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Implementing an Antimicrobial Stewardship Program in Out-Patient Dialysis Units

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Abstract

Purpose of review—Rates of multidrug-resistant organisms (MDRO), including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and multidrug-resistant gram-negative bacteria continue to rise among the population of chronic hemodialysis. Antimicrobial exposure is the main risk factor for MDRO emergence and dissemination. Up to 30% of antimicrobial doses administered in out-patient dialysis units may not be indicated. Antimicrobial stewardship programs (ASP) improve antimicrobial prescribing patterns. The purpose of this review is to highlight the key elements and interventions of ASP.

Recent Findings—The Infectious Disease Society of America and the Society of Healthcare Epidemiology of America have provided evidence-based guidelines for the development and implementation of an ASP. Many of their recommendations can be adapted to the out-patient dialysis setting.

Summary—Developing and implementing an ASP by following key elements and interventions in the out-patient dialysis setting can lead to reduced mortality, adverse events, costs and improvement in antimicrobial susceptibility rates.

Keywords

antimicrobial stewardship program; multidrug-resistant organisms; antimicrobials; methicillin-resistant *Staphylococcus aureus*; vancomycin-resistant enterococci; multidrug-resistant gram-negative bacteria

Introduction

Patients receiving chronic hemodialysis are at an increased risk of colonization and infection with multi-drug resistant organisms (MDRO) [1-3]. Antimicrobial exposure is the main risk factor for harboring MDRO, promoting both their emergence and dissemination [4]. Over 30% of antimicrobial doses administered in out-patient hemodialysis units are not indicated,

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as per national guidelines [5]. Thus, improving antimicrobial prescribing practices would have a substantial impact on limiting the ongoing spread of MDRO.

Antimicrobial stewardship programs (ASP) are designed to optimize the selection of antimicrobial regimens, including dose, duration and route [6]. Benefits of implementing an ASP include improvement in antimicrobial susceptibility rates and reduced mortality, adverse events and costs. [5-7]. The Infectious Disease Society of America (IDSA) and the Society of Healthcare Epidemiology of America (SHEA) have provided evidence-based guidelines for the implementation of an ASP. Although these guidelines focus primarily on the hospital setting, many aspects are applicable to the out-patient hemodialysis setting. In this review, the key elements of an effective ASP and specific interventions that can be implemented in the dialysis setting are reviewed. References to publications that provide more in-depth information about specific elements of an ASP are also provided.

A. Elements of an ASP (Table 1)

1. Identify the ASP team—Identifying the key personnel that will lead the ASP is critical. This team should include the leader, or champion, who will direct the program and will be accountable for coordinating, reporting, and measuring outcomes. An individual with expertise in antimicrobials is also necessary. In the hospital setting, an infectious disease specialist or a pharmacist is part of the ASP team. If assistance from these individuals is not possible in the dialysis setting, then a staff member in the unit should be identified who will undergo formal training [6]. Many societies, including SHEA and IDSA, provide educational courses towards this goal. Lastly, leadership support is also critical for an effective ASP, by providing the appropriate authority and compensation for the team, as well as access to information technology for ASP measurement purposes. Further guidance in the knowledge and skills required for the ASP team are provided in detail by Cosgrove *et al.* [8].

2. Education—Education is another important component of any ASP, and when accompanied by other key elements of stewardship, its impact is magnified and effectiveness increased [9-11]. To be most effective, all prescribers must be kept up to date on optimal use of antimicrobials, antimicrobial resistance rates and management of infectious diseases. Numerous web-based resources are available and are provided by leading US hospitals [11]. Other educational activities, such as posters or pamphlets, should be used to complement the above as they are not sufficient when used alone [6].

3. Restricted Antimicrobials/Pre-authorization—Pre-authorization can help limit overprescribing of antimicrobials with high potential for resistance or cost. Rather than outright restriction, having dialysis center specific guidelines or specific antibiotic order forms that outline when and what agents should be utilized for specific infections may help minimize excessive and suboptimal antibiotic use. Compliance with these forms should be reviewed regularly by the ASP team. Since prescribing patterns vary between different units, the ASP team should review overall prescribing patterns in their unit, in order to identify which antimicrobials should be focused upon [5]. Potential antimicrobials to target in dialysis units include meropenem and daptomycin since they do not require dosing in between dialysis sessions. (Table 2).

4. Facility-specific practice guidelines for common infections—The IDSA/SHEA guidelines for implementing an effective ASP support the implementation of specific clinical practice guidelines and algorithms in order to standardize prescribing patterns. Many guidelines, which are applicable to the dialysis setting, are provided by the IDSA and SHEA [6]. Dissemination in electronic or hard-copy formats, audits and feedback, checklists or incorporation into electronic order sets are several strategies for success of this ASP element.

5. Tracking, Reporting and Feedback—Awareness of antimicrobial prescribing patterns and improvements as a result of the ASP is another important component. Daily review of all antimicrobials prescribed and whether they meet appropriate indications is optimal. If this is not logistically possible, then alternatives include targeting specific antimicrobials or increasing the interval between reviews. In addition to antimicrobial use, tracking, reporting and feedback should also include adherence to guidelines, requesting and following up on the appropriate diagnostic tests (see below) and patient outcomes.

B. Interventions (Table 1)

Numerous strategies to improve antimicrobial prescribing patterns have been developed and their efficacy confirmed [7]. Reasons for inappropriate antimicrobial use vary between individual units and therefore each unit should review their prescribing patterns and identify the main areas of focus. For example, a study in two out-patient dialysis units identified that the majority of inappropriate administered antimicrobial doses did not meet criteria for infection, represented failure to choose a more narrow-spectrum antimicrobial or did not meet criteria for surgical prophylaxis. The latter however, was predominantly identified in only one of the two units [5].

1. De-escalation based on culture results—One of the main areas of inappropriate prescribing in out-patient dialysis units is the treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA) infections with vancomycin instead of cefazolin, in the absence of allergies to β-lactam antimicrobials [5,13,14]. Use of vancomycin in this setting, instead of cefazolin, is associated with substantially worse outcomes, including greater mortality, treatment failure and hospitalization [15-17]. Use of broad-spectrum cephalosporins, such as ceftazidime or cefepime, instead of cefazolin, is another main area of inappropriate prescribing that de-escalation strategies should focus upon [5]. Once antimicrobial susceptibility profiles of the causative gram-negative bacteria are available, patients should be switched to cefazolin, if susceptible and in the absence of a β-lactam allergy, since continued exposure to the broad-spectrum cephalosporins will lead to the emergence of multidrug-resistant gram-negative bacteria.

2. Switch from intravenous to oral therapy—ASP should monitor patients who can be safely changed from intravenous to oral forms of antimicrobials [6]. Quinolones, for example, are a perfect antimicrobial class to target since absorption is 100%. Timing of administration of other medications, such as calcium supplements, however should be addressed, so as not to decrease absorption of the quinolones.

3. Discontinuation of empiric therapy based on no evidence of infection— Although empiric antimicrobial therapy is necessary when an infection is suspected, there are two areas when empiric therapy is prescribed inappropriately in dialysis units. First, in up to 43% of first doses of antimicrobials administered empirically in out-patient dialysis units, there are insufficient criteria for a suspected infection, based on national guidelines [5]. Secondly, in many instances, empiric antimicrobials are started appropriately but then continued despite lack of microbiology and laboratory diagnostics that support a true infection [5]. ASP should determine if these inappropriate prescribing patterns are substantial in their unit and implement intervention towards their improvement, such as education and developing specific guidelines.

4. Microbiology and laboratory diagnostics—Chronic hemodialysis patients are frequently hospitalized and after discharge, return to the out-patient unit receiving antimicrobials, which were prescribed during their hospital admission. In many cases, details regarding the indication for the antimicrobial and its duration are unclear due to limited transfer of data from the outside healthcare facility. Furthermore, the microbiology report may not be available or difficult to obtain, and therefore patients may remain on the hospital-prescribed antimicrobial regimen when a more appropriate antimicrobial is indicated. For example, a patient with an MSSA infection is discharged on vancomycin prior to final susceptibility data. As a result, they may remain on this drug rather than being switched to cefazolin, which is superior in terms of efficacy, can be dosed with dialysis, and requires less monitoring. Also, if it is not clear why antimicrobials were started in the hospital, therapy may be continued well beyond what is necessary, leading to unnecessary and avoidable costs and potential adverse events. The optimal strategy for facilitating the transfer of information from the outside facility to the unit needs to be explored by each unit. One strategy that may be applicable to all, however, would be to contact the infection prevention personnel at the transferring facility.

5. Duration of therapy—An antimicrobial should be given for the shortest *ne*eded duration for cure, using the highest dose possible without causing toxicity in order to minimize collateral damage from the antimicrobials. Adverse events as a result of antimicrobial exposure include drug-drug interactions, *Clostridium difficile* infections, allergic reactions and drug fever. The latter can lead to significant additional work-up and potentially more antimicrobial exposure [18,19]. Thus, ASP should provide guidelines and implement strategies to reduce the antimicrobial therapy to its shortest effective duration.

C. Measurement of antimicrobial use and the impact of the ASP

Antimicrobial use should be reported as total antimicrobial doses and antimicrobial doses by type of antimicrobial per 100 patient months. This denominator is currently used for reporting rates of blood stream infections to the National Safety Healthcare Network.

An overall decrease in total antimicrobial use should not be expected since prescribing of certain types of antimicrobials will decrease and others will increase as a result of the ASP. For example, vancomycin doses will decrease as more MSSA infections are treated with cefazolin, as a result of implementing the ASP. In addition, there may be periods where

overall antimicrobial use will increase as a result of outliers. For example, in certain months, a unit may have a patient with an infection that requires prolonged treatment with multiple antimicrobials. Examples include treatment of endocarditis or osteomyelitis. This is especially relevant for smaller units where one patient may skew the trend of antimicrobial use. Thus, when reviewing data on antimicrobial use, specific attention should be given to potential outliers and trends in specific types of antimicrobials.

Other outcomes that can be measured include adverse events related to antimicrobials, such as *C. difficile* infections and rates of antimicrobial susceptibility over time [18,19]. Although many institutions also track improved costs associated with the ASP, this outcome only takes into account costs associated with decreasing antimicrobial use and does not take into consideration the tremendous cost savings of preventing the emergence of antimicrobial resistance or the economic burden associated with *C. difficile* infections and hospitalizations.

Conclusions—Implementation of ASP can lead to improvements in antimicrobial prescribing patterns in out-patient hemodialysis units, resulting in reduced mortality, adverse events, costs and a decrease in antimicrobial susceptibility rates.

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Key Points

1. Rates of multidrug-resistant organisms are among the highest in the population of chronic hemodialysis
2. Antimicrobial exposure is the main risk factor for harboring resistant bacteria
3. Up to 30% of antimicrobial doses administered to patients in out-patient hemodialysis units are not indicated based on national guidelines.
4. Antimicrobial stewardship programs improve antimicrobial prescribing practices and lead to reduced mortality, adverse events, costs and improvement in antimicrobial susceptibility rates.

Table 1

Key elements and interventions of an antimicrobial stewardship program (ASP)

Key Elements	
1	Identify the ASP team
2	Education
3	Restricted Antimicrobials/Pre-authorization
4	Facility-specific practice guidelines for common infections
5	Tracking, Reporting and Feedback
Interventions	
1	De-escalation based on microbiology culture results
2	Switch from intravenous to oral route
3	Discontinuation of empiric therapy based on no evidence of infection
4	Improve tracking of microbiology and laboratory diagnostics from outside facilities
5	Limit duration of therapy

Table 2

Selected Antibiotics for Dialysis Dosing (Regimens that do not require doses inbetween dialysis sessions)

Antibiotic	ESRD ($t_{½}$ h)	Clinical Spectrum	Dialysis Dosing*
Cefazolin	40 hours	MSSA Aerobic GNBs	2g (IV) q HD*
Cefepime	18 hours	P. aeruginosa Aerobic GNBs	2g (IV) q HD*
Ceftazidime	21 hours	P. aeruginosa Aerobic GNBs	2g (IV) q HD*
Daptomycin	30 hours	MSSA, MRSA, VSE, VRE	10g/Kg (IV) q HD*
Levofloxacin	40 hours	P. aeruginosa Aerobic GNBs MSSA	500 mg (IV/PO) q HD*
Meropenem	7 hours	P. aeruginosa, Aerobic GNBs	2g (IV) q HD*

MSSA = methicillin sensitive Staphylococcus aureus, MRSA = methicillin resistant Staphylococcus aureus, VSE = vancomycin sensitive enterococci, VRE = vancomycin resistant enterococci, GNB = Gram negative bacilli, ESRD = end stage renal disease, HD = hemodialysis

*No intra-HD dosing needed with these antibiotics when dosed as suggested.

Adapted from: Cunha CB, Cunha BA (Eds) Antibiotic Essentials (15 ed.) JayPee Medical Publishers, New Delhi, 2016 [12].