Management of Infections with Drug-Resistant Organisms in Critical Care: An Ongoing Battle

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KEYWORDS

• Multidrug-resistant organisms • Carbapenem-resistant organisms
• Initial appropriate antimicrobial therapy • Adjunctive aerosolized antimicrobial therapy

KEY POINTS

- Infections with multidrug-resistant organisms (MDROs) are common in critically ill patients and are challenging to manage appropriately.
- Strategies that can be used in the treatment of MDRO infections in the intensive care unit (ICU) include combination therapy, adjunctive aerosolized therapy, and optimization of pharmacokinetics with higher doses or extended-infusion therapy as appropriate.
- Rapid diagnostic tests could assist in improving timely appropriate antimicrobial therapy for MDRO infections in the ICU.

INTRODUCTION

Patient care in intensive care units (ICUs) routinely includes diagnosing and managing infectious diseases. Infections can be either the immediate indication or the consequence of a patient requiring ICU care. ICUs are associated with a greatly increased risk of hospital-acquired infections. There is also an increased risk that the infection is caused by an organism that has acquired or developed resistance to most antibiotics; a multidrug-resistant organism (MDRO). Infections with MDROs are associated with increased morbidity and mortality. Among other factors, the delay in appropriate antibiotic therapy contributes significantly to the increased mortality of these infections. Prompt recognition and timely, appropriate treatment of infections caused by MDROs present a serious challenge to ICU providers. This article reviews recent literature on the management of difficult-to-treat organisms relevant to infections in the ICU.

TREATMENT

The decision to start antimicrobial therapy for a suspected infection in a critically ill patient is an important one. With the increasing prevalence of MDROs, providers are faced with the difficult situation of balancing the mortality benefit of early appropriate antibiotic therapy with the environmental damage (selection and development of such organisms) caused by unnecessary antimicrobial medications. In patients with septic shock, the delay of empiric antimicrobial therapy is associated with increased mortality.[1] The same applies to documented hospital-acquired infections, such as pneumonia or bloodstream infections, for which inappropriate or delayed empiric initial antibiotic therapy is associated with an increased risk of

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death that is not attenuated by treatment escalation.[2,3] Thus, in the setting of documented infection or suspected infection with hemodynamic instability, appropriate empiric antimicrobials should be started promptly. In hemodynamically stable patients requiring critical care for noninfectious reasons with a suspicion of having acquired an infection that is not yet documented, the answer is not as clear. Hranjec and colleagues[4] suggest that, in this scenario, waiting for objective evidence of infection before starting empiric antimicrobials may not worsen outcomes. This possibility requires further research.

Antibiotic therapies in critically ill patients require specific considerations. They often have an altered volume of distribution of antibiotics, low plasma albumin concentrations that significantly affect pharmacokinetics, as well as altered renal excretion. It is widely known that patients in the ICU frequently develop acute kidney injury and require dose adjustment of antimicrobials; however, the opposite effect has been described as well. Patients in the ICU can develop a state of augmented renal clearance, with increased glomerular filtration, tubular secretion, and reabsorption.[5,6] The DALI (Defining Antibiotic Levels in Intensive Care Patients) study, a multinational pharmacokinetic analysis of β-lactam antibiotics, described how 20% of patients fail to achieve the minimum antibiotic concentration required for adequate treatment and up to 50% failed to meet the preferred level when standard recommended doses are used.[7] Insufficient antibiotic exposure leads to the development of antimicrobial resistance as well as worse clinical outcomes. The dosing of antibiotics in infected critically ill patients should be personalized to achieve optimal concentrations, and higher doses are often required.

The selection of an empiric antibiotic regimen that will reliably qualify as initially appropriate antibiotic therapy (IAAT) for patients with risk factors for MDROs is also challenging. It is widely recommended that the regimen include activity against both methicillin-resistant *Staphylococcus aureus* (MRSA) and resistant gram-negative organisms (eg, *Pseudomonas aeruginosa*). In the past, the use of an additional agent that covers gram-negative organisms (eg, an aminoglycoside, quinolone, or colistin) was recommended empirically in this specific population.[8] The current evidence, at least for ventilator-associated pneumonia (VAP), does not show any benefit and shows potential harm with this approach.[9,10] Despite this evidence, there might still be a role for this strategy in a specific population, such as patients with a history of carbapenem-resistant Enterobacteriaceae (CRE), *Pseudomonas* spp, or *Acinetobacter* spp infections.

Gram-negative Infections

Infections caused by gram-negative MDROs are frequently seen in the ICU. The organisms encountered include *Enterobacter* spp (AmpC-type β-lactamase), extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae, CRE, as well as *Acinetobacter baumannii* and *P aeruginosa*. These organisms can develop resistance to most commonly used antibiotics (so-called extensively drug-resistant [XDR] organisms) and occasionally become colistin-only susceptible (COS) or even pandrug resistant (PDR). There are limited therapeutic options for infections caused by gram-negative MDROs. A summary of therapeutic options is given in **Table 1**.

Enterobacter spp is commonly encountered in the ICU as the causal agent of nosocomial infections. Its treatment can be particularly challenging, because it is known to harbor AmpC-type β-lactamases and develop resistance during therapy with β-lactamase inhibitors. Historically, experts have recommended treatment with carbapenems, especially for bloodstream infections (BSIs). Cefepime is a poor inducer and more stable to AmpC-type β-lactamases, providing a therapeutic option that should be effective and also provide less environmental pressure for the development of carbapenem resistance. Siedner and colleagues[11] reported a retrospective analysis of 368 cases of *Enterobacter* spp bacteremia, in which cefepime was as effective as carbapenems for this particular infection. Cefepime can be used as a carbapenem-sparing agent for the treatment of *Enterobacter* spp bacteremia. This action is specific for this AmpC-type β-lactamase–producing organism and does not apply for ESBL-producing Enterobacteriaceae (*Escherichia coli*, *Klebsiella* spp, and so forth), in which cefepime is inferior to carbapenems.[12,13]

Once a rarity, infections with ESBL-producing Enterobacteriaceae have now become common in ICUs around the world. The mainstay of therapy for serious infections with ESBL-producing organisms is carbapenem monotherapy. An emerging challenge in the ICU setting is the treatment of infections with organisms that are now resistant to carbapenems (CRE, *Pseudomonas* spp, and *Acinetobacter* spp). Recently the US Centers for Disease Control and Prevention reported that the proportion of Enterobacteriaceae that were CRE increased from 1.2% in 2001 to 4.2% in 2011, with most of the increase observed in *Klebsiella* spp (from 1.6% to 10.4%).[14] Antibiotic treatment