Seminars in Dialysis

Antimicrobial Use and Stewardship Programs Among Dialysis Centers

Erika M.C. D'Agata
Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

ABSTRACT

Antimicrobial exposure contributes to the emergence and spread of multidrug-resistant organisms. As rates of colonization and infection with these organisms are among the highest in the population of chronic hemodialysis patients and antimicrobial exposure among this patient population is extensive, it is imperative to prescribe antimicrobials judiciously. Thirty to forty percent of chronic hemodialysis patients receive at least one dose of antimicrobials in outpatient centers over a one-year period. Up to 30% of these antimicrobials are prescribed inappropriately, as per national guidelines. The predominant reasons include (i) failure to de-escalate to a more narrow-spectrum antimicrobial, (ii) criteria for infection, especially skin and soft tissue infections, are not met, and (iii) indications and duration for surgical prophylaxis for minor vascular-access-related procedures do not follow recommended guidelines. Vancomycin, third- or fourth-generation cephalosporins and cefazolin are the most common antimicrobials or antimicrobial classes prescribed inappropriately. Antimicrobial stewardship programs reduce both inappropriate antimicrobial exposure and associated costs. Effective strategies include (i) education, (ii) guidelines and clinical pathways, (iii) antimicrobial order forms, (iv) de-escalation therapy, and (v) prospective audit and feedback. Dialysis centers need to identify a team of individuals that will lead the antimicrobial stewardship program. Administrative and financial support for this team is essential. After implementation of the program, regular monitoring for compliance with strategies, and identifying factors that are preventing compliance are necessary. The efficacy of the program should also be evaluated at regular intervals through process and outcome measures.

Antimicrobial exposure is one of the main risk factors for the emergence and spread of multidrug-resistant organisms (1–3). Antimicrobial exposure is also associated with substantial adverse events (4,5); some of these adverse effects might be more common in dialysis settings given the altered pharmacokinetics and polypharmacy in patients requiring chronic hemodialysis (CHD). Improving antimicrobial prescribing practices and thereby minimizing exposure to antimicrobials that may not be indicated, is therefore crucial for curtailing the ongoing increase in the prevalence of multidrug-resistant organisms and improving patient outcomes.

Overall Antimicrobial Use in the Dialysis Population

In 2006, the Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC NHSN) reported antimicrobial use among 32 outpatient hemodialysis centers (6). All antimicrobial starts, by vascular-access type, were recorded with new starts defined as those occurring at least 21 days after a prior one. During the 12-month study period, 977 starts were recorded providing a pooled mean of 3.5 starts per 100-patient months.

Chronic hemodialysis patients with permanent central lines had the highest rate of antimicrobial starts (6.4 starts/100 patient-months) followed by those with grafts (2.4 starts/100 patient-months) and fistulas (1.8 starts/100 patient-months). Although CHD patients with temporary central lines had a higher pooled mean of antimicrobial starts (25.4 starts/100 patient-months), this value is difficult to interpret given the low number of patients with temporary central lines.

Vancomycin accounted for 73% of all antimicrobial starts. Pooled mean rates of vancomycin starts, by vascular-access type, were as follows: 1.2 starts/100 patient-months for fistulas, 1.6 starts/100 patient-months for grafts, 5.0 starts/100 patient-months for permanent central lines and 16.1 starts/100 patient-months for temporary central lines (6) (Table 1).

George et al. (2006) used a similar study design to quantify antimicrobial starts in one 112-bed outpatient dialysis unit in London, England (7). Overall, rates of antimicrobial starts and vancomy-

Address correspondence to: Erika D'Agata MD MPH, Beth Israel Deaconess Medical Center, Division of Infectious Diseases, Lowry Medical Office Building, 110 Francis St., Suite 6A, Boston, MA 02215, Tel.: +617.632.0760, Fax: +617.632.7626, or e-mail: edagata@bidmc.harvard.edu
Seminars in Dialysis—Vol 26, No 4 (July–August) 2013 pp. 457–464
DOI: 10.1111/sdi.12090

TABLE 1. Comparison of pooled means of intravenous (IV) antimicrobial starts, by study

Study	IV Antimicrobial starts (per 100 patient-months)	
	All IV antimicrobials	Vancomycin
Klevens et al. (2008)	3.5	2.6
George et al. (2006)	7.7–4.1[a]	6.4–3.6[a]
Snyder et al. (2011)	7.6	5.3
NHSN (2007–2011)[b]	3.1	2.2

[a]Lower means reflect implementation of a blood-stream infection surveillance scheme with feedback (7).
[b]Centers for Disease Control and Prevention, National Healthcare Safety Network Dialysis Event Data (personal communication).

TABLE 2. Pooled means of intravenous (IV) antimicrobial starts, by antimicrobial type, in two dialysis centers (8)

Type of Antimicrobial	IV Antimicrobial Use (doses/ 100 patient-months [range])
All IV antimicrobials	32.9 (5.2–67.2)
Vancomycin	22.3 (5.2–50.0)
Cefazolin	5.1 (0.0–25.9)
Third- or fourth-generation cephalosporins[a]	3.0 (0.0–13.0)
Aminoglycosides[b]	1.0 (0.0–12.1)
Daptomcyin	1.3 (0.0–13.0)
Carbapenems[c]	0.2 (0.0–5.5)
Piperacillin-tazobactam	0.03 (0.0–2.3)
Levofloxacin	0.03 (0.0–1.1)

[a]Third- or fourth-generation cephalosporins include ceftriaxone, ceftazidime, and cefepime.
[b]Aminoglycosides include gentamicin, amikacin, and tobramycin.
[c]Carbapenems include ertapenem and meropenem.

cin starts were substantially higher in this study compared with the above mentioned CDC study, although these rates fell substantially after implementation of a blood-stream infection surveillance scheme with feedback (6) (Table 1).

The National Healthcare Safety Network Dialysis Event has also recently reported rates of antimicrobial starts from 2007 through 2011 among 193 dialysis centers which are presented in Table 1 (personal communication). The reasons for different rates are unclear but may be due to differences in patient populations, including percent of patients with permanent central lines or prescribing practices.

The most recent study addressing antimicrobial use in dialysis centers quantified all antimicrobials doses (both starts and continuing doses) administered in two dialysis centers in Boston, Massachusetts from 2008 through 2011 (8). The pooled mean for all antimicrobial doses was 32.3 doses per 100 patient-months. The pooled mean for only antimicrobial starts was 7.6 per 100 patient-months, a mean similar to the George et al.'s study (7,8) (Table 1).

The Boston-based two-unit dialysis study also quantified pooled means of all antimicrobials (8) (Table 2). Vancomycin was the most commonly prescribed antimicrobial, followed by cefazolin and third- or fourth-generation cephalosporins. The finding that third- or fourth-generation cephalosporins were the third most commonly prescribed antimicrobials is a novel finding. It is also a concerning finding, since these classes of antimicrobials are key risk factors for the emergence and spread of multidrug-resistant gram-negative bacteria, which cause infections associated with substantial morbidity and mortality (9).

Data on antimicrobial use are also available through the United States Renal Data System (10). In their 2009 Annual Data Report, which provided data from 1994 through 2007, the percent of CHD patients with at least one outpatient antibiotic claim increased from 31% in 1994 to 41% in 2007. The percent of patients with at least one antimicrobial claim in 2007 by type of antimicrobial was as follows (percent of patients): vancomycin (28%), cefazolin (18%), aminoglycosides (15%), and broad-spectrum cephalosporins (5%). Although there was an increase in vancomycin and cefazolin claims from 1994 through 2007, the percent of claims remained stable for aminoglycosides and broad-spectrum cephalosporins.

There is a paucity of data pertaining to antimicrobial use among CHD patients in the hospital setting. One study suggests that the rate of vancomycin exposure among CHD patients is substantially higher than other hospitalized patients. Green et al. (2000) quantified vancomycin use among hospitalized CHD patients (11). Over the 3-month prospective study, 103 patients requiring chronic hemodialysis during 144 admissions were followed. Patients received at least one dose of vancomycin during 39% of admissions. When compared with patients hospitalized during the same time period, who did not require chronic hemodialysis, dialysis patients had an 11-fold higher risk of receiving vancomycin. One recent study also documented that in-hospital vancomycin use among dialysis patients is increasing. In this 5-year study, the percent of patients treated with vancomycin for methicillin-susceptible *Staphylococcus aureus* (MSSA) bloodstream infections was 49.4% in 2006 and rose to 66.4% in 2010 ($p < 0.001$) (12).

Inappropriate Antimicrobial Use

Few studies have quantified inappropriate antimicrobial prescribing among the CHD population. Two hospital-based studies quantified and characterized vancomycin prescribing among CHD patients admitted to tertiary care hospitals. Conclusions from both studies were similar. Green et al. (2000) followed hospitalized CHD patients over a 3-month study period and used the Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines for determining the appropriateness of vancomycin administrations (11,13).

The investigators modified these guidelines to include, as appropriate, empiric administration of vancomycin for the febrile CHD patient, given the high rates of methicillin-resistant *Staphylococcus aureus* infections.

Among the 164 prescribed vancomycin doses, 20% were categorized as inappropriate. Continued therapy despite negative cultures for a β-lactam resistant organism and absence of a β-lactam allergy accounted for 14% of inappropriate vancomycin doses. Prophylaxis for indwelling vascular catheters was the next most common inappropriate indication accounting for 3% of doses, followed by not indicated surgical prophylaxis among 2% of doses. Only 1% of inappropriate vancomycin doses were for the treatment of a single positive blood culture contaminated with coagulase-negative staphylococci.

Zvonar et al. (2008) followed 105 hospitalized patients requiring CHD over a 12-month study period and also used the modified HICPAC guidelines for vancomycin prescribing (14). Among the 163 courses of vancomycin, 12% were considered to be inappropriate. As in the Green et al. (2000) study, treatment of β-lactam susceptible pathogens in the absence of a β-lactam allergy was the most common inappropriate indication accounting for the great majority of inappropriate vancomycin doses (11,14).

Only one study quantified and characterized inappropriate antimicrobial prescribing in the outpatient dialysis setting. Snyder et al. (2011) prospectively followed 278 patients receiving chronic hemodialysis in two Boston-based centers over a 12-month study period (8). In this study, all intravenous antimicrobial doses administered to patients were evaluated. Reasons for inappropriate administration of antimicrobials were categorized into (i) criteria for infection was not met, based on national guidelines, (ii) failure to use a more narrow-spectrum antimicrobial based on culture data, and (iii) indication for surgical prophylaxis were not met, including no indication or prolonged duration ($\geq$24 hours). A total of 1003 doses of antimicrobials were administered. Thirty-two percent of patients received at least one antimicrobial dose over the one-year study period. CHD patients received 11.3 doses (range 1–78) and 1.5 (range 1–5) different antimicrobials, on average. Overall, 29.8% of doses were classified as inappropriate.

The most common category of inappropriate prescribing was that the criteria for infection were not met, accounting for 52.9% of all doses. Among these, presumed blood-stream infection, that did not meet criteria, was the most common, with approximately half of these doses administered for a single positive blood culture for coagulase-negative staphylococci in the absence of any clinical signs or symptoms of infection.

The second most common infection for which criteria were not met was skin and soft tissue infections (SSTI). Criteria for an SSTI required either purulent drainage or $\geq$2 of the following: erythema, swelling, tenderness, and warmth (15). Criteria for vascular-access-related SSTI required pus, increased swelling or redness at the vascular-access site (16). A total of 51.6% of inappropriate doses for SSTI represented treatment of lower extremity cellulitis whereby only redness or swelling was present. The remaining 48.4% of doses represented vascular-access-related infection whereby only tenderness was present. The remaining sites of infection in which criteria were not met were urinary tract infections and pneumonia (4.8% and 2.7% of inappropriate doses in this category, respectively).

The second most common category for which antimicrobials were prescribed inappropriately was failure to choose a more narrow-spectrum antimicrobial, accounting for 26.8% of all inappropriate doses. Approximately two-thirds of these doses represented administration of vancomycin, instead of a β-lactam antimicrobial in the absence of a β-lactam allergy. The remaining one-third of these doses represented administration of third- or fourth-generation cephalosporins instead of a first-generation cephalosporin despite available antimicrobial susceptibility data.

Failure to meet the indications and duration for surgical prophylaxis was the third most common category for which antimicrobials were prescribed inappropriately and accounted for 20.3% of all inappropriate doses. Among these, vascular-access-related procedures predominated. Of note, the great majority of these doses were administered in one of the two dialysis centers, suggesting that these findings may not be generalizable to all dialysis centers, highlighting the value of understanding local antimicrobial prescribing patterns in individual dialysis centers to help target interventions (8).

Lastly, this study also addressed inappropriate prescribing patterns by type of antimicrobial. Thirty-seven percent of vancomycin doses, 36% of cefazolin doses, and 13% of third-generation or fourth-generation cephalosporins doses were prescribed inappropriately (8).

Antimicrobial Stewardship Programs (ASP)

The predominant goals of an ASP are to improve the selection of an appropriate antimicrobial and optimize the dose and duration of therapy. The duration should be adequate for infection cure while minimizing toxicity and emergence of antimicrobial resistance. The great majority of data pertaining to ASP reflect the hospital setting. These ASP have demonstrated reductions in antimicrobial exposure ranging from 22–36% and decreases in hospital costs ranging from $200,000–$900,000 (17–21). The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) have provided guidelines for developing an institutional program to enhance antimicrobial

stewardship (22). Although these guidelines are hospital-based, many of the strategies can be implemented in dialysis centers.

Strategies for an Effective ASP

The concept of an effective ASP as per the IDSA/SHEA guidelines is that there is dedicated team of healthcare personnel, consisting of an infectious disease physician and a clinical pharmacist, with the inclusion of a clinical microbiologist, hospital epidemiologist, and information system specialist (22). This extended team approach is not logistically feasible in individual dialysis centers. However, identifying several individuals in dialysis centers who would be responsible for ensuring antimicrobial stewardship could be a more feasible approach. Examples of these individuals include medical directors or designee, nurses, or pharmacists, if available. Adequate authority and compensation for these individuals with support from administration and leadership would be key to a successful ASP. These individuals would then be responsible for developing an ASP with input from other healthcare personnel and administration and, subsequently implementing and monitoring the ASP.

Education

Clinician education is an essential component of any ASP. A dedicated lecture series and providing guidelines for appropriate antimicrobial use are some examples. Lecture topics to consider include treatment of the common infections in hemodialysis patients, epidemiology of antimicrobial-resistant bacteria in the dialysis population and an overview of ASP. These efforts should not only target the nephrologists but also all healthcare workers in the dialysis unit since in this setting a team approach is central to patient care.

Unfortunately, education alone is not sufficient. Studies have shown that, although effective, the benefit is limited without active intervention. For example, in a study to improve physicians' prescribing of antimicrobial prophylaxis for preventing surgical site infections, educational efforts in the form of an antibiotic handbook increased compliance with suggested therapies from 11% to 18%. When an active intervention was introduced, a perioperative preprinted physician order form, compliance increased from 17% to 78%. (23).

Guidelines and Clinical Pathways

Providing evidence-based guidelines for the treatment of infections and appropriate antimicrobial use is an effective strategy. A study by South et al. (2003) provided laminated cards with guidelines for the treatment of three common pediatric infections. A marked improvement in the treatment of orbital/periorbital cellulitis was documented, with appropriate prescribing increasing from 19% without the cards to 78% with the cards. Appropriate treatment of other infections also increased but to a lesser extent (24).

Implementation of guidelines and clinical pathways in dialysis centers would require identifying the most common infections that patients develop. Potential infections to target would include bacteremia, especially when coagulase-negative staphylococci are implicated, and skin and soft tissue infections, including vascular-access site infections (8). Guidelines should also be developed for the most commonly prescribed antimicrobials. For vancomycin, the HICPAC guidelines **(**13**)** could be implemented with the modification that empiric vancomycin administration is appropriate in the setting of the febrile patient, due to the high prevalence of methicillin-resistant *Staphylococcus aureus* infection (11). Other antimicrobials to target will require knowledge of prescribing patterns in individual dialysis centers. Given the high rates of antimicrobial resistance, knowledge of local antimicrobial susceptibility patterns should guide the development of all guidelines (22). Ideally, all antibiotic prescribing guidelines that are developed for dialysis centers should be reviewed by an infectious disease specialist.

Developing and disseminating guidelines, however, may not result in compliance with their implementation and therefore a strategy which involves monitoring compliance should also be considered, and is discussed below. Lastly, effective guidelines should be reviewed and updated regularly to reflect the most recent data, pertaining to optimal treatment regimens and antimicrobial susceptibility patterns.

Antimicrobial Order Forms

Antimicrobial order forms requiring justification for physician prescribing can lead to a 30% reduction in antimicrobial use (25). In dialysis centers, forms providing a checklist of indications for the appropriate use of antimicrobials for specific infections or antimicrobials, could be developed and implemented. As with guidelines, monitoring of compliance and providing clinicians feedback would be essential.

Streamlining or De-escalation Therapy

Changing to a more narrow-spectrum antimicrobial, after collecting clinical cultures and, culture data with antimicrobial susceptibility patterns are available, is a key strategy to reduce inappropriate antimicrobial use and costs. This strategy is especially relevant to dialysis centers since prescribing of vancomycin instead of beta-lactam antimicrobials is one of the most common inappropriate indications for antimicrobial use (11,14). One of the main reasons for ongoing vancomycin therapy, instead of a beta-lactam antimicrobial, is the ease of its administration during dialysis sessions.

The importance of de-escalation to a beta-lactam antimicrobial from vancomycin, however, cannot be overemphasized. A study comparing treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA) with nafcillin or cefazolin demonstrated a 79% lower mortality hazards compared with vancomycin treatment (26). Although nafcillin administration in dialysis patients may not be feasible given its dosing schedule, cefazolin is a reasonable alternative. Schweizer et al. followed 123 hemodialysis-dependent patients with MSSA blood-stream infections. Treatment failure was lower among patients treated with cefazolin compared with those treated with vancomycin (31.2% vs. 13%, $p = 0.02$). Of note, retention of the vascular-access was also associated with treatment failure (26).

Another study addressing outcomes of vancomycin vs. cefazolin treatment of MSSA blood-stream infection among hemodialysis patients also showed that cefazolin therapy was superior. In this study, patients treated with cefazolin had a 38% lower risk of hospitalization or death compared with patients treated with vancomycin (12).

Third-generation or fourth- generation cephalosporins have recently been shown to be common antimicrobials that are also frequently prescribed inappropriately due to failure to de-escalate to a first-generation cephalosporin (8). In addition to substantial cost savings, use of more narrow-spectrum cephalosporins would minimize the emergence of multidrug-resistant organisms.

Prospective Audit with Intervention and Feedback

This intervention is referred to as a "core strategy" in the IDSA/SHEA guidelines for ASP (22). This strategy involves reviewing physicians' prescribing patterns of specific antimicrobials, identifying indications or duration of therapy which can be improved, and then providing an intervention, such as an educational one, with either verbal or written feedback to the prescribing physician. In the hospital setting, prospective audit with intervention and feedback usually mandates an infectious disease specialist or pharmacist, as per the IDSA/SHEA guidelines (22). This approach may not be feasible in dialysis centers but modified versions could be developed. For example, antimicrobial order forms that require a checklist for indications for infections or antimicrobial choice, as mentioned above, could be reviewed by those individuals identified to implement the ASP. Using guidelines and clinical pathways, these individuals could then provide feedback to the prescribing nephrologist, not only regarding their compliance rate but also providing de-identified comparison compliance data for other prescribers, and potentially other dialysis centers.

Another strategy for dialysis centers could entail reviewing orders for vancomycin, since it is the most common antimicrobial prescribed inappropriately, and determine (i) if vancomycin is indicated, (ii) if cefazolin would be more appropriate, and (iii) if the duration of therapy could be shortened. Determining whether culture data were obtained would also be included in this strategy.

Formulary Restriction and Preauthorization Requirements for Specific Agents

This intervention is the second "core strategy", as per the IDSA/SHEA guidelines that provide the foundation for an effective ASP (22). Formulary restriction refers to restricting the use of an antimicrobial to specific indications or patients or, restricting the duration of therapy. For example, linezolid use may be restricted for use only in the treatment of MRSA infections or among patients with a vancomycin allergy. Preauthorization requires approval for the use of a specific antimicrobial or its duration. As with the prospective audit and feedback strategy, this intervention requires the ongoing participation of an individual dedicated to the ASP. To minimize the time commitment associated with this strategy, focusing on specific antimicrobials, such as those that provide the last available therapy for specific pathogens or high-cost antimicrobials, may be considered.

Computer Surveillance and Decision Support

A computer decision-support system linking antimicrobial prescribing to medical records is another effective strategy (27). There are numerous different systems, including those that provide the prescriber with information about the optimal antimicrobial to prescribe, antimicrobials that should not be prescribed, drug interactions, and duration of courses. Ultimately, they provide the prescriber with support regarding the best decision for prescribing antimicrobials. There are several limitations to this intervention, however. First, the technology may not be available to all dialysis centers. Second, even if implemented, these support systems, as with any intervention, require monitoring for compliance, feedback to nephrologists, and regular updating to reflect the most recent information (28).

Evaluating the Efficacy of ASP

Two measures are used to evaluate the efficacy of an ASP; process and outcome measures (22,29,30). Examples of process measures include total antimicrobial use, type of antimicrobial use and inappropriate indications for antimicrobial administration. Outcome measures include rates of antimicrobial resistance, adverse drug events and costs. These measures should be collected before and after implementation of the ASP and values compared. In addition, collection of these measurements should continue at regular intervals to document the ongoing efficacy of the ASP.

Unique Aspects of ASP in Dialysis Centers

Antimicrobial Orders from Outside the Dialysis Centers

In some cases, antimicrobials administered in the outpatient dialysis unit are prescribed in the hospital setting or by surgeons and radiologists after outpatient minimally invasive interventions for dialysis access-related procedures. These antimicrobials are then continued once the patient returns to the outpatient center. In these situations, determining whether both the initial and ongoing administration of the prescribed antimicrobials is appropriate may be difficult if documentation from the nonunit physician is unavailable or suboptimal. Ongoing antimicrobial therapy in dialysis centers for dialysis-related procedures, for example, was identified as one of the most common inappropriate indications for antimicrobial prescribing in one dialysis unit (8). The great majority of prescribed antimicrobials in this category were for prophylaxis related to a minimally invasive procedure and was either not indicated or continued for ≥ 24 hours post procedure. Individual dialysis centers should determine if this finding is relevant to their unit and, if so, review if the prophylactic antimicrobials are warranted and if the duration of therapy is appropriate.

Role of Nurses and Physician Extenders in Prescribing Antimicrobials

Many orders for antimicrobials are prescribed via phone conversations when nurses or physician extenders call the nephrologist with concern of a possible infectious process. This role, in addition to many others related to patient care, emphasizes the major contribution that these healthcare workers play in prescribing antimicrobials. It is therefore imperative that any effort towards a successful ASP should clearly mandate the involvement of these individuals (e.g., dialysis nurse, nurse manager).

Measuring Antimicrobial Use in the Dialysis Unit

The optimal metric for measuring antimicrobial use in dialysis centers is the mean number of doses as it captures exposure to all antimicrobial doses. This approach might not be feasible for facilities that rely upon manual data collection methods to perform surveillance. An alternative is to measure antimicrobial starts per 100-patient months. This antimicrobial start metric has become the standard for dialysis reporting and is used by the Centers for Disease Control and Prevention National Healthcare Safety Network (6). Familiarity with this metric will therefore facilitate data collection on antimicrobial use. A large proportion of dialysis facilities use electronic health records, including electronic records for medications administered. For these facilities, collecting and reporting all doses might be simpler than trying to identify antimicrobial starts. CDC is interested in exploring the feasibility of changing the metric from antimicrobial starts to all doses as it would capture more complete exposure information.

ASP in Long-term Care Settings (LTCF)

Although implementation of a multifaceted ASP is optimal, resources may not be available in healthcare facilities outside of the hospital setting. In LTCF, for example, modified versions of ASP have been investigated and have shown to successfully reduce antimicrobial prescribing: potential parallels from these investigations could be drawn for dialysis centers.

Given the limited resources, ASP in LTCF has focused predominantly on educational efforts and the implementation of guidelines for improving antimicrobial use. (31–33). These long-term care-targeted programs improved adherence to recommended guidelines and reduced inappropriate antimicrobial prescribing by 20.5% (31,32). More recently, and given the increased concern for antimicrobial-resistant bacteria in the LTCF setting (3), full ASP programs with dedicated personnel have been evaluated. In a 60-bed long-term acute care facility, for example, two individuals were provided with 10 additional hours per month to dedicate to the ASP. These individuals developed stewardship policies and discussed the program with the medical staff. They also performed medical chart reviews for antimicrobial prescribing patterns, provided written feedback to prescribers and, recommended infectious disease consultation if indicated. This ASP resulted in a 21% reduction in antimicrobial use (34). Another ASP program in a LTCF introduced an infectious disease consultation service, which resulted in a 30% reduction in antimicrobial use (35). While the cost-effectiveness of these programs in LTCF has not been shown, it is more than likely that, as in hospital settings, the benefits introduced by an ASP would greatly outweigh the costs.

Conclusions

Developing an effective ASP requires a complete understanding of specific areas of antimicrobial prescribing patterns that need improvement. It also requires careful attention to what processes and strategies will be most effective for a particular dialysis unit. Once implemented, monitoring for compliance with strategies, factors that are preventing compliance and the efficacy of the ASP are essential. It is important to identify individuals within each dialysis unit that will lead the ASP and ensure that they have administrative, leadership and financial support (Table 3). Although difficult to employ an infectious disease physician or pharmacist to be involved with the ASP, centers should consider obtaining some input from these individuals who

TABLE 3. Key approaches for an effective antimicrobial stewardship program (ASP) in dialysis settings

Identify individuals who will lead the ASP ("champions")
Obtain leadership support
Tailor interventions to dialysis center-specific areas of inappropriate antimicrobial prescribing through:
- reviewing and understanding prescribing patterns
- reviewing and understanding culturing practices
- understanding when antimicrobials are being prescribed inappropriately (e.g., type, duration, lack of de-escalation, surgical prophylaxis)
Develop strategies to address specific areas of inappropriate prescribing patterns

have relevant expertise. Ultimately the implementation of an effective ASP will not only improve patient outcomes but will also reduce costs. The Centers for Disease Control and Prevention Get Smart for Healthcare provides further information, tools (e.g. templates for antimicrobial approval forms, ASP proposal form) and other resources for implementing an ASP (36).

Current guidelines for developing and implementing an ASP reflect data generated from the hospital setting (22). Although LTCF have begun to address this issue, dialysis centers also need to define, in more detail, the strategies that would be most effective in their unique healthcare setting. It is possible that nephrologists and infectious disease specialists could collaborate on a national level to begin to address key issues. For example, should ASP in dialysis centers monitor antimicrobial starts or all antimicrobial doses? Monitoring only the former would miss a substantial proportion of doses administered inappropriately (6). However, it remains to be determined if monitoring all doses is logistically feasible and, which approach is most cost-effective.

Another important area requiring further research is to characterize the subpopulation of CHD patients at highest risk of receiving antimicrobials inappropriately. These findings would provide important knowledge for improving the efficacy of ASP.

Lastly, antimicrobial improvement strategies in dialysis centers have predominantly focused on vancomycin since it is both the most commonly prescribed antimicrobial and the most common inappropriately prescribed antimicrobial. However, over the last decades, the armamentarium of different antimicrobials to treat infections has increased and many more antimicrobials are available than the standard combination of "vancomycin and gentamicin". It is therefore imperative that dialysis centers also begin to focus their attention on other types of antimicrobials and identify which types, other than vancomycin, are being prescribed inappropriately. As mentioned above, one study identified third-generation or fourth-generation cephalosporins as the second most common antimicrobial classes prescribed inappropriately after vancomycin (8). Given the rise in multidrug-resistant gram-negative bacteria in the dialysis population, it is more than likely that these antimicrobial classes will be used in greater frequency over the ensuing years (1).

Conflicts of interest

None declared.

References

1. Pop-Vicas A, Strom T, D'Agata EMC: Multidrug-resistant gram-negative bacilli among chronic hemodialysis patients. *Clin J Am Soc Nephrol* 3:752–758, 2008
2. Marchaim D, Chopra T, Bhargava A, Bogan C, Dhar S, Hayakawa K, Pogue JM, Bheemreddy S, Blunden C, Shango M, Swan J, Lephart PR, Perez F, Bonomo RA, Kaye KS: Recent exposure to antimicrobials and carbapenem-resistant *Enterobacteriaceae*: the role of antimicrobial stewardship. *Infect Control Hosp Epidemiol* 33:817–830, 2012
3. O'Fallon E, Kandel R, Schreiber R, D'Agata EM: Acquisition of multidrug-resistant gram-negative bacteria: incidence and risk factors within a long-term care population. *Infect Control Hosp Epidemiol* 31:1148–1153, 2010
4. Shehab N, Patel PR, Srinivasan A, Budnitz DS: Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis* 47:735–743, 2008
5. Lessa FC, Gould CV, McDonald LC: Current status of Clostridium difficile infection epidemiology. *Clin Infect Dis* 55(S2):S65–S70, 2012
6. Klevens RM, Edwards JR, Andrus ML, Peterson KD, Dudeck MA: Horan TC; NHSN Participants in Outpatient Dialysis Surveillance. Dialysis Surveillance Report: National Healthcare Safety Network (NHSN)-data summary for 2006. *Semin Dial* 21:24–28, 2008
7. George A, Tokars JI, Clutterbuck EJ, Bamford KB, Pusey C, Holmes AH: Reducing dialysis associated bacteraemia, and recommendations for surveillance in the United Kingdom: prospective study. *BMJ* 332:1435–1440, 2006
8. Snyder G, Patel PR, Kallen AJ, Strom JA, Tucker JK, D'Agata EMC. Antimicrobial use in out-patient hemodialysis units. *Infect Control Hosp Epidemiol* 34:349–357, 2013
9. Schwaber MJ, Carmeli Y: Mortality and delay in effective therapy associated with extended-spectrum β-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother* 60:913–920, 2007
10. U.S. Renal Data System: *USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health*. National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2009
11. Green K, Schulman G, Haas DW, Schaffner W, D'Agata EMC: Vancomycin prescribing practices in hospitalized chronic hemodialysis patients. *Am J Kid Dis* 35:64–68, 2000
12. Chan KE, Warren HS, Thadhani RI, Steele DJ, Hymes JL, Maddux FW, Hakim RM: Prevalence and outcomes of antimicrobial treatment for Staphylococcus aureus bacteremia in outpatients with ESRD. *J Am Soc Nephrol* 23:1551–1559, 2012
13. Hospital Infection Control Practices Advisory Committee: Recommendations for preventing the spread of vancomycin resistance. *Infect Control Hosp Epidemiol* 16:105–113, 1995
14. Zvonar R, Natarajan S, Edwards C, Roth V: Assessment of vancomycin use in chronic hemodialysis patients: room for improvement. *Nephrol Dial Transplant* 23:3690–3695, 2008
15. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC: Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis* 41(10):1373–1406, 2005
16. Centers for Disease Control and Prevention. NHSN Dialysis Event Protocol. 2012; http://www.cdc.gov/nhsn/psc_da_de.html. Accessed 7/10/2012
17. Schentag JJ, Ballow CH, Fritz AL, Paladino JA, Williams JD, Cumbo TJ, Ali RV, Galletta VA, Gutfeld MB, Adelman MH: Changes in antimicrobial agent.usage resulting from interactions among clinical pharmacy, the infectious disease division, and the microbiology laboratory. *Diagn Microbiol Infect Dis* 16:255–264, 1993
18. Lutters M, Harbarth S, Janssens P, Freudiger H, Herrmann F, Michel JP, Vogt N: Effect of a comprehensive, multidisciplinary, educational program on the use of antibiotics in a geriatric university hospital. *J Am Geriatr Soc* 52:112–116, 2004
19. Scheckler WE, Bennett JV: Antibiotic usage in seven community hospitals. *JAMA* 213:264–267, 1970

20. Carling P, Fung T, Killion A, Terrin N, Barza M: Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol* 24:699–706, 2003
21. Ansari F, Gray K, Nathwani D, Phillips G, Ogston S, Ramsay C, Davey P: Outcomes of an intervention to improve hospital antibiotic prescribing: interrupted time series with segmented regression analysis. *J Antimicrob Chemother* 52:842–848, 2003
22. Dellit TH, Owens RC, McGowan JE, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM: Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. *Clin Infect Dis* 44:159–177, 2004
23. Girotti MJ, Fodoruk S, Irvine-Meek J, Rotstein OD: Antibiotic handbook and pre-printed perioperative order forms for surgical antibiotic prophylaxis: do they work?. *Can J Surg* 33:385–388, 1990
24. South M, Starr M: A simple intervention to improve hospital antibiotic prescribing. *Med J Aust* 178:207–209, 2003
25. Echols RM, Kowalsky SF: The use of an antibiotic order form for antibiotic utilization review: influence on physicians' prescribing patterns. *J Infect Dis* 150:803–807, 1984
26. Schweizer ML, Furuno JP, Harris AD, Johnson JK, Shardell MD, McGregor JC, Thom KA, Cosgrove SE, Sakoulas G, Perencevich EN: Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible Staphylococcus aureus bacteremia. *BMC Infect Dis* 11:279, 2011
27. Evans RS, Pestotnik SL, Classen DC, Burke JP: A computer-assisted management program fro antibiotics and other antiinfective agents. *N Engl J Med* 338:232–238, 1998
28. Kuperman GJ, Gibson RF: Computer physician order entry: benefits, costs, and issues. *Ann Intern Med* 139:31–39, 2003
29. Ohl CA, Luther VP: Antimicrobial stewardship for inpatient facilities. *J Hosp Med* 6:S4–S15, 2011
30. Fishman N: Antimicrobial stewardship. *Am J Med* 119:553–561, 2006
31. Monette J, Miller MA, Monette M, Laurier C, Boivin JF, Sourial N, Le Cruguel JP, Vandal A: Cotton-Montpetit M.Effect of an educational intervention on optimizing antibiotic prescribing in long-term care facilities. *J Am Geriatr Soc* 55:1231–1235, 2007
32. Naughton BJ, Mylotte JM, Ramadan F, Karuza J, Priore RL: Antibiotic use, hospital admissions, and mortality before and after implementing guidlines for nursing home-acquired pneumonia. *J Am Geriatr Soc* 49:1020–1024, 2001
33. Loeb M, Brazil K, Lohfeld L, McGeer A, Simor A, Stevenson K, Zoutman D, Smith S, Liu X, Walter SD: Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomized controlled trail. *BMJ* 331:669, 2005
34. Pate PG, Storey DF, Baum DL: Implementation of an antimicrobial stewardship program at a 60-bed long-term acute care hospitals. *Infect Control Hosp Epidemiol* 33:405–408, 2012
35. Jump RL, Olds DM, Seifi N, Kypriotakis G, Jury LA, Peron EP, Hirsch AA, Drawz PE, Watts B, Bonomo RA, Donskey CJ: Effective antimicrobial stewardship in a long-term care facility through an infectious disease consultation service: keeping a LID on antibiotic use. *Infect Cont Hosp Epidemiol* 33:1185–1192, 2012
36. Centers for Disease Control and Prevention: Get Smart For Healthcare: 2012; http://www.wiley.com/bw/submit.asp?ref=0894-0959. Accessed 01/08/2013