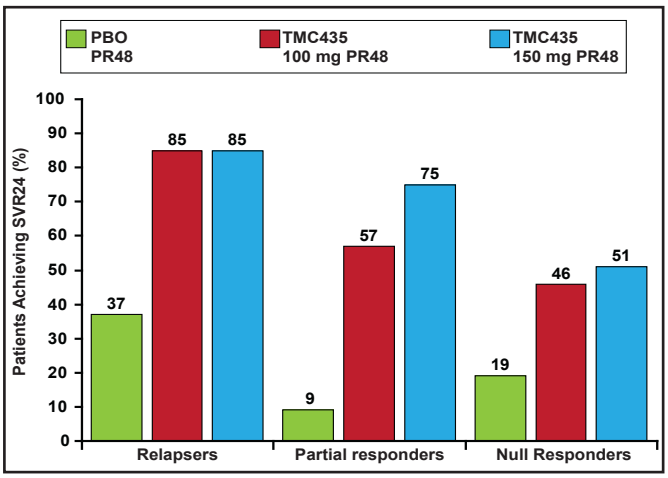
Figure 1. ASPIRE Study: TMC435 plus RBV in Genotype Treatment-Experienced.



RBV=ribavirin; SVR=sustained virologic response; PBO=placebo.

Dr. Terrault noted that although SVR rates have improved with the use of PI-triple therapy, there is still a need for better drug therapies, especially in difficult-to-cure populations, in which SVR rates are still ≤50%. Additionally, current PI-triple therapy has limited genotype coverage, requires long (48-week) treatment duration in some patients, is associated with frequent side effects, has drug-drug interactions, and has resistance issues. The next generation of triple or quad therapies is expected to have higher SVR rates, a shorter duration of therapy, broader genotype application, and simpler regimens. Deciding whether to treat now or wait for future therapies depends on the likelihood of response and risk of waiting, tolerability of PegIFN + RBV, and practical issues such as insurance status and home/work support.

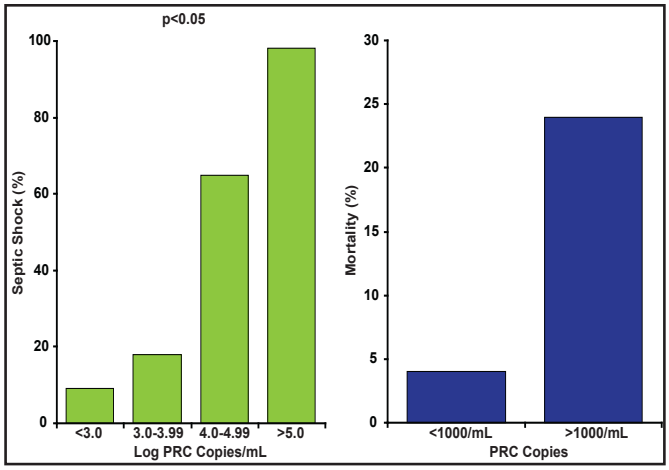
Combination Antibiotics and Outcome of Life-Threatening Bacterial Infections and Septic Shock

Written by Phil Vinall

Untreated septic shock is usually fatal within 24 to 36 hours. Clinical trials with anti-inflammatory agents in patients with sepsis are based on the assumption that the pathogenesis of sepsis is primarily driven by excessive proinflammatory activity of the cytokine network even though the triggering infection may have been eliminated by appropriate antimicrobial therapy [van der Poll T, van Deventer SJ. *Infect Dis Clin North Am* 1999]. Anand Kumar, MD, University of Manitoba, Winnipeg, Canada, suggested that the failure of these trials to show clinical benefit, in conjunction with recent experimental data, raises doubt about the validity of this assumption.

In patients with pneumococcal pneumonia, bacterial load is associated with the likelihood of death and the risk of septic shock [Rello J et al. *Chest* 2009]. As the log PCR copies of the organism go up, so does the probability of septic shock and death (Figure 1). Many studies have shown that time to antimicrobial therapy is a critical determinant of survival in meningococcal sepsis. However, when the relative impact of blood bacterial load and time to antimicrobial therapy on mortality in patients with meningococcal sepsis is considered, the critical factor is blood bacterial load. This suggests that delays in antimicrobial treatment simply mark the development of a greater bacterial load with delays in therapy and that bacterial load is the key driver of sepsis [Lala HM et al. *J Infect* 2007]. Prof. Kumar suggested that the speed of clearance of the microbial pathogen is the critical determinant of outcome in septic shock.

Figure 1. Pneumococcal Pneumonia and Risk of Septic Shock.

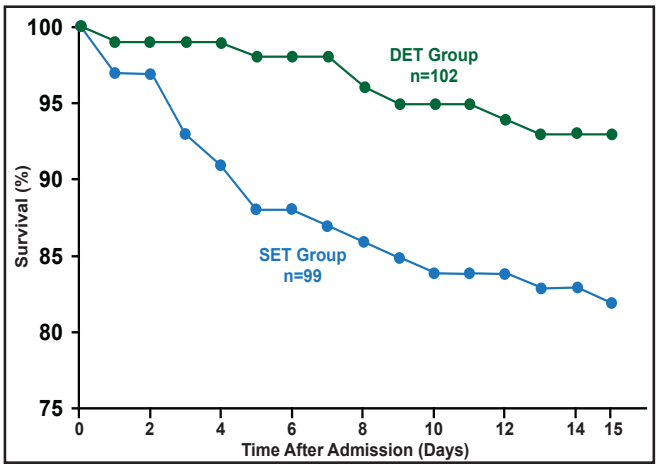


Reprinted with permission from the American College of Chest Physicians. Rello J. Severity of pneumococcal pneumonia associated with genomil bacteria load. *Chest* 2009; 136(3): 832.

What then is the best approach for treatment? Prof. Kumar believes that early appropriate antimicrobial therapy is the simplest effective approach and has shown that early therapy is associated with significant improvement in mortality rates across a variety of clinical infections and microbes [Kumar A et al. *Crit Care Med* 2006]. "But what can you do if you miss the early window of opportunity?" asked Prof. Kumar. One option is to increase the intensity of the therapy by using a cidal versus static drug or increasing the dose to speed elimination of the pathogen.

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