ICU
MANAGEMENT & PRACTICE

What's the effective antibiotic dosing in critically ill patients?

Mortality due to severe infections in the intensive care unit (ICU) remains high despite recent therapeutic advancements. It is believed that ICU pathogens are relatively different from those in the general wards as they commonly have reduced antibiotic susceptibility. However, despite profound physiological and pharmacokinetic differences to the non-critically ill population, critically ill patients are typically given conventional antibiotic dosing regimens, which increase the likelihood of therapeutic failures and the emergence of bacterial resistance, according to an Editorial published in Critical Care.

The article notes that appropriate antibiotic administration, including spectrum of activity and therapeutic exposure, is "rarely a straightforward process" in ICU patients. This is because patients with critical illness commonly develop extreme pathophysiological changes that can alter antibiotic pharmacokinetics and consequently affect drug exposure in this population.

The volume of distribution and drug clearance are the pharmacokinetic parameters of greatest relevance to determining drug dosing requirements, and both parameters may be significantly deranged during critical illness. To amplify its point, the Editorial cites a recent study by Ehmann et al. that indicates the complexity of beta-lactam dosing in critically ill patients. In this study of 48 critically ill patients with severe sepsis, the investigators evaluated the pharmacokinetic/pharmacodynamic target attainment of standard meropenem dosing (1000/2000 mg every 8 hours as a 30-minute infusion) in critically ill patients. Large variation in meropenem concentration was observed in this study, corroborating the findings of earlier studies. The investigators then developed a tool ("MeroRisk Calculator") that may improve meropenem exposure in this population.

The Editorial explains: "As the beta-lactams are predominantly cleared by the kidney, elevated renal function may likely lead to suboptimal antibiotic exposure, particularly when conventional dosing regimens are used. Patients with severe infections commonly develop a systemic inflammatory response syndrome, which increases renal blood flow and glomerular filtration rates. These factors enhance renal clearance of some drugs, a phenomenon referred to as augmented renal clearance (ARC)."

A measured creatinine clearance (CLCR) ≥ 130 ml/min has been used to correlate ARC with suboptimal antibiotic exposures. Although ARC is highly prevalent in most ICUs, the Editorial says most clinicians fail to address the phenomenon, persisting with conventional beta-lactam dosing that is likely flawed, particularly when less susceptible pathogens are present.

In their study, Ehmann et al. observed that increasing estimated CLCR significantly reduced the likelihood of pharmacokinetic/pharmacodynamic target attainment. This further highlights that those patients who are at risk for ARC, usually those with apparently “normal” renal function, have to be identified earlier so that dose modification can be made earlier. Although the MeroRisk Calculator was developed based on a broad range of CLCR (25–255 ml/min), the prediction uncertainty increases for the extremes of renal function due to the limited number of patients representing this subpopulation.

This promising tool can be improved upon, according to the Editorial. Severity of illness may influence meropenem exposure, particularly in terms of the volume of distribution, and its impact should be incorporated into the Calculator. Actual minimum inhibitory concentration (MIC) must be provided for accurate prediction as opposed to population estimates.

The Editorial concludes, "Conventional beta-lactam dosing is flawed in critically ill patients. Useful tools such as the MeroRisk Calculator need to be comprehensively evaluated clinically, and if successful should be added into clinical practice to guide effective antibiotic dosing."

Source: Critical Care
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