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SPECIAL ARTICLE

Antibiotic dose optimization in critically ill patients

M.O. Cotta[a,b,c,d,*], **J.A. Roberts**[a,b,d], **J. Lipman**[a,b]

[a] *Burns Trauma and Critical Care Research Centre, University of Queensland, Brisbane, Queensland, Australia*
[b] *Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia*
[c] *Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia*
[d] *School of Pharmacy, University of Queensland, Brisbane, Queensland, Australia*

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Abstract The judicious use of existing antibiotics is essential for preserving their activity against infections. In the era of multi-drug resistance, this is of particular importance in clinical areas characterized by high antibiotic use, such as the ICU. Antibiotic dose optimization in critically ill patients requires sound knowledge not only of the altered physiology in serious infections – including severe sepsis, septic shock and ventilator-associated pneumonia – but also of the pathogen–drug exposure relationship (i.e. pharmacokinetic/pharmacodynamic index). An important consideration is the fact that extreme shifts in organ function, such as those seen in hyperdynamic patients or those with multiple organ dysfunction syndrome, can have an impact upon drug exposure, and constant vigilance is required when reviewing antibiotic dosing regimens in the critically ill. The use of continuous renal replacement therapy and extracorporeal membrane oxygenation remain important interventions in these patients; however, both of these treatments can have a profound effect on antibiotic exposure. We suggest placing emphasis on the use of therapeutic drug monitoring and dose individualization when optimizing therapy in these settings.

PALABRAS CLAVE
Antibióticos;
Optimización de la dosis;
Críticamente enfermo;
Sepsis grave;
Choque séptico

Optimización de la dosis de antibióticos en pacientes críticamente enfermos

Resumen El uso sensato de los antibióticos existentes resulta fundamental para mantener su actividad contra las infecciones. En la era de la resistencia a múltiples fármacos, esto resulta especialmente importante en áreas clínicas caracterizadas por un uso elevado de antibióticos, como por ejemplo las UCI. La optimización de la dosis de antibióticos en pacientes críticamente enfermos requiere sólidos conocimientos no solo sobre las alteraciones fisiológicas asociadas a las infecciones graves (incluida la sepsis grave, el choque séptico y la neumonía asociada a la ventilación) sino también sobre la relación entre patógenos y la exposición a fármacos (esto

* Corresponding author.
E-mail address: meninocotta@gmail.com (M.O. Cotta).

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es, el índice farmacocinético/farmacodinámico). Es importante considerar el hecho de que los cambios extremos en la función orgánica, como los observados en pacientes hiperdinámicos o en aquellos con síndrome de disfunción multiorgánica, pueden tener un efecto sobre la exposición a los fármacos, por lo que se requiere una vigilancia constante al revisar los regímenes posológicos de los antibióticos en los pacientes críticamente enfermos. La terapia de reemplazo renal continuo y la oxigenación por membrana extracorporal siguen constituyendo intervenciones importantes en este tipo de pacientes; no obstante, ambos tratamientos pueden tener un profundo impacto sobre la exposición a los antibióticos. Sugerimos poner un especial énfasis sobre el uso de la monitorización farmacoterapéutica y sobre la individualización de la dosis al optimizar el tratamiento en estos entornos terapéuticos.

Introduction

Given an era of accelerating bacterial resistance and dwindling antimicrobial resources, optimization of existing antibiotic therapy is an increasingly important consideration for clinicians worldwide. There is perhaps added significance among intensive care unit (ICU) patients, as these patients are at high risk of infection-related mortality.[1] They are also more prone to acute and often marked changes in pathophysiology and are subject to invasive intervention, both of which have the potential to significantly alter drug exposure.[2]

Antibiotics are one of the most commonly prescribed drug classes in the ICU and they have the ability to dramatically improve patient outcomes.[3,4] Therefore, it stands to reason that maximizing the likelihood of eradicating infection whilst lowering the risk of unwanted effects should be the end goal for all prescribed antibiotic therapy. This is perhaps why determining the relationship between exposure of antibiotics in vivo (i.e. pharmacokinetics, PK) and what clinical response it elicits (pharmacodynamics, PD) has gained much prominence in critical care literature. The purpose of this review is to discuss variations in PK that commonly occur among the critically ill, through both existing pathophysiology as well as associated interventions, and to offer insights on how antibiotic therapy can be tailored accordingly so as to optimize desired PD effects.

Severe sepsis and septic shock

Sepsis is a common occurrence within the ICU and is defined as a systemic inflammatory response to infection, which can be complicated by organ dysfunction ('severe sepsis') or persistent hypotension refractory to fluid resuscitation ('septic shock').[5] Although the incidence of sepsis worldwide is currently unknown, extrapolations from United States data conservatively estimate an occurrence of 19 million cases annually.[6,7] Added to this high burden are reports indicating a severe sepsis mortality rate of nearly 30% in developed countries.[8,9]

Initial pathophysiology and its impact on antibiotic pharmacokinetics (Fig. 1)

One of the first clinical observations during severe sepsis and septic shock is significant fluid shift from the intravascular compartment (i.e. blood vessels) into interstitial space due to endothelial damage and increased capillary leak.[10] The resultant hypotension is often fulminant, requiring urgent and aggressive delivery of intravenous resuscitation fluid, which in turn can further increase interstitial volume. Depending on the physiochemical properties of the antibiotic, these large amounts of extravascular fluid may have a significant impact on drug distribution and hence dosing strategies. For example, initial doses of hydrophilic antibiotics (i.e. that concentrate more in blood and interstitial fluid of tissues) will need to take into account these increased volumes. In this case, due to the greater volume of distribution (V_d) noted for these drugs, use of loading doses should be considered to ensure early achievement of therapeutic concentrations.[11,12] Lipophilic antibiotics (i.e. that concentrate intra-cellularly and in adipose tissue), on the other hand, are not greatly influenced by changes in fluid volume and may not require alterations in initial dosing.[13]

A main element of the systemic inflammatory response during sepsis is that initial vasodilation is associated with a hyperdynamic cardiovascular state.[14] Increased cardiac output is further driven by use of resuscitation fluid and vasopressors, resulting in increased blood flow to major organs including the kidneys. Although the exact mechanism has not been fully elucidated, the end result may be that of increased renal blood blow and glomerular filtration leading to enhanced renal drug elimination, termed 'augmented renal clearance' (ARC). ARC has previously been defined as a creatinine clearance $\geq$ 130 mL/min/1.73 m^2.[15] There are now numerous reports of the prevalence of ARC in septic as well as other groups of critically ill patients.[16–18]

Mathematical formulae to estimate glomerular filtration rate have all been derived from outside of the ICU and so have limited applicability in determining this increased renal clearance.[19] Additionally, serum creatinine concentrations are not sensitive enough to identify patients with ARC and so a measured urine creatinine clearance collection over a specified period remains the preferred method