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MAJOR ARTICLE

Outpatient Antibiotic Prescribing Patterns for Adult End-Stage Renal Disease Patients in New York State

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Background. Infections are important complications of end-stage renal disease (ESRD) with few studies having investigated oral antibiotic use. Inappropriate antibiotic prescribing can contribute to multidrug-resistant organisms and *Clostridioides difficile* infections seen in ESRD. This study investigates antibiotic prescribing practices in ESRD across New York State (NYS).

Methods. Retrospective case-control study from 2016 to 2017 of NYS ESRD and non-ESRD patients analyzing Medicare part B billing codes, 7 days before and 3 days after part D claims. Frequencies of each infection, each antibiotic, dosages, and the antibiotics associated with infections were assessed using χ^2 analysis. A NYS small dialysis organization comprising approximately 2200 patients was also analyzed. Outcomes measured were the frequencies of infections and of each antibiotic prescribed. Incidence measures included antibiotics per 1000 and individuals receiving antibiotics per 1000.

Results. A total of 48 100 infections were treated in 35 369 ESRD patients and 2 544 443 infections treated in 3 777 314 non-ESRD patients. ESRD patients were younger, male, and African American. ESRD and non-ESRD patients receiving antibiotics was 520.29/1000 and 296.48/1000, respectively ($P < .05$). The prescription incidence was 1359.95/1000 ESRD vs 673.61/1000 non-ESRD patients. In 36%, trimethoprim-sulfamethoxazole dosage was elevated by current ESRD guidelines. Top infectious categories included nonspecific symptoms, skin, and respiratory for ESRD; and respiratory, nonspecific symptoms, and genitourinary in non-ESRD.

Conclusions. This study identifies issues with appropriate antibiotic usage stressing the importance of antibiotic education to nephrologist and nonnephrologist providers. It provides support for outpatient antibiotic stewardship programs.

Keywords. ESRD; hemodialysis; oral antibiotics; antibiotic stewardship.

Infections are an important complication of end-stage renal disease (ESRD) representing the second most common cause of death [1]. In both general and ESRD populations, infectious disease research has focused on the potential overuse of broad-spectrum antibiotics in the inpatient setting and the subsequent emergence of bacterial resistance. In hemodialysis, studies have emphasized bloodstream infections and the excessive use of central venous catheters [2, 3].

Studies investigating outpatient oral antibiotic use are limited, with even fewer pertaining to ESRD. These patients carry multiple comorbid diagnoses and have higher hospitalization rates than non-ESRD patients [4, 5]. Given their increased risk of infection, they are more likely to receive intravenous (IV) and oral antibiotics compared to non-ESRD patients [6–8].

Prescribing antibiotics in ESRD presents physicians with additional challenges. Given their impaired renal clearance, appropriate prescribing must optimize agent selection, dose, frequency, and duration for the given infection. Inappropriate antibiotic use may contribute to the increased prevalence of multidrug-resistant organisms (MDROs) in ESRD patients, as well as opportunistic *Clostridioides difficile* infections (CDIs) [4, 5, 9–11].

A recent study of >19 million antibiotic prescriptions in the general population indicated that 23.2% were inappropriate, 35.5% were potentially inappropriate, and 28.5% were not associated with a recent diagnosis code [12]. In a review of 2 outpatient hemodialysis units, researchers found that 29.8% of IV antibiotics were prescribed inappropriately [13]. Additionally, an Australian observational study of ESRD patients demonstrated that about 29% of oral and 21% of IV antibiotics could be inappropriate [7].

The current study investigates outpatient oral antibiotic prescribing practices across New York State (NYS), assessing differences between ESRD and non-ESRD patients. Additionally, a small dialysis organization (SDO) in New York City was examined for a more detailed evaluation of prescribing patterns; comparing providers affiliated to the SDO to other specialists, such as in family medicine, emergency department (ED), and urgent care.

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METHODS

Network 2, responsible for all of NYS, is 1 of 18 networks contracted out by the Centers for Medicare and Medicaid Services (CMS) for monitoring quality and improving ESRD care in the United States. Island Peer Review Organization (IPRO) is contractually responsible for the 290 dialysis units and >29 000 patients in network 2, NYS. Medicare data were collected from IPRO for NYS from 1 January 2016 to 31 December 2017 on both ESRD and non-ESRD outpatient populations enrolled in Medicare Parts B and D. Patients with chronic kidney disease were excluded from the non-ESRD group. Medicare part B *International Classification of Diseases, Tenth Revision* (*ICD-10*) billing codes were analyzed 7 days before and 3 days after a part D claim was filed for an infectious diagnosis. An infection diagnosis was not part of the inclusion criteria; rather, oral outpatient antibiotic prescriptions were. Specific variables included any antibiotic prescribed (dose and duration), sex, race, county of residence, source of prescription (inpatient, outpatient, office, or ED), and *ICD-10* billing codes. *Current Procedural Terminology* codes were used to divide the database into ESRD and non-ESRD. By assessing the billing codes associated with the medications prescribed, as well as the locations of the provider who prescribed them, it was possible to remove inpatient prescriptions. Medications may have been prescribed to inpatients on their way home and filled at an outpatient pharmacy. Only oral antibiotics were included. Patients <18 years of age, pregnant, on peritoneal or home hemodialysis, or with a kidney transplant were excluded. CMS data exclude undocumented patients.

Additional similar clinical data including demographic and antibiotics (doses prescribed and duration) from 2016 and 2017 were collected from an SDO caring for nearly 2500 patients in 12 New York City and Long Island outpatient dialysis centers. This cohort is separate and does not include the NYS ESRD and non-ESRD data. In particular, data included whether the provider was an SDO-affiliated nephrologist, physician assistant, or nurse practitioner, vs an outside provider (OP): an ED, primary care, family medicine, or urgent care provider. The provider specialty was ascertained through the use of National Provider Identifier numbers. The SDO data include all patients regardless of insurance from their units. Infection diagnoses and categories were not available from the SDO. Exclusion criteria were the same as for the NYS analysis. Only patients with ESRD on hemodialysis that were part of the SDO were included.

To assess infection diagnoses and their respective antibiotic usage, *ICD-10* codes were separated into 13 infectious categories: cardiology, ear/nose/throat, gastrointestinal, genitourinary, lymphatics, musculoskeletal, neurological, ophthalmology, respiratory, skin, systemic, nonspecific symptoms, and other infections. The specific organism and its type were identified when possible (bacterial, viral, unknown, etc). Infections were further subcategorized using the full *ICD-10* coding documentation in order to create more specific groupings (eg, sinusitis, cervicitis, osteomyelitis). Unclear categorizations were resolved by consensus among the researchers.

Data were analyzed by observing frequencies of each category of infection, each antibiotic, the antibiotics associated with specific categories of infections, and the varying dosages of each antibiotic. Using χ^2 testing, the frequencies were compared between ESRD and non-ESRD patients. Incidence of individual prescriptions per 1000 patients was calculated based on the total number of patients in their respective groups. As some patients received multiple antibiotic prescriptions during the year, the incidence of patients receiving antibiotics per 1000 patients was also calculated.

RESULTS

In 2016–2017, 48 100 antibiotics were prescribed to treat presumed infections in 35 369 ESRD patients enrolled in Medicare parts B and D. Similarly, 2 544 443 antibiotics were prescribed for 3 777 314 non-ESRD patients. Since most of the individuals were in both years 2016 and 2017 and may have received multiple doses of antibiotics, the data are based on the adjusted numbers of 18 410 ESRD patients and 1 119 897 non-ESRD patients. These numbers ensured that each person appeared only once in the data to not create bias in demographic data (Table 1). ESRD patients tended to be younger and male, with a significant difference in race driven by the higher African American profile (Table 1). Incidence proportion of prescriptions of antibiotics per 1000 patients was 520.29 in ESRD and 296.48 in non-ESRD ($P < .05$; Table 2). Since some individuals were prescribed multiple antibiotics, the rates of prescriptions

Table 1. Characteristics of End-Stage Renal Disease (ESRD) and Non-ESRD Populations

Characteristic	ESRD[b]		Non-ESRD[b]		*P* Value
Age, mean ± SD	18 402[a]	64.80 ± 14.80	1 119 897[a]	71.00 ± 12.21	<.001
Sex					
Female	8330	(45.30)	704 700	(62.90)	<.001
Male	10 072	(54.70)	415 197	(37.10)	
Race/ethnicity					
Asian	945	(5.10)	33 680	(3.00)	<.001
Black	5931	(32.20)	84 622	(7.60)	
Hispanic	1282	(7.00)	28 264	(2.50)	
North American Native	67	(0.40)	1401	(0.10)	
Other	588	(3.20)	23 717	(2.10)	
Unknown	409	(2.20)	26 818	(2.40)	
White	9180	(49.90)	921 395	(82.30)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ESRD, end-stage renal disease; SD, standard deviation.

[a]Individual patients who have received at least 1 antibiotic prescription in 2016 and 2017 ± SD.

[b]From Centers for Medicare and Medicaid Services parts B and D (patients with chronic kidney disease were excluded from the non-ESRD group).

Table 2. Incidence of Patients Receiving Antibiotics and Incidence of Prescriptions Administered, Both per 1000 Patients, and the Mean Number of Days of Antibiotics and Prescriptions per Patient[a]

Prescription data	ESRD	Non-ESRD	*P* Value
Incidence of patients prescribed (per 1000 patients)	520.29	296.48	<.001
Incidence of prescriptions (per 1000 patients)	1359.95	673.61	<.001
Days of antibiotics supplied, mean ± SD	10.30 ± 2.10	8.90 ± 1.74	<.001
No. of prescriptions per patient, mean ± SD	2.20 ± 0.12	2.00 ± 0.32	<.001

Abbreviations: ESRD, end-stage renal disease; SD, standard deviation.
[a]From Centers for Medicare and Medicaid Services parts B and D.

were 1359.95 per 1000 ESRD patients vs 673.61 per 1000 non-ESRD patients. Antibiotics were supplied from outpatient pharmacies with average treatment duration significantly longer in ESRD patients (10.3 vs 8.9 days; $P < .05$; Table 2).

Based on *ICD-10* codes, 32.4% of ESRD patients and 29.2% of non-ESRD patients received antibiotics without an associated infection specific diagnosis, significantly higher in ESRD ($P < .001$). The frequency of each infection category is detailed in Table 3. The 3 most common indications for antibiotics were nonspecific symptoms, skin infections, and respiratory infections in ESRD, and respiratory infections, nonspecific symptoms, and genitourinary infections in non-ESRD. Fifty-two percent of prescriptions in ESRD either did not have an associated infection diagnosis or were for viral conditions or nonspecific symptoms.

ESRD patients also received significantly different antibiotics (Supplementary Appendix Table 1). Azithromycin was most commonly prescribed in both groups, with trimethoprim-sulfamethoxazole (TMP-SMX) and the fluoroquinolones more often in ESRD. When investigating specific dosages, 36% of TMP-SMX prescriptions were prescribed at a dose (800–160 mg) higher than that recommended by infectious disease guidelines for renal failure [14]. Figure 1A and 1B display dosing information for TMP-SMX as well as the fluoroquinolones. Nitrofurantoin comprised 1.28% of prescriptions in ESRD. Antibiotic selection for the most common infection sources based on organ systems differed in ESRD vs non-ESRD (Supplementary Appendix Table 2).

In the SDO, 806 (49.5%) prescriptions came from affiliated renal providers and 821 (50.5%) from OPs (Table 4). While both were prescribed at similar frequencies, antibiotic selection differed. Affiliated renal providers prescribed azithromycin, amoxicillin, and ciprofloxacin most frequently, while OPs prescribed TMP-SMX, amoxicillin, and amoxicillin-clavulanate most frequently. SDO renal providers prescribed TMP-SMX approximately 4 times less frequently than the OPs, whereas azithromycin was more prescribed. For reference, the antibiotic selections of the SDO and OPs were compared to the total NYS ESRD prescriptions, which originated from both renal and outside providers and are included in Table 4.

Table 3. Categorized Indications for Antibiotics Prescribed Organized by Percentage in the End-Stage Renal Disease Population[a]

	ESRD, %	Non-ESRD, %	*P* Value
No diagnosis	32.42	29.21	**<.001**
Nonspecific	15.10	15.26	**.34**
Viral	4.70	1.60	**<.001**
Skin	14.84	10.16	<.001
Respiratory	14.55	15.89	<.001
GU	6.62	13.48	<.001
GI	6.04	2.14	<.001
Systemic	5.10	1.59	<.001
ENT	2.49	9.51	<.001
Other	1.46	1.35	.05
MSK	0.81	0.64	<.001
Ophthalmology	0.25	0.46	<.001
Lymphatics	0.22	0.26	.06
Cardiology	0.07	0.03	<.001
Neurology	0.04	0.02	.05

Figures in bold are indicators with no clear evidence for bacterial antibiotic use. Abbreviations: ENT, ear nose and throat; ESRD, end-stage renal disease; GI, gastrointestinal; GU, genitourinary; MSK, musculoskeletal.
[a]From the Centers for Medicare and Medicaid Services parts B and D.

DISCUSSION

Our study of antibiotic prescribing patterns in NYS indicates that ESRD patients received almost twice as many antibiotics compared to non-ESRD patients (Table 2). Skin infections were the most common reason for antibiotics in ESRD, compared to respiratory infections in non-ESRD patients. We also found significant differences in antibiotic selection in ESRD patients compared to the general public. Additionally, while the percentages of antibiotic prescriptions between renal and nonrenal providers were similar in the SDO sample, selection varied significantly.

Antibiotic overuse and misuse are important factors leading to antibiotic resistance in the general population [15, 16]. Previous studies examining the effects of IV antibiotic prescriptions have demonstrated higher MDRO infection rates [10]. Yearly, at least 2 million people are affected by antibiotic-resistant infections, resulting in up to 23 000 deaths [16, 17].

ESRD patients have multiple comorbidities with hospitalization rates higher than the general population. In just the first year on dialysis, the incidence of infection-related hospitalizations is 32% [18]. Hospital exposure and inappropriate antibiotic use contribute to the high prevalence of MDRO colonization and infections in ESRD [5, 9–11]. Not surprisingly, infections in patients with renal disease are more severe and carry a higher mortality [18]. Moreover, colonized patients returning to outpatient dialysis can then be sources of transmission [19].

Infection control research in ESRD has emphasized the restriction of central venous catheter use and IV antibiotic selection

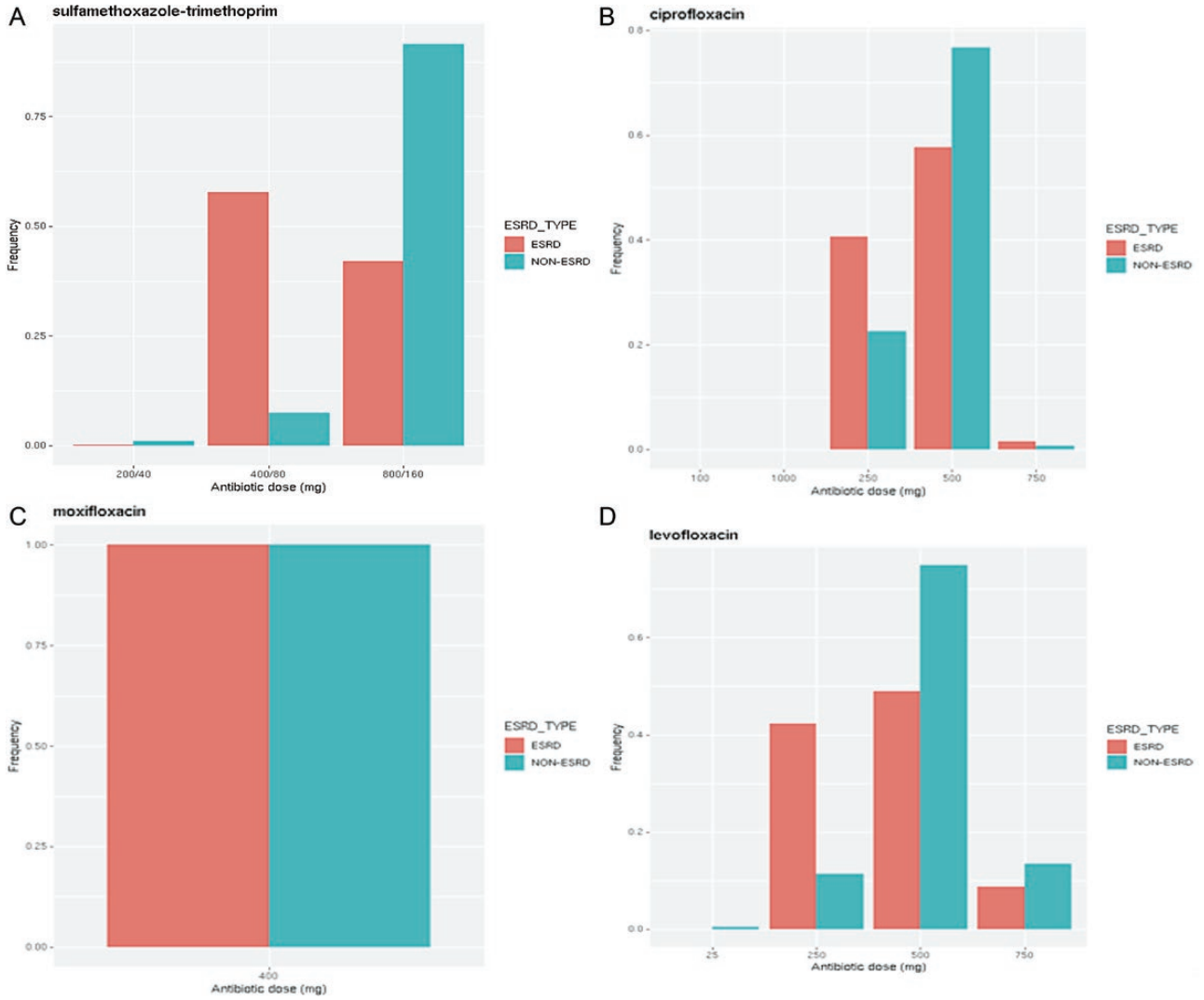

Figure 1. Range of dosages for trimethoprim-sulfamethoxazole (*A*) and the fluoroquinolone antibiotics ciprofloxacin (*B*), moxifloxacin (*C*), and levofloxacin (*D*). Abbreviation: ESRD, end-stage renal disease.

Table 4. Antibiotic Prescriptions From Small Dialysis Organization Providers Compared to Outside Providers and to End-Stage Renal Disease Data of the Centers for Medicare and Medicaid Services

Antibiotic	ESRD, % (n = 48 100)	SDO, % (n = 806)	OP, % (n = 821)	*P* Value (ESRD vs SDO)	*P* Value (SDO vs OP)
Azithromycin	12.71	38.09	10.35	<.001	<.001
Amoxicillin	8.27	13.90	12.67	<.001	.50
Ciprofloxacin	9.98	10.30	8.40	.8	.20
Cephalexin	9.29	7.69	9.01	.1	.40
Levofloxacin	11.32	6.58	10.35	<.001	.008
Amoxicillin-clavulanate	9.69	6.33	10.84	.002	.002
Cefuroxime	2.27	4.09	1.46	<.001	.002
TMP-SMX	10.38	3.47	13.52	<.001	<.001
Doxycycline	7.71	2.61	7.43	<.001	<.001
Clindamycin	4.20	2.48	3.53	.02	.30

Abbreviations: ESRD, end-stage renal disease; OP, outside provider; SDO, small dialysis organization; TMP-SMX, trimethoprim-sulfamethoxazole.

[20–22]. Recently, a prevalence study of IV antimicrobials in Pennsylvania revealed that almost 60% were inappropriately prescribed [23]. Few ESRD studies have focused specifically on oral antibiotics. Rather, emphasis has been on IV antibiotics [13] or IV combined with oral antibiotics; with the conclusion that up to 30% are prescribed inappropriately [7].

The greater use of oral antibiotics in ESRD may reflect the higher incidence of infection diagnoses compared to non-ESRD patients. Still, >50% of prescriptions were for absent indications, nonspecific symptoms, or viral illnesses (Table 3). Although high rates of prescriptions without a diagnosis have previously been demonstrated in the general public [12], the rate in the ESRD population was significantly higher compared to the general CMS population (32.4% vs 29.2%; $P < .001$). This higher rate is especially concerning due to the greater propensity toward antibiotic-associated infections in ESRD [5, 9–11].

The aforementioned findings along with longer antibiotic duration (11.8 vs 9.3 days), questionable selections and their dosing (TMP-SMX, nitrofurantoin), and questionable indications suggest possible inappropriate prescribing. At very least it reveals opportunities to improve antibiotic prescribing. For example, >20% of the antibiotics prescribed in ESRD patients were fluoroquinolones, which are renally cleared. They have been associated with hypoglycemia, QT interval prolongation, interaction with phosphate binders, and mental health side effects [14]—all being risks of particular consequence in ESRD.

In addition, antibiotic selection differed most notably in the greater frequency of TMP-SMX in the ESRD population, comprising >10% of prescriptions. TMP-SMX with its broad coverage is an attractive choice in unclear diagnoses such as fever of unknown origin and cellulitis. Its preference may be related to the increased skin infection diagnoses, possibly treating cutaneous access infections [14]. In fact, 17% of TMP-SMX was prescribed for skin infections, higher than any other infection. TMP-SMX is not recommended in creatinine clearances <15 mL/minute due to potential hyperkalemia [14, 24], and in 36% of prescriptions the dose was not halved as recommended for creatinine clearances of 15–30 mL/minute.

In the SDO sample, affiliated renal practitioners prescribed antibiotics as often as OPs, but significantly less TMP-SMX. This suggests that elevated TMP-SMX use seen statewide may originate from providers not routinely caring for ESRD patients. The comorbidity and dose adjustment challenges in prescribing for ESRD patients may explain differences in antibiotic selection between types of providers in the SDO sample. In support, a recent study found that inappropriate antibiotic dosing decreased when primary care physicians co-managed patients with nephrologists [25].

Diagnoses based on *ICD-10* codes may not accurately reflect the reasoning behind prescriptions and do not allow for relevant clinical details such as organism susceptibility patterns. Therefore, these prescription selections may be justified, but due to the nature of our data, assessing specific details is not possible. Other limitations include that our data are retrospective and pertain only to NYS and, specifically, those covered by CMS.

The current study highlights the need for effective antibiotic stewardship in ESRD with aims in reducing CDI rates as well MDROs. Resistant infections result in increased morbidity and mortality [26, 27] and contribute 2 billion dollars per year to ESRD costs [4, 5]. Benefits of such programs in hospitals include decreasing CDI rates [28] and reducing intensive care unit antimicrobial costs and consumption [29]. Inappropriate antibiotic was reduced by 20.5% in long-term care facilities and by 22%–36% in hospital settings [30]. In 2014 the Centers for Disease Control and Prevention recommended that all hospitals have antimicrobial stewardship programs.

There are no stewardship programs or clear designs to optimize antibiotic usage specifically for ESRD. Outpatient stewardship programs have used various mechanisms successfully in restraining antibiotic usage [31] and, therefore, potentially may be implemented in dialysis units. However, outpatient dialysis supports a specific population cared for by multiple general and specialized providers, adding to the complexity and difficulty of establishing such programs. It would necessitate an educational process involving renal personnel—medical directors, nephrologists, physician's assistants, nurse practitioners, technicians, and nurses—but also directed toward primary care, ED, and urgent care physicians. This is particularly significant, as physicians underestimate their level of inappropriate antibiotic use [32]. Importantly, the education process must include the patient, creating learned consumers who can question capricious antibiotic use and report it to renal providers. Programs will also need mechanisms of reporting and feedback. If implemented, based on a model analysis that assumed a 20% decrease in antibiotic prescribing, stewardship programs may lead to cost savings of up to $11 million annually, 4.6% reduction in mortality, and a 4.8% reduction in infections [5]. Being a modeled estimate derived from assumptions and probabilities, these findings have limitations [5].

In conclusion, the current study indicating increased antibiotic usage in ESRD suggests that there is a need for antibiotic stewardship aimed at ESRD patients and their providers. Timely detection of antibiotic usage would allow for appropriate antibiotic adjustments. Further research may evaluate implementation, feasibility, and effectiveness of an antibiotic stewardship intervention in decreasing overall antibiotic usage, improving antibiotic appropriateness, and decreasing morbidity.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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