Appropriateness of Gram-Negative Agent Use at a Tertiary Care Hospital in the Setting of Significant Antimicrobial Resistance

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Background. Practicing antimicrobial stewardship in the setting of widespread antimicrobial resistance among gram-negative bacilli, particularly in urban areas, is challenging.

Methods. We conducted a retrospective cross-sectional study at a tertiary care hospital with an established antimicrobial stewardship program in New York, New York to determine appropriateness of use of gram-negative antimicrobials and to identify factors associated with suboptimal antimicrobial use. Adult inpatients who received gram-negative agents on 2 dates, 1 June 2010 or 1 December 2010, were identified through pharmacy records. Clinical data were collected for each patient. Use of gram-negative agents was deemed optimal or suboptimal through chart review and according to hospital guidelines. Data were compared using χ^2 or Fischer's exact test for categorical variables and Student t test or Mann–Whitney U test for continuous variables.

Results. A total of 356 patients were included who received 422 gram-negative agents. Administration was deemed suboptimal in 26% of instances, with the most common reason being spectrum of activity too broad. In multivariable analysis, being in an intensive care unit (adjusted odds ratio [aOR], .49; 95% confidence interval [CI], .29–.84), having an infectious diseases consultation within the previous 7 days (aOR, .52; 95% CI, .28–.98), and having a history of multidrug-resistant gram-negative bacilli within the past year (aOR, .24; 95% CI, .09–.65) were associated with optimal gram-negative agent use. Beta-lactam/beta-lactamase inhibitor combination drug use (aOR, 2.6; 95% CI, 1.35–5.16) was associated with suboptimal use.

Conclusions. Gram-negative agents were used too broadly despite numerous antimicrobial stewardship program activities.

Keywords. antimicrobial agents; gram-negative bacteria.

Antimicrobial resistance is on the rise worldwide [1]. The emergence of resistance has been linked to extensive antimicrobial use, whereas a reversal in this trend has been documented through improved antimicrobial stewardship [2–4]. Hospitals are important targets for antimicrobial stewardship, given that rates of inappropriate use of antimicrobials in hospitals may be as high as 30%–50% and because many instances of drug resistance occur in hospitals [1, 5]. Antimicrobial resistance among gram-negative bacteria is particularly concerning [6]. Novel mechanisms of drug resistance continue to be identified among *Enterobacteriaceae*, whereas previously discovered resistant organisms such as *Klebsiella pneumoniae* carbapenemase (KPC)-producing organisms are on the rise [7–9]. The limited number of reserve antimicrobials currently available, coupled with stagnancy in the development of novel antimicrobials, poses a major challenge to clinicians and for public health [10, 11].

New York City has become an epicenter for multidrug-resistant (MDR) gram-negative bacilli (GNB), including KPC-producing *Enterobacteriaceae*. Practicing

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antimicrobial stewardship in this setting is challenging, because the need to provide active empiric antimicrobial coverage must be weighed against the need to conserve broad-spectrum antimicrobials. To balance these competing priorities, we have created institutional antimicrobial use guidelines based on local susceptibility data [12]. Our primary objective was to determine the appropriateness of use of gram-negative agents at a tertiary care hospital located in a setting of extensive antimicrobial resistance and that has implemented institutional antimicrobial use guidelines. We hypothesized that despite these guidelines, use of overly broad gram-negative antimicrobials would be among the most common reasons for suboptimal antimicrobial use given clinicians' concern for gram-negative resistance [13–15].

MATERIALS AND METHODS

Healthcare Setting
This retrospective study was performed at a 700-bed academic hospital in New York, New York on 2 snapshot dates, 1 June 2010 and 1 December 2010. The hospital provides care for adults only, and it has 8 intensive care units (ICUs) along with a large solid organ transplant population. Multidrug-resistant GNB are common, with 27% of inpatient *K. pneumoniae* isolates being carbapenem-resistant, compared with 10% nationally [11].

Our institution has an antimicrobial stewardship program (ASP) developed by infectious diseases (ID) physicians and pharmacists. Since 2000, the ASP includes formulary restriction, and certain antimicrobials require preprescription approval by a member of the ASP team (ID fellow, ID attending physician or ID pharmacist). In addition, hospital-specific antimicrobial use guidelines have been created based on local epidemiology and expert opinion, and they are available through the hospital intranet [12]. Since 2005, these guidelines have most often recommended piperacillin-tazobactam as the backbone for regimens to treat healthcare-associated GNB infections, and piperacillin-tazobactam does not require preprescription approval. Finally, targeted education about antimicrobial use, hospital-specific guidelines, and stewardship is conducted for housestaff at least annually.

This study was approved by the Institutional Review Board of Columbia University Medical Center with a waiver of informed consent.

Selection of Patients
Any adult inpatient who received a dose of an antimicrobial with gram-negative activity on one of the snapshot dates was included in the study. Patients were identified using pharmacy dispensing records. Gram-negative agents that required preprescription approval were as follows: amikacin, cefepime, ceftazidime, ciprofloxacin, imipenem, levofloxacin, meropenem, polymyxin B, ticarcillin-clavulanate, and tigecycline. Those that did not require preprescription approval were as follows:

ampicillin-sulbactam, aztreonam, cefpodoxime, ceftriaxone, gentamicin, piperacillin-tazobactam, and tobramycin.

Data Collection
Basic demographic and clinical information were collected on each patient, and data on study antimicrobials that were administered were also collected. Antimicrobial use was categorized as empiric (patient with evidence of infection without an identified source or with a localized infection but no conclusive microbiologic data), documented (patient with an infection and confirmatory microbiologic data), or prophylactic (patient without evidence of infection but on antimicrobials as a preventative measure). We also noted whether study patients had a history of MDR GNB within the past year. The definition of MDR GNB recognized by our clinicians is the definition used for contact precautions at our hospital and includes any GNB that is as follows: (1) nonsusceptible to carbapenems; (2) susceptible to 1 or fewer antimicrobials excluding polymyxin B and tigecycline; or (3) a probable carrier of extended-spectrum beta-lactamase, ie, *Escherichia coli*, *Klebsiella*, or *Proteus* with nonsusceptibility to ceftriaxone, or any other *Enterobacteriaceae* nonsusceptible to cefepime. Whether ID consultation was performed within the 7 days before the snapshot date was also recorded. All information was available through the hospital electronic medical record.

Appropriateness of Antimicrobial Use
Study antimicrobial use was determined to be "optimal" or "suboptimal" based on adherence to hospital antimicrobial use guidelines, along with available microbiologic data [12]. Hospital guidelines allow for departure from recommendations if a patient has a prior known history of antimicrobial-resistant organisms. Dosing had to be adjusted for renal and hepatic function, and known allergies had to be avoided. Any deviation from hospital guidelines, if not based on available microbiologic data, was deemed suboptimal and categorized as follows: (1) spectrum of activity too broad, (2) spectrum of activity too narrow, (3) no indication for antimicrobials, (4) duration of use too long, (5) incorrect route of administration, (6) incorrect dose, (7) incorrect frequency of administration, or (8) insufficient penetration to site of infection. In cases of dual or triple therapy with gram-negative agents, each antimicrobial was assessed individually.

The appropriateness of antimicrobial use for each patient included in the study was determined by an internal medicine resident physician, an ID attending physician, or an ID pharmacist, none of whom had been directly involved in the patient's care. Each person worked independently of each other to make an assessment, except when uncertainties arose, in which case the entire group reached a consensus. In addition, 20% of the charts reviewed by the internal medicine resident physician were audited at random by the ID physician or ID pharmacist to confirm accuracy and consistency of assessments.

Statistical Analysis

The primary objective, whether gram-negative agent use was optimal or not, was calculated as the proportion of antimicrobials used optimally of all antimicrobials evaluated. In addition, among suboptimal antimicrobials, the proportion due to overly broad use was evaluated. Patient and antimicrobial characteristics were compared between instances of optimal and suboptimal use. Comparisons were made using χ^2 or Fischer's exact test for categorical variables and the Student t test or Mann–Whitney U test for continuous variables. A P value < .05 was considered significant and all tests were 2-tailed. All variables with a P value <.1 on univariate comparisons were evaluated for inclusion into a multivariable logistic regression model to identify independent factors associated with suboptimal use. Statistical analyses were performed with PASW 18.0 (SPSS Inc., Chicago, Illinois).

RESULTS

A total of 356 patients received ≥1 gram-negative agent on the snapshot dates and were included. Baseline characteristics of all patients from both snapshot dates are shown in Table 1 (data were combined because there were no significant differences between the snapshot dates). Forty-seven percent of the patients had been hospitalized at least once within the 3 months preceding the snapshot date. Sixteen percent of patients had a positive culture for MDR GNB within the past year.

Between the 2 snapshot dates, 295 patients received monotherapy, 56 received dual therapy, and 5 received triple therapy with study antimicrobials. Beta-lactam/beta-lactamase inhibitor (BLBLI) drugs were the most frequently used antimicrobials (Table 2). The majority of antimicrobials were used as part of an empiric regimen (59%). Approximately one third of patients were in an ICU.

Twenty-six percent (n = 109) of study antimicrobials were deemed suboptimal; there was no significant difference in the rate of suboptimal use between the 2 dates. Reasons for suboptimal use are presented in Table 3. The most common reason an antimicrobial was considered suboptimal was that its spectrum was too broad for its intended purpose (44%). Of these instances of overly broad antimicrobials (n = 48), 69% were used for empiric treatment, 27% were used for documented infections, and 4% were used for prophylaxis. Piperacillin-tazobactam accounted for the large majority of these broad therapies (75%), followed by carbapenems (10%) and cefepime (8%). When considering the infection types, they were almost evenly split between genitourinary, intra-abdominal, and respiratory sources (29%, 29%, and 25%, respectively). Thirteen percent of these patients were in an ICU at the time of snapshot, 21% had been seen by an ID consult within the previous 7 days, and none had a history of a MDR GNB within the 1 year prior.

There were 166 instances in which piperacillin-tazobactam was used, 71 of which were deemed suboptimal (43%). Of the 36 instances in which piperacillin-tazobactam use was too broad, the majority (78%) were for empiric treatment.

Factors associated with suboptimal use are compared in Table 4. The use of BLBLI drugs was associated with suboptimal antimicrobial use, whereas almost all use of a third-generation cephalosporin was considered optimal. Being in an ICU location, having a history of a MDR GNB within the past year, having an ID consultation within the previous 7 days, and receiving an antimicrobial that required ID preprescription approval were associated with optimal use. Results of a multivariable analysis incorporating all of these variables are presented in Table 5. Being in an ICU at the time of snapshot, having an ID consultation within the previous 7 days, and having a history of MDR GNB within the past year were predictive of optimal use, whereas use of BLBLI drugs was predictive of suboptimal use.

Table 1. Characteristics of All Patients Receiving Gram-Negative Agents[a]

Variable	All Patients Receiving Gram-Negative Agents on Snapshot Dates (n = 356)
Snapshot date	
1 June 2010	170 (48)
1 December 2010	186 (52)
Age, median in years (IQR)	63 (52–75)
Male gender	201 (56)
Underlying Conditions	
Cardiac disease	161 (45)
Pulmonary disease	73 (21)
Chronic renal insufficiency	68 (19)
Dialysis	13 (4)
Cirrhosis	30 (8)
Liquid malignancy	19 (5)
Solid malignancy	66 (19)
Diabetes	90 (25)
Solid organ transplant	52 (15)
Human immunodeficiency virus	20 (6)
Home steroids	57 (16)
Immunosuppressive medications	78 (22)
Primary hospital service	
Medicine	221 (62)
Surgery	92 (26)
Neurology	21 (6)
Neurosurgery	15 (4)
Other	7 (2)
Length of hospital stay to snapshot date, median in days (IQR)	9 (5–19)
ICU care during hospitalization	137 (38)
Previous hospitalization within past 3 months	167 (47)
History of MDR GNB within past year	57 (16)

Abbreviations: GNB, gram-negative bacilli; ICU, intensive care unit; IQR, interquartile range; MDR, multidrug-resistant.

[a] Data presented as n (%) unless otherwise specified.

Table 2. Details of Antimicrobial Therapies Evaluated[a]

Variable	All Antimicrobials (n = 422)
Antimicrobial category	
BLBLI	189 (45)
Third-generation cephalosporins	44 (10)
Cefepime	38 (9)
Aztreonam	7 (2)
Carbapenems	39 (9)
Aminoglycosides	41 (10)
Quinolones	44 (10)
Polymyxin B	15 (4)
Tigecycline	5 (1)
Type of treatment	
Empiric	249 (59)
Documented	159 (38)
Prophylaxis	14 (3)
Infection type targeted by antimicrobial	
Bacteremia	17 (4)
Bone/joint	9 (2)
Central nervous system	14 (3)
Endocarditis	3 (1)
Genitourinary	64 (15)
Intra-abdominal	74 (18)
Respiratory	187 (44)
Sepsis	13 (3)
Skin/soft tissue	39 (9)
Other	2 (1)
ICU location on snapshot day	145 (34)
ID consultation within previous 7 days	133 (32)
Median days of therapy before snapshot (IQR)	4 (2–8)

Abbreviations: BLBLI, beta-lactam/beta-lactamase inhibitor; ICU, intensive care unit; ID, infectious diseases; IQR, interquartile range.

[a] Data presented as n (%) unless otherwise specified.

Table 3. Reasons Use of Gram-Negative Agents Were Deemed Suboptimal[a]

Reason	Number of Instances of Suboptimal use (n = 109)
Spectrum of activity too broad	48 (44)
Spectrum of activity too narrow	18 (17)
No indication for use	18 (17)
Duration of use too long	3 (3)
Incorrect route of administration	1 (1)
Incorrect dose	6 (6)
Incorrect frequency of administration	15 (14)

[a] Data presented as n (%).

DISCUSSION

The main objective of this study was to determine the appropriateness of gram-negative agent use at a tertiary care hospital in an area of high prevalence of GNB antimicrobial resistance. To our knowledge, few recent studies have assessed antimicrobial appropriateness in the setting of such a high degree of MDR GNB. Despite numerous ASP activities including preprescription approval, easily accessible guidelines and educational efforts, over the 2 time points evaluated, we found that 26% of the antimicrobials administered were used suboptimally. This rate of suboptimal use is in the range described in previous studies, highlighting the ongoing need for enhanced antimicrobial stewardship in hospitals [16, 17].

The most frequent reason antimicrobial use was deemed suboptimal was due to the spectrum of activity being too broad for its intended purpose. It is likely that the significant prevalence of MDR GNB in our healthcare setting predisposes clinicians to assume that most infections should be covered broadly, even when not recommended by hospital guidelines. Nearly one third of instances in which unnecessarily broad-spectrum antimicrobials were used occurred despite having microbiology data available. Only 3% of suboptimal use was due to the duration being too long, which might reflect the emphasis in our ASP outreach efforts on discontinuing antibiotics after an appropriate duration of therapy. Studies performed at other institutions reveal variability in the top reasons identified for suboptimal antimicrobial use, with some identifying overly broad antimicrobials, too long a duration, or no indication for use as the major reasons for suboptimal use [17–19]. Differences in the common reasons for suboptimal antimicrobial use between these studies might reflect differences in microbial ecology, patient populations, study methodologies, or stewardship practices.

We were not surprised to find that use of BLBLI drugs, particularly piperacillin-tazobactam, was significantly associated with suboptimal use. Piperacillin-tazobactam is not restricted at our institution; given its broad spectrum of coverage and easy availability, it is often a first-line antimicrobial choice, and we found that it was used suboptimally more frequently than any other agent. Moreover, most of the instances in which its use was suboptimal were because its spectrum was overly broad for the situation. Other studies have also identified piperacillin-tazobactam as a drug commonly used suboptimally [18, 20]. Institutions in which this drug is restricted have found its use appropriate, so some type of restriction is likely to be beneficial [5]. In contrast, we found that quinolones, a restricted class of drugs at our institution and often a center point for stewardship education, were not associated with suboptimal antimicrobial use. However, other studies in which quinolone use was more common have identified these drugs as a risk factor for suboptimal antimicrobial use [5, 21]. This suggests that our ASP activities focused on limiting quinolone use have borne fruit, and we plan to explore the utility of implementing a 72-hour automatic stop order for piperacillin-tazobactam, in which

Table 4. Comparison of Characteristics Associated With Suboptimal Use of Gram-Negative Agents[a]

Characteristic	Suboptimal Use (n = 109)	Optimal Use (n = 313)	P Value
Median days of hospital stay before snapshot (IQR)	8 (5–16)	10 (5–23)	.008
Median days of therapy before snapshot (IQR)	4 (2–6)	4 (2–8)	.17
ICU location on snapshot day	24 (22)	121 (39)	.002
ID consultation within previous 7 days	17 (16)	116 (37)	<.001
Previous hospitalization within past 3 months	45 (41)	162 (52)	.076
History of MDR GNB within past year	5 (5)	78 (25)	<.001
Empiric treatment	80 (73)	169 (54)	.001
Documented treatment	25 (23)	134 (43)	<.001
Genitourinary infection	22 (20)	42 (13)	.123
Intra-abdominal infection	25 (23)	49 (16)	.115
Respiratory tract infection	49 (45)	138 (44)	.964
Surgery service	25 (23)	83 (27)	.541
Medicine service	70 (64)	193 (62)	.719
Antimicrobial requires ID preprescription approval	21 (19)	124 (40)	<.001
Antimicrobial category			
BLBLI	74 (68)	115 (37)	<.001
Third-generation cephalosporins	4 (4)	40 (13)	.006
Cefepime	7 (6)	31 (10)	.368
Aztreonam	1 (1)	6 (2)	.683
Carbapenems	6 (6)	33 (11)	.17
Aminoglycosides	9 (8)	32 (10)	.682
Quinolones	7 (6)	37 (12)	.16
Polymyxin B	1 (1)	14 (5)	.130
Tigecycline	0 (0)	5 (2)	.334

Abbreviations: BLBLI, beta-lactam/beta-lactamase inhibitor; GNB, gram-negative bacilli; ICU, intensive care unit; ID, infectious diseases; IQR, interquartile range; MDR, multidrug-resistant.

[a] Data presented as n (%) unless otherwise specified.

Table 5. Independent Factors Associated With Suboptimal Use of Gram-Negative Agents

Variable	Adjusted Odds Ratio	95% Confidence Interval	P Value
ICU location on snapshot day	.49	.29–.84	.01
ID consultation within previous 7 days	.52	.28–.98	.044
History of MDR GNB within past year	.24	.09–.65	.005
Empiric treatment	1.36	.79–2.35	.275
Antimicrobial requires ID preprescription approval	1.42	.65–3.08	.381
BLBLI	2.64	1.35–5.16	.004

Abbreviations: BLBLI, beta-lactam/beta-lactamase inhibitor; GNB, gram-negative bacilli; ICU, intensive care unit; ID, infectious diseases; MDR, multidrug-resistant.

continued use beyond 72 hours would require approval from an ID physician or pharmacist.

These data have important implications for antimicrobial stewardship efforts. They confirm the importance of prescription approval, because suboptimal use was more often associated with unrestricted antimicrobials such as piperacillin-tazobactam and less often associated with restricted antimicrobials such as quinolones. Our study further confirms the importance of de-escalation strategies for ASPs, particularly with respect to narrowing antimicrobial therapy through postprescription review, which is not currently performed routinely at our institution [22, 23]. Although de-escalation and postprescription review have been touted as key components of ASPs in general, our data suggest that de-escalation activities may be particularly crucial in settings such as ours, where the high prevalence of antimicrobial resistance frequently requires empiric use of broad-spectrum antimicrobials. Our findings are specific to our institution, and although they may be applicable to other academic medical centers with high prevalence of MDR GNB, it is also important for these institutions to specifically evaluate their own antimicrobial use and provide feedback to clinicians. Furthermore, in addition to the traditional methods for promoting antimicrobial stewardship that have been outlined through published guidelines, healthcare information technology might also prove to be an increasingly useful ally for promoting antimicrobial stewardship. In the future, we will explore methods to better utilize the electronic medical record system at our own institution to engage clinicians in antimicrobial stewardship efforts, such as postprescription review [24].

Twenty percent of the instances of suboptimal antimicrobial use were due to incorrect administration of antimicrobials, such as incorrect dosage, route of administration, or frequency of administration. This finding emphasizes the importance of education for improving prescribing practices [25]. That said, correct administration of antimicrobials can be challenging in settings of substantial antimicrobial resistance given the higher minimum inhibitory concentrations that are observed, and our retrospective evaluation may have overcalled the higher dosing used as suboptimal. Other strategies to consider are to raise awareness about institutional guidelines for empiric antimicrobial use [12].

Being in an ICU and having a history of a MDR GNB were significantly associated with optimal antimicrobial use. The association between being in an ICU and appropriate antimicrobial use has been previously reported in adults, although the

association might not apply to pediatric ICUs where use has been reported as inappropriate for some antimicrobials [18, 21]. To our knowledge, few studies have evaluated a prior history of MDR GNB when evaluating appropriate antimicrobial use; our data suggest that knowing this prior history is important in tailoring antimicrobial use for subsequent infections. It seems that our ASP efforts around educating clinicians to look in the medical record for this information are beneficial, and this is a practice that other institutions can consider implementing. Finally, as would be hoped, having had an ID consultation was associated with optimal antimicrobial use. This has been investigated in prior studies, and the available evidence is conflicting on this issue with some studies showing an association between ID consultation and appropriateness and others failing to demonstrate such a relation [18, 26, 27]. One possible explanation for the latter is due to a selection bias in which ID consults are requested for more severely ill patients, making treatment decisions more complicated and prone to disagreement between clinicians [18, 28].

There are several limitations to this study. This is a single-center study, which limits generalizability to other settings. That said, it highlights some of the reasons that have been identified in other investigations that contribute to suboptimal antimicrobial use. Furthermore, the retrospective nature of this study can lead to error, particularly with regards to judging clinical decisions that were already made. The ability to evaluate the appropriateness of antimicrobial choice when used for empiric treatment of critically ill patients is especially challenging given the need to cover a broad range of pathogens in this precarious setting, and what we considered a suboptimal choice due to use of an overly broad antimicrobial might be an overestimate. Finally, we did not evaluate whether antimicrobials used empirically were effective for the organisms that eventually grew from culture or how clinical outcomes differed depending on whether antimicrobial use was optimal versus suboptimal.

Despite these limitations, this study provides useful insight into patterns of antimicrobial use and helps to target areas for improvement. Given that MDR GNB infections will likely increase for the foreseeable future and will drive use of broad-spectrum antimicrobials, ASP activities will become increasingly important [6, 29].

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