Saving Lives With Optimal Antimicrobial Chemotherapy

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(See the Major Article by Dulhunty et al, on pages 236–44, and the Invited Article by Falagas et al, on pages 272–82.)

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The introduction of antimicrobial chemotherapy was an unprecedented advance in the practice of medicine. Previously fatal infections became treatable and antimicrobials were the agents of that salvage of life. In the more modern era, these agents also became the drugs that were permissive for many of the other modern medical miracles that we currently enjoy. The ability to treat serious infections in neutropenic cancer patients allowed the use of intensive oncologic chemotherapy. In the same vein, immunosuppressive therapy for organ and bone marrow transplants are made possible by antimicrobial therapy, as has the routine use of interventions that cross natural anatomic boundaries.

In the early days of antimicrobial therapy, pioneers such as Harry Eagle recognized that certain administration profiles of drug prompted better therapeutic effect. This was demonstrated in a landmark paper published in the New England Journal of Medicine [1]. Certain agents such as penicillin had a better therapeutic effect when administered on very short administration intervals, whereas drugs such as the tetracyclines had antimicrobial effects that were somewhat independent of administration schedule. Unfortunately much of this information became lost in the 1960s and 1970s.

In the late 1980s and early 1990s, these principles were rediscovered by the laboratory of William Craig [2–4]. These studies linked the effect of different antimicrobial classes, doses, and schedules to the reduction in colony-forming units (CFUs) in murine thigh or pneumonia models. Shortly thereafter, the burgeoning science of pharmacodynamics and pharmacometrics allowed identification of relationships between drug exposure indexed to the minimum inhibitory concentration (MIC) of the infecting pathogen and clinical and/or microbiological outcomes [5–7]. The first study was a retrospective evaluation, but the last 2 were prospectively designed with analysis plans filed with the Food and Drug Administration (FDA). Such studies demonstrated conclusively that it was relatively straightforward to derive exposure-response relationships in the midst of clinical trials, employing a number of different mathematical techniques.

The next step was to demonstrate the link between the animal model findings and the clinical trial pharmacodynamics relationships. Ambrose and colleagues [8] examined outcomes from clinical trials relative to the effect breakpoints determined from murine pharmacodynamic studies. They demonstrated a strong concordance between the preclinical and clinical pharmacodynamic studies for a number of different antimicrobial classes. Consequently, we can say that another brick was laid in the edifice of antimicrobial dynamics.

While these data are convincing, it is also important to demonstrate that attainment of the “correct” antimicrobial targets has an impact on endpoints other than traditional clinical and microbiological outcomes in “real world” clinical practice settings. The clinical benefits of prolonged β-lactam infusion among critically ill patients were highlighted by the study performed at Albany Medical Center Hospital by Lodise and colleagues. Based on the results of a Monte Carlo simulation, prolonged infusion of piperacillin-tazobactam (3.375 g administered over a 4-hour period every 8 hours) was adopted as the standard hospital-wide piperacillin-tazobactam dosing scheme at their institution in February 2002. To evaluate the real-world effectiveness of this automatic dose substitution program, 14-day mortality and hospital length of stay after culture collection were
compared among patients with documented piperacillin-tazobactam-susceptible *Pseudomonas aeruginosa* infections who received intermittent infusions of this agent (2000–2002) prior to the switch or prolonged piperacillin-tazobactam infusion (2002–2004) after implementation of the dose substitution program. Overall, there were significantly fewer deaths and significantly shorter lengths of stay for seriously ill patients (APACHE II score, ≥17). These findings were recapitulated [9] in a recent multicenter retrospective comparative evaluation of critically ill patients who received prolonged or intermittent infusions of piperacillin-tazobactam. In this study of critically ill patients infected with a broad range of gram-negative causative pathogens, extended infusion of piperacillin-tazobactam was found to prolong survival 3 days on average and considerably reduced the risk of mortality. More recently, Scaglione et al prospectively studied patients with hospital-acquired pneumonia receiving a wider range of antibiotics. He demonstrated that dose optimization through feedback control significantly altered both survivorship and length of stay [10]. This study included β-lactams. Dose alteration occurred if the measured drug concentration was less than the MIC of the infecting pathogen; the drug concentration was checked at 70% of the dosing interval.

The theory set forth in preclinical model systems, combined with Monte Carlo simulation, was upheld in these evaluations. The drawback is that both evaluations were retrospective [9, 11], and the Scaglione study used patients who did not have both an MIC measurement and a plasma concentration measurement as the control group [10]. In this issue of Clinical Infectious Diseases, there are 2 sets of observations: one is a meta-analysis of continuous infusion or extended infusion compared with short-term infusions of β-lactams and the other is a randomized, double-blind, double-dummy evaluation of continuous infusion versus intermittent infusion of β-lactams. While previous meta-analyses of randomized clinical trials (RCTs) did not conclude there were any clinical benefits in extending the infusion duration of β-lactams [12–14], the meta-analysis by Falagas et al [15], comprising mainly observational studies, found mortality to be significantly lower among patients receiving extended or continuous infusion of carbapenems or piperacillin-tazobactam compared with those receiving short-term infusions (relative risk, 0.59; 95% confidence interval, 0.41–0.83), and this difference in mortality was most pronounced in patients with pneumonia (relative risk, 0.50; 95% confidence interval, 0.26–0.96).

Beyond differences in antibiotics studied in the included studies (only a few RCTs focused on carbapenems or piperacillin-tazobactam), there are several possible explanations for the discordance in results between the Falagas et al and “RCT” meta-analyses [12–14]. Disease severity in the studies included in the RCT meta-analysis was generally low, as evidenced by low mortality rates in the majority of studies. In addition, diverse groups of patients and infection types were included in the RCTs and a higher antibiotic dose was used in the intermittent administration group in most studies included in the RCT meta-analyses. In contrast, the studies included in the meta-analysis by Falagas et al [15] largely comprised critically ill patients with nosocomial infections, namely pneumonia, receiving comparable dosing regimens. Collectively, the null result from the RCT meta-analyses and positive data from the observational studies meta-analysis suggest that prolonged or continuous infusion of β-lactams is unlikely to be advantageous for all hospitalized patient populations, but may be beneficial for specific groups, such as critically ill patients with higher MIC pathogens. This was demonstrated clearly by the Lodise study [11], where benefit from prolonged infusion only occurred in patients with APACHE II scores of ≥17, and was also seen in the study by Yost and colleagues [9], where all patients were in the intensive care unit (ICU).

The finding of lack of difference between prolonged and intermittent dosing on outcomes of patients who are not seriously infected should not come as a surprise. Recently, it has been demonstrated [16, 17] that the ability of granulocytes to kill invading bacteria is a saturable process. With relatively low bacterial burdens, granulocytes can reduce counts by 1–2 log10 CFUs/g/day. As counts meet and exceed the burdens seen in infections such as nosocomial pneumonia, the ability to prevent outgrowth of the infecting bacterium is lost. Consequently, the adequacy of the antimicrobial regimen becomes paramount in these types of infectious conditions. With seriously ill patients with dense bacterial burdens, the antibiotic regimen must have an impact which will render the burden less than the saturation point of granulocytes, allowing ultimate successful treatment of the patient. With lesser burdens, the antimicrobial regimen needs to do little, as the host defenses, especially the granulocytes, participate to drive a good outcome. An example is seen in the oral cephalosporins, for which FDA claims were granted for community-acquired pneumonia. The majority of these patients, had they had a PORT score, would undoubtedly have had scores of 1 and 2, with relatively low bacterial burdens. The antibiotic need only achieve stasis in order to allow the granulocytes to achieve the cell kill required to drive a good outcome.

As an important first step in delineating the outcomes associated with intermittent infusion relative to continuous infusion in infected, critically ill patients, Dulhunty et al conducted a small-scale, prospective, double-dummy, randomized controlled trial of continuous infusion versus intermittent bolus dosing of piperacillin-tazobactam, meropenem, and ticarcillin-clavulenate in 5 ICUs across Australia and Hong Kong [18].
The primary endpoint of this study was in achieving free-drug concentrations above the MIC of the infecting pathogen for the entire dosing interval. Indeed, the superiority of continuous infusion was directly demonstrated for this endpoint; antibiotic concentrations were in excess of the MIC in 18 (82%) of 22 patients in the continuous arm versus 6 (29%) of 21 patients in the short-infusion arm (P = .001). They were also able to demonstrate that continuous infusion of β-lactam antibiotics results in higher rates of clinical cure compared with intermittent administration in these critically ill patients (clinical cure at 7–14 days after study drug cessation was 27% higher [70% vs 43%] in the continuous infusion group relative to the intermittent dosing group, and this finding persisted even after adjusting for therapy changes; P = .037). It should be noted that the study was only powered for the endpoint of maintaining free-drug concentration above the MIC for the entire dosing interval. Nonetheless, other endpoints such as ICU-free days and mortality, while not achieving statistical significance (19.5 days vs 17 days and 90% vs 80% for continuous vs intermittent infusion), each showed a trend in favor of continuous infusion. The positive findings from this study provide strong rationale for further multicenter trials with sufficient power to delineate differences in outcomes such as clinical and microbiological outcome as well as mortality and length of stay. Indeed, Dulhunty and colleagues [18] have pointed out that previous authors [19] have shown the way to employ smaller but well-focused clinical trials such as the one in this issue of Clinical Infectious Diseases as a means of optimizing the design of larger randomized trials and also providing reasonable power estimates for those trials for endpoints of interest.

The papers of Falagas et al [15] and Dulhunty et al [18] are important steps forward. We have seen the progression of evidence for optimizing antimicrobial chemotherapy from in vitro and animal model data through to retrospective examinations of clinical data. Here, we have a well-done meta-analysis that is concordant with previous preclinical data. We also have a prospective randomized double-blind, double-dummy clinical trial focused in ICU patients that had a positive outcome for its primary endpoint, but also demonstrated a significant improvement in clinical outcome. We must eagerly await the final capstone of a prospective multicentered, randomized trial powered for outcomes such as clinical or microbiological outcome, length of stay, and perhaps mortality.

**Note**

**Potential conflicts of interest.** All authors: No reported conflicts.

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**References**