

Addressing the Problem of Multidrug-Resistant Organisms in Dialysis

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Introduction

Multidrug-resistant organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and multidrug-resistant gram-negative bacteria, are a major public health threat, especially in the population of patients on maintenance hemodialysis. The objective of this paper is to provide an overview of the transmission dynamics of multidrug-resistant organisms and review infection prevention strategies in hemodialysis facilities.

Infections caused by multidrug-resistant organisms are associated with substantial morbidity and mortality, causing approximately 2 million infections and 23,000 deaths per year in the United States, with an excess cost of \$20 billion (1). The ongoing spread of multidrug-resistant organisms is compounded by the constant emergence of novel multidrug resistance profiles, severely limiting therapeutic options (1). For example, extended spectrum β -lactamase-producing gram-negative bacteria are resistant to all penicillins, cephalosporins, and aztreonam, leaving only carbapenems as the antimicrobials of choice. Of even greater concern is the emergence and rapid worldwide spread of carbapenemase-producing gram-negative bacteria. Carbapenems in addition to cephalosporins and many other antimicrobials are no longer effective against these multidrug-resistant organisms, leaving polymyxins, such as colistin, as the only remaining effective antimicrobial. The recent identification of plasmid-mediated colistin resistance may render even this single remaining antibiotic ineffective for some infections. If this plasmid is transferred to a carbapenemase-producing gram-negative bacteria, the result could be a strain of gram-negative bacteria that is resistant to all available antimicrobials. Although novel antimicrobials are being developed, which have activity against carbapenemase-producing gram-negative bacteria, such as ceftazidime/avibactam and ceftolozane/tazobactam, clinical experience with these agents is limited, and resistance to them has already been documented (1).

The threat of multidrug-resistant organisms is particularly high for patients on maintenance hemodialysis. Rates of colonization with multidrug-resistant organisms are among the highest in this population, ranging from 3% to over 20% (2–4). Risk factors include prior hospitalization, temporary dialysis access, residence in nursing homes, and antimicrobial exposure

(2,3,5,6). If a patient on maintenance hemodialysis who is colonized with multidrug-resistant organisms develops a clinical infection, there is a high likelihood that the multidrug-resistant organisms are causing that infection. In fact, studies have shown that, among patients on maintenance hemodialysis, the risk of VRE bloodstream infections is 22-fold higher if VRE colonized and 11-fold higher if MRSA colonized (2,3). Because infections caused by multidrug-resistant organisms are associated with two to five times higher rates of morbidity and mortality compared with infections caused by antimicrobial-susceptible infections, preventing colonization and infection with multidrug-resistant organisms is crucial.

Infection Prevention Strategies

The spread of multidrug-resistant organisms occurs through contact with patients colonized or infected with multidrug-resistant organisms, contaminated hands and clothes of health care workers, and/or the environment. Outpatient dialysis facilities are an optimal setting for the dissemination of multidrug-resistant organisms, because multiple patients and health care workers are in constant contact for prolonged and recurrent periods of time. A prospective cohort study performed in one outpatient dialysis unit characterized the transmission dynamics of multidrug-resistant organisms by collecting serial rectal and nasal samples from patients and environmental surfaces (dialysis machines and patient chairs) over a 6-month period (6). Acquisition of multidrug-resistant organisms was defined as a negative baseline sample and at least one positive follow-up sample for multidrug-resistant organisms. The study showed that acquisition of one or more multidrug-resistant organisms was frequent, occurring in 40% of patients. In total, 13% and 15% of patients acquired MRSA or VRE, respectively. Multidrug-resistant gram-negative bacteria acquisition, however, was even more common, occurring in 20% of patients. Environmental contamination of dialysis machines and chairs, predominantly due to multidrug-resistant gram-negative bacteria, was detected from 9% of cultures. Using pulsed-field gel electrophoresis, similar strains were identified between patients and the environment, strongly implying crosstransmission of multidrug-resistant organisms. Although health care worker contamination with

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multidrug-resistant organisms was not addressed, their role in MRSA and VRE spread is well established. This study clearly shows the potential for widespread dissemination of multidrug-resistant organisms within dialysis facilities.

Recommendations to prevent the spread of multidrug-resistant organisms and other bacterial pathogens have been provided by the Centers for Disease Control and Prevention. These recommendations, primarily extrapolated from data in the hospital setting, include (1) wearing gloves and performing hand hygiene in between patients and stations (recommended for all patient contacts in hemodialysis facilities), (2) following published guidelines for judicious antimicrobial use, (3) avoiding multiuse medication vials and common medication carts, (4) disinfection and cleaning of equipment, nondisposable items, and the surrounding environment, and (5) separate clean/contaminated areas and medication preparation in a dedicated room or a clean area away from treatment stations. Additional precautions are recommended for patients who are at high risk of multidrug-resistant organisms or other pathogen transmission, which is defined as those patients colonized or infected with multidrug-resistant organisms who have an infected wound with drainage not contained by a dressing, fecal incontinence, or diarrhea. For these patients, recommendations also include wearing a separate gown dedicated to the patient, removing the gown when patient care duties are completed, and dialyzing the patient at a station with as few adjacent stations as possible (7).

The efficacy of these recommendations is difficult to quantify using classic epidemiologic techniques, because multidrug-resistant organism transmission involves numerous inter-related and dynamic factors. Mathematic modeling addresses these limitations. One such model quantified the efficacy of various infection prevention strategies in decreasing VRE colonization in in-center hemodialysis facilities (8). Simulations showed that improving adherence with hand hygiene from 40% to 100% or reducing the ratio of health care workers to patients from 1:4 to 1:1 would reduce the endemic prevalence of VRE from 12% to 2.5%. Although reducing the ratio to 1:1 is not realistic, the simulation emphasizes the importance of the health care worker as a transient vector of multidrug-resistant organisms. The simulated tactic with the highest effect on VRE transmission was increasing the frequency of antimicrobial exposure. The endemic prevalence of VRE reached 70% when repeated 1-year exposure to antimicrobials was modeled. This suggests that limiting unnecessary antimicrobial use would have a marked beneficial effect in preventing the spread of multidrug-resistant organisms among patients on hemodialysis.

Antimicrobial Prescribing Practices in Outpatient Dialysis Facilities

The benefits of antimicrobials to treat infections cannot be overemphasized. However, antimicrobials may also have substantial unintended negative consequences. In addition to the emergence and spread of multidrug-resistant organisms, antimicrobials can lead to adverse drug-drug interactions, side effects ranging from rashes to anaphylaxis, and *Clostridium difficile* diarrhea. Optimizing antimicrobial use is, therefore, critical.

In a study of two outpatient hemodialysis facilities, approximately 30% of antimicrobial doses administered in outpatient hemodialysis facilities were not indicated on the basis of national consensus guidelines (9). Among these, vancomycin, cefazolin, and third/fourth generation cephalosporins (e.g., ceftriaxone, ceftazidime, and cefepime) were the most frequently inappropriately prescribed antimicrobials. Specific scenarios where antimicrobials were not indicated included the treatment of blood culture contaminants and the treatment of presumed skin and soft tissue infections that do not meet criteria for infection (9). Another frequent reason for inappropriate administration of antimicrobials was the absence of de-escalation (9). This term refers to tailoring the initial empirical antimicrobial regimen to a more appropriate one after microbiology reports and antimicrobial susceptibility profiles are available. A common scenario where de-escalation frequently does not occur is the treatment of a methicillin-susceptible *S. aureus* infection with vancomycin instead of cefazolin. Not only is it optimal to change to cefazolin to prevent unnecessary exposure to vancomycin, but also, numerous studies have shown the superiority of cefazolin in the treatment of methicillin-susceptible *S. aureus* infections compared with vancomycin. Another example of a missed opportunity for de-escalation is the scenario where a patient is started on third or fourth generation cephalosporins for the empirical treatment of a presumed infection caused by gram-negative bacteria. After microbiology reports show that the bacteria is susceptible to cefazolin, the broad spectrum third/fourth generation cephalosporins should be de-escalated or narrowed to cefazolin.

Antimicrobial stewardship programs aimed at improving antimicrobial prescribing patterns are effective in decreasing unnecessary antimicrobial exposure in hospitalized patients in addition to decreasing rates of multidrug-resistant organisms and *C. difficile* diarrhea and decreasing health care costs (10). Recommendations for developing and implementing a successful antimicrobial stewardship program have been provided by the Centers for Disease Control and Prevention, the Agency of Healthcare Research and Quality, the Society for Healthcare Epidemiology of America, and the Infectious Disease Society of America. These recommendations focus on the hospital and nursing home setting, and unfortunately, they do not provide guidance for outpatient hemodialysis facilities. Although many antimicrobial stewardship program elements can be extrapolated to the dialysis setting, evidence-based antimicrobial stewardship program recommendations targeting outpatient dialysis facilities are urgently needed.

Future Directions

Despite the negative effect of infections caused by multidrug-resistant organisms and their ongoing spread, there is a paucity of research in this area among the maintenance hemodialysis population. Future studies are required to further our understanding of the transmission dynamics of multidrug-resistant organisms within dialysis facilities. Although there is an ongoing need for improved adherence with current infection prevention strategies, evaluation of need and feasibility of additional control strategies are also necessary. Lastly, further research in

optimizing antimicrobial prescribing patterns in the maintenance hemodialysis population is also needed, especially in developing antimicrobial stewardship programs that target the unique aspects of this population.

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Disclosures

None.

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