assessed for patients who had cystic fibrosis. The authors hope that the dissemination of these reviews will lead clinicians and researchers to consider primarily these outcomes when appraising or designing clinical research. These are the outcomes that clinicians target when treating the patient. Systematic reviews have the virtue of a broad, systematic, and explicit search. In some areas, such as the use of combination therapy to treat gram-positive infections

in general, and specifically to treat endocarditis and Pseudomonas aeruginosa bacteremia, the main contribution of the reviews was to show that current practice is based on very limited clinical evidence. This finding does not refute current practice but should serve to guide future trials and opens the possibility for a different choice of therapy when standard guidelines are difficult to implement. The fact that to date no evidence has been accrued for these infections is not surprising. The clinical question of combination therapy is of no major interest to pharmaceutical companies sponsoring most trials; the infections are rare; and the study design is complex. This gap in knowledge calls for a new trial paradigm: collaborative investigator-initiated, multicenter trials. When randomized, controlled trials are unfeasible, the use of novel methods for adjustments in observational studies, such as propensity analyses using large databases, might approximate the true effect of combination therapy in a wider patient population.

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Meta-analyses on the optimization of the duration of antimicrobial treatment for various infections.

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A mainstay of antibiotic treatment is its optimal duration for the management of infections. Many randomized control trials have been conducted on these issues during the last years. The results from these randomized control trials have been analyzed by various meta-analyses. To address the role of meta-analyses that compared a short-duration with a long-duration of the same antibiotic treatment for various infections a search was made in PubMed, Scopus, and Cochrane databases for relevant meta-analyses.

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Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy.

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OBJECTIVE: To describe the incidence and outcomes associated with early acute kidney injury (AKI) in septic shock and explore the association between duration from hypotension onset to effective antimicrobial therapy and AKI. DESIGN: Retrospective cohort study. SUBJECTS: A total of 4,532 adult patients with septic shock from 1989 to 2005. SETTING: Intensive care units of 22 academic and community hospitals in Canada, the United States and Saudi Arabia. MEASUREMENTS AND MAIN RESULTS: In total, 64.4% of patients with septic shock developed early AKI (i.e., within 24 h after onset of hypotension). By RIFLE criteria, 16.3% had risk, 29.4% had injury and 18.7% had failure. AKI patients were older, more likely female, with more co-morbid disease and greater severity of illness. Of 3,373 patients (74.4%) with hypotension prior to receiving effective antimicrobial therapy, the median (IQR) time from hypotension onset to antimicrobial therapy was 5.5 h (2.0-13.3). Patients with AKI were more likely to have longer delays to receiving antimicrobial therapy compared to those with no AKI [6.0 (2.3-15.3) h for AKI vs. 4.3 (1.5-10.8) h for no AKI, $P < 0.0001$). A longer duration to antimicrobial therapy was also associated an increase in odds of AKI [odds ratio (OR) 1.14, 95% CI 1.10-1.20, $P < 0.001$, per hour (log-transformed) delay]. AKI was associated with significantly higher odds of death in both ICU (OR 1.73, 95% CI 1.60-1.9, $P < 0.0001$) and hospital (OR 1.62, 95% CI, 1.5-1.7, $P < 0.0001$). By Cox proportional hazards analysis, including propensity score-adjustment, each RIFLE category was independently associated with a greater hazard ratio for death (risk 1.31; injury 1.45; failure 1.56). CONCLUSION: Early AKI is common in septic shock. Delays to appropriate antimicrobial therapy may contribute to significant increases in the incidence of AKI. Survival was considerably lower for septic shock associated with early AKI, with increasing severity of AKI, and with increasing delays to appropriate antimicrobial therapy.