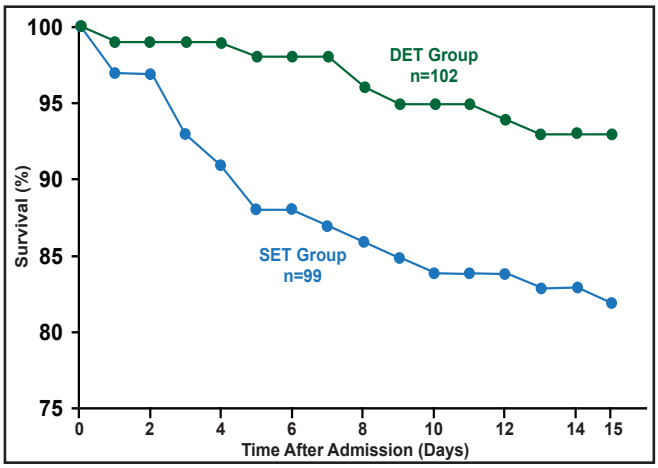
Another possible approach might be combination therapy (with drugs from different antiobiotic classes to which a pathogen is known to be sensitive), but monotherapy versus combination therapy studies show mixed results (Figure 2) [Safdar N et al. *Lancet Infect Dis* 2004; Micek S et al. *Antimicrob Agents Chemother* 2010].

Figure 2. Monotherapy Versus Combination Therapy in Severe Bacteremic Pneumococcal Pneumonia.



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Among critically ill patients (but not less ill patients) with pneumococcal bacteremia, combination antibiotic therapy was associated with lower 14-day mortality (23.4% vs 55.3%; p=0.0015) [Baddour LM et al. *Am J Respir Crit Care Med* 2004]. Patients with community-acquired pneumonia with shock receiving combination therapy do better than those receiving monotherapy, but no difference is seen in patients not in shock [Rodríguez A et al. *Crit Care Med* 2007]. Prof. Kumar said that a meta-analysis study showed that combination antibiotic therapy yielded improved survival and clinical response of high-risk, life-threatening infections, particularly those associated with septic shock, but was detrimental to survival in low-risk patients [Kumar A et al. *Crit Care Med* 2010]. In another propensity-matched study of septic shock, the percentage of patients surviving at 28 days was greater for combination therapy compared with monotherapy (p=0.0002) across a broad range of clinical syndromes and pathogens [Kumar A et al. *Crit Care Med* 2010].

Prof. Kumar noted that there appears to be an underlying principle that explains divergent results in combination therapy, which implies that the benefits of combination therapy are primarily restricted to the critically ill, particularly those with shock, and that combination therapy is only required for short periods. In addition, combination therapy likely only makes sense when the combination of local antibiotic use patterns and local resistance/frequency distribution of pathogens results in suboptimal cidality with monotherapy.

New ASHP/SHEA/IDSA/SIS Guidelines for Surgical Prophylaxis

Written by Phil Vinall

Soon-to-be published guidelines from the American Society of Health-System Pharmacists (ASHP), Infectious Diseases Society of America (IDSA), Society for Healthcare Epidemiology of America (SHEA), and Surgical Infection Society (SIS) will offer updated clinical directives for antimicrobial prophylaxis in surgery. They will be the first collaborative guidelines offered by the 4 societies. E. Patchen Dellinger, MD, University of Washington, Seattle, USA, presented an overview of the guidelines. The recommendations apply primarily to adults aged ≥19 years and children 1 to 18 years, although Dr. Dellinger cautioned that there is a lack of prospective studies for the pediatric group.

When making these recommendations, the guideline writing group thought in terms of the goals of an "ideal agent." It should prevent surgical site infection (SSI) and related morbidity and mortality, be safe, have no consequences to the microbial flora of the patient or hospital, and reduce the duration and cost of health care. In addition, an ideal agent should be active against the pathogens likely to be in the wound and given at an appropriate dose but for the shortest possible time. As for selection of first-choice drug for each procedure, the guidelines are based mostly on expert opinion and take into account a number of factors such as cost, safety, allergy potential, ease of administration, pharmacokinetics, antibacterial activity, and efficacy in a specific procedure. Dr. Dellinger added that there is no evidence that broad-spectrum agents are more effective. For most procedures cefazolin is effective, while metronidazole can be added when anaerobic activity is needed.

Cephalosporins should not be used in patients with documented IgE-mediated allergic reactions (such as anaphylaxis, urticaria, bronchospasm), Stevens-Johnson syndrome, and toxic epidermal necrolysis to β-lactam antibiotics. Cephalosporins and carbapenems can safely be used in patients with reactions to penicillin other than those listed. The optimal time to administer the preoperative

dose is within 60 minutes of incision; for vancomycin and fluoroquinolones the time is 120 minutes, and there does not seem to be convincing evidence that administration closer to the time of incision is less effective. Dosing should ensure that there are adequate levels of drug present in serum both in the early and late phases of the procedure. The guidelines recommend weight-based dosing. The re-dosing interval should be measured from the time of the initial preoperative dose and applied at 2 half-lives of the drug. Duration should be <24 hours for most procedures.

Patients colonized with *Staphylococcus aureus* are at increased risk for SSI. Mupirocin is recommended for decolonization. Although not recommend for routine use, vancomycin may be included when there is a cluster of methicillin-resistant *S. aureus* (MRSA) or methicillin-resistant *Staphylococcus* epidermidis (MRSE) SSI or for patients known to be colonized with methicillin-sensitive *S. aureus* (MSSA). Because of its superior efficacy against MSSA, cefazolin can be added in patients without serious β-lactam allergy.

For colorectal operations, mechanical bowel prep plus oral antibiotics the day before operation combined with appropriate parenteral antibiotics achieves a lower SSI rate than parenteral antibiotics alone with or without bowel prep. The guidelines recommend 3 doses of oral antibiotics (neomycin plus erythromycin or metronidazole) taken the day before surgery (over approximately 10 hours after bowel prep). Dr. Dellinger suggested 8 areas where he believes future antibiotic research should be directed (Table 1). The new guidelines are expected to be published later this year.

Table 1. Areas for Future Research.

1.	Risk/benefit of continuing prophylaxis after the procedure is completed
2.	Specific recommendations for weight-based dosing and intraoperative repeat doses
3.	Timing for antibiotics that must be administered over a prolonged period (vancomycin and fluoroquinolones)
4.	Targeted antimicrobial concentrations and intraoperative monitoring for optimal efficacy
5.	The role of topical antimicrobial agents as alternatives or adjuncts to IV administration
6.	Better data for selection of agents for patients allergic to β-lactam antibiotics
7.	Validated strategies to optimize prophylaxis for patients and facilities with high risk or prevalence of resistant organisms
8.	Outcomes studies on the impact of quality assurance measures and pay for performance