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Optimizing Antimicrobial Therapy in Critically Ill Patients

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Dr Laterre presents the case for appropriate dose adjustment of antimicrobial agents with critically ill patients.

Inadequate antimicrobial therapy during the first 24 hours of severe infection is associated with an increased morbidity and mortality. Antibiotic readjustment following pathogen susceptibility does not improve outcome. This has been demonstrated in various clinical conditions including community-acquired and ventilator- associated pneumonia (Alvarez-Luna 1996; Kollef 1999). Optimal antibiotic therapy in critically ill patients is not limited to adequate antimicrobial agent selection, but should include appropriate dose adjustment.

Bactericidal activity depends on pharmacokinetic and pharmacodynamic parameters. Typically, amino- glycosides and fluoroquinolones activity is concentrationdependent and these agents possess a prolonged postantibiotic effect. High peak serum concentration to minimum inhibitory concentration (MIC) ratio and high area under the curve to MIC (AUIC) should be reached for aminoglycosides and fluoroquinolones to achieve clinical success. For many other antimicrobials including all beta-lactams, bactericidal activity depends on the length of time that the concentration remains above the MIC for the causative pathogen. It has been recommended to maintain a serum concentration 4 to 5 times above the MIC with these agent, to achieve maximal killing activity (Graig 1992; Mouton 1994).

Most dosage regimens for drugs have been based on pharmacokinetic data obtained from healthy volunteers. However, drug disposition in critically ill patients varies significantly from healthy subjects. Physicians initiating antimicrobial therapy in critically ill patients face multiple challenges; empirical treatment should be prompt and cover all expected pathogens often presenting a reduced susceptibility. The inoculums may be large and the drug penetration poor. The drug distribution volume is rarely predictable, the serum concentration is not well correlated to tissue concentration and antibiotic proteinbinding determination may not available at the bedside. Finally, severe sepsis is a dynamic process and pharmacokinetic parameters present at baseline change rapidly within a few days. All these elements may lead to clinical failure, emergence of resistance or toxicity.

To achieve optimal therapy, loading dose should be adjusted for severity and not based on renal function. Drug distribution volume is increased in most critically ill patients at the time shock develops and the first dose should be maintained or increased compared to less severe patients, even in the presence of acute renal failure. The subsequent doses will be adapted on creatinine clearance for the vast majority of antibiotics. For aminoglycosides in particular, peak serum concentration to MIC ratio should be above 10. This corresponds to a target peak serum value of 40 to 60 µg/ml for amikacin (Bartal 2003). Data from studies in critically ill patients demonstrate that this can only be achieved in all patients if the loading dose of amikacin is well above 15 mg/kg.

For beta-lactams, the time above the MIC is considered as the best parameter to predict bactericidal activity and the antibiotic serum concentration should reach 4 to 5 times the MIC to exert maximal killing rate. Also, serum drug concentrations too close to MIC are at risk of bacterial regrowth and potential emergence of resistance. These in vitro data support the indication of betalactams administration by a continuous infusion in the ICU setting. This method of administration provides a steady state serum drug concentration, eliminates the problem of the short half-life of most of these agents, and the values obtained in the serum are much more predictable compared to intermittent infusion. Also, antibiotic tissue and extravascular fluids concentrations are higher than the ones obtained by bolus infusion (Buijk 2002). To date, no large randomized controlled trial has been performed to demonstrate the impact on outcome of this mode of antibiotic administration, but in vitro studies and pharmacokinetic data collected in critically ill patients support the potential benefits of this mode of administration on bacterial killing rate, emergence of resistance and eventually on the clinical success rate. A normal to increased loading dose of beta-lactams must be given first to initiate the continuous infusion. After day one, the total daily dose needs to be adjusted for renal function.

The large variability in distribution volume together with a modified drug half-life supports the need to monitor antibiotics serum concentration in severely ill patients. Unfortunately this is not possible routinely for the betalactams, but should be recommended for aminoglycosides and glycopeptides. This would not only help to limit the risk of toxicity, but also optimize antibiotic therapy in critically ill patients.

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