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Multidrug-resistant bacteria in solid organ transplant recipients

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Abstract

Bacteria are the leading cause of infections after solid organ transplantation. In recent years, a progressive growth in the incidence of multidrug-resistant (MDR) and extensively-drug-reistant (XDR) strains has been observed. While methicillin-resistant *Staphylococcus aureus* (MRSA) infection is declining in non-transplant and SOT patients worldwide, vancomycin-resistant enterococci, MDR/XDR Enterobacteriaceae and MDR/XDR non-fermenters are progressively growing as a cause of infection in solid organ transplant (SOT) patients and represent a global threat. Some SOT patients develop recurrent infections, related to anatomical defects in many cases, which are difficult to treat and predispose patients to the acquisition of MDR pathogens. As the antibiotics active against MDR bacteria have several limitations for their use, which include less clinical experience, higher incidence of adverse effects and less knowledge of the pharmacokinetics of the drug, and, in most cases, are only available for parenteral administration, it is mandatory to know the main characteristics of these drugs to safely treat SOT patients with MDR bacterial infections. Nonetheless, preventive measures are the cornerstone of controlling the spread of these pathogens. Thus, applying the Center for Disease Control and Prevention's and the European Society of Clinical Microbiology and Infectious Diseases's recommended antibiotic policies and strategies to control the transmission of MDR strains in the hospital setting is essential for the management of SOT patients.

Keywords: MDR Enterobacteriaceae, MDR non-fermenters, MRSA, multidrug-resistant bacteria, solid organ transplantation, vancomycin-resistant enterococci

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Hot Topics

- A bacterial strain is defined as multidrug resistant (MDR) when it is not susceptible to one or more agents in three or more antimicrobial categories active against the isolated bacteria.
- To prevent the acquisition of MDR strains during hospitalization, the procedures recommended by the Center for Disease Control and Prevention (CDC) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines should be applied.
- In addition to antibiotic treatment, which is unavoidable in most solid organ transplantation (SOT) recipients, certain features related to the surgical technique of the transplantation alter the risk of bacterial infection.
- While methicillin-resistant *Staphylococcus aureus* (MRSA) infection is declining in non-transplant and SOT patients worldwide, vancomycin-resistant enterococci, MDR/extensively-drug resistant (XDR) Enterobacteriaceae and MDR/XDR non-fermenters are progressively growing as a cause of infection in SOT patients and represent a global threat.
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Main Characteristics of MDR Bacterial Infection after SOT

Recommendations

- To prevent the acquisition of MDR strains during hospitalization, the procedures recommended by the CDC should be applied (A-I).
- For empirical treatment of suspected bacterial infections in SOT patients, the selection of antimicrobial agents should be based on local epidemiological data and on the patient's history of colonization or infection with antibiotic-resistant organisms (A-II).

General principles, definitions and risk factors for MDR bacterial infection after solid organ transplantation

Bacteria are the leading cause of infections after solid organ transplantation (SOT). After the surgical procedure, transplant patients should remain in the hospital for a period of time, which varies according to the type of allograft, previous existence of co-morbidities, the underlying disease responsible for transplantation and the development of complications. During prolonged hospitalization, most patients receive broad-spectrum antibiotics and some develop infections with multidrug-resistant (MDR) bacteria. The use of central line and urinary catheters, parenteral nutrition and prolonged intubation and the need for renal replacement therapy all increase the risk of this complication.

The most widely accepted definition of MDR includes lack of susceptibility to one or more agents in three or more antimicrobial categories active against the isolated bacteria (Table 1) [1]. In the case of *S. aureus*, methicillin resistance on its own defines the strain as MDR, regardless of resistance to other antimicrobials. Many transplant patients may be infected with extensively-drug resistant (XDR) bacteria, which is defined as susceptibility to no more than two classes of active categories of antimicrobials (Table 1) [1]. In recent years, certain bacterial strains have shown a lack of susceptibility to all the active drugs for treating the microorganism; in this case, the isolated bacterium is defined as pan-drug resistant (PDR). A group of six organisms representing the paradigm of pathogenesis, transmission and potential antibiotic resistance have been recently defined and labeled as the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.) [2,3]. As identifying novel antimicrobial agents with reliable activity against these pathogens is very difficult, special efforts to identify optimal strategies for infection control and antimicrobial use are warranted.

Multidrug-resistant organisms lead to increased use of hospital resources due to extended hospital stays, more frequent physician consultations and laboratory tests, and costly medications [4]. Specifically, their presence increases the costs derived from solid organ transplantation (SOT). In addition, MDR bacterial infection jeopardizes patient and graft survival. Infection is the second leading cause of death in renal transplant recipients, and the incidence of mortality related to bacterial infection in this group of patients has remained stable over the last decade [5]. Approximately 14% of patients with renal transplantation develop an infectious episode caused by MDR bacteria in the post-transplant period, including enteric Gram-negative bacilli, non-fermentative Gram-negative bacilli, enterococci and *S. aureus* [6]. This complication is associated with poorer graft and patient survival [6]. One of the greatest dangers when treating an SOT patient with fever and risk of MDR bacterial infection is the use of inappropriate empirical antibiotic therapy. Several studies have demonstrated an increase in mortality when bacteraemic patients with MDR pathogens receive inappropriate treatment [7,8]. In one retrospective cohort study evaluating empirical antibiotic therapy in SOT patients, inappropriate antibiotic therapy was administered to 54% of patients, resulting in a 3.5-fold increase in mortality compared with those receiving adequate therapy [9]. Therefore, in order to initiate appropriate antibiotic therapy it is important to know the local rates of antimicrobial resistance. Early therapy may also reduce the mortality associated with severe sepsis and septic shock, which occur in nearly 15% of bacteraemic infections in SOT recipients and have a mortality rate of 50% [10].

There are two main strategies for the prevention of MDR transmission in the hospital [11]. Vertical infection-prevention strategies are designed to reduce colonization or infection due to a specific pathogen; they involve a microbiological screening test and carry high resource utilization, direct costs and opportunity costs [12]. Horizontal strategies are population-based, applied universally, and use interventions effective in controlling all pathogens transmitted by means of