The Culture of Carbapenem Overconsumption: Where Does It Begin? Results of a Single-Center Survey

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Abstract

Purpose: The United States has seen an increased consumption of carbapenem antibiotics in recent years. The increased utilization of these agents has potential negative consequences, including the increasing incidence of carbapenem-resistant Enterobacteriaceae. Reasons for the rise in carbapenem use among providers in acute care hospitals are not well elucidated in literature. The objectives of this study were to identify factors that influence empiric carbapenem use among providers in a single academic medical center, and to assess therapeutic knowledge pertaining to carbapenem use. **Methods:** A cross-sectional, single-center, 9-item electronic research survey was developed independently and validated by an infectious diseases pharmacist and infectious diseases physician. The survey was distributed to email accounts of providers at a single academic medical center. Demographic data, factors affecting carbapenem prescription, and baseline therapeutic knowledge were assessed. **Results:** Ninety-five of 416 providers responded to the survey (response rate of 22.8%). Respondents were well distributed across all levels of training with primary roles in internal medicine and surgery. The most important factors influencing empiric carbapenem use were suspected pathogens at the site of infection, drug allergies, history of multidrug resistant organisms, severity of illness, type of infection, and local resistance rates. A recommendation from a pharmacist was selected as the most likely factor for deterring carbapenem use. Misconceptions pertaining to penicillin drug allergy and beta-lactam cross reactivity, knowledge of local resistance rates according to the institutional antibiogram, and comparative efficacy data for carbapenems were apparent across all levels of training. **Conclusions:** Provider misconceptions regarding several factors appear to contribute to unnecessary use of carbapenems. An opportunity exists for hospital pharmacists to improve the prescribing patterns of carbapenems by correcting provider misconceptions through education.

Keywords

anti-infectives, physician prescribing, infectious diseases, pharmacists

Introduction

Carbapenems are a critically important class of antibiotics in our current armamentarium for treating severe infections, particularly those caused by multidrug resistant (MDR) Gram-negative bacteria.¹ The use of these agents continues to increase throughout the United States, with an estimated 37% increase in use in acute care hospitals in recent years.² Alarming, the increased consumption of carbapenems has been identified as a driving force for the rising incidence of carbapenem-resistant Enterobacteriaceae,³ and in the majority of cases, the empiric use of these agents is not warranted.⁴ Factors that affect carbapenem use among providers in acute care hospitals are not well elucidated. The objective of this study was to identify factors that influence empiric carbapenem use among providers of a single academic medical center. In addition, we sought to identify knowledge deficits pertaining to allergic cross reactivity between beta-lactam agents, institutional resistance patterns, and comparative efficacy between carbapenems and other agents.

Methods

Study Design and Setting

We conducted a cross-sectional, single-center, 9-item electronic research survey at a 472-bed academic medical center with designations in stroke, trauma, and burn care. The medical center has 5 intensive care units (ICUs), a variety of consulting services, and 24-hour pharmacy services. Pharmacy residents round daily with 2 of the 10 medicine services at our institution, and a trained clinical pharmacist with or without a pharmacy resident rounds with 1 of the 2

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medical ICU services and the surgical ICU service. Decentralized staff pharmacists are positioned throughout the hospital and interact with the teams on an as-needed basis. This study was granted exemption from institutional review board review.

Current Antimicrobial Stewardship Initiatives

Antimicrobial prescription is regulated by an interdisciplinary antimicrobial stewardship team as well as an antimicrobial stewardship and restriction policy. Current policies in place include antibiotic “time outs,” prior authorization, and prospective audit and feedback. Our formulary carbapenem agents are meropenem and ertapenem, and these agents are subject to prior authorization, whereby when ordered for a patient, a single dose will be released by pharmacy pending infectious diseases antimicrobial stewardship team approval (ID approval) if the order does not meet a prespecified approved indication. An infectious diseases–trained pharmacist meets daily Monday through Friday with the infectious diseases attending physician and fellow to discuss patients meeting stewardship criteria, and the pharmacist communicates the antimicrobial stewardship recommendations to the teams. Other antimicrobial stewardship interventions are made by decentralized pharmacists according to institutional guidelines. No formalized institution-wide education has been provided on behalf of the antimicrobial stewardship team to date at our institution.

Survey Development, Distribution, and Domains Assessed

The survey was created by a single investigator and independently validated by an infectious diseases pharmacist and infectious diseases physician to ensure that questions were suitable to answer the study objectives. The survey was divided into 3 domains, including (1) provider demographics, (2) relative importance of various factors on the decision to prescribe a carbapenem empirically, and (3) baseline therapeutic knowledge. The survey was distributed to providers via email on October 30, 2017. A reminder email was distributed 1 week following the initial email, and the survey remained open for a total of 2 weeks. A full copy of the survey is available in the Supplementary Appendix.

Demographic data collected included current year of postgraduate training, practice area, percentage of time caring for patients in an ICU, and self-reported average number of patients treated weekly with a carbapenem. A Likert-type scale of 1 to 5 (1 being *least important*; 5 being *most important*) was used in the assessment of factors influencing empiric carbapenem prescription. These factors included type of infection, severity of illness, suspected pathogens at the site of infection, institutional resistance rates, history of MDR organisms, immune status of the patient,

drug penetration at site of infection, drug allergies, attending physician preference, cost of medication, and dosing frequency. A Likert-type scale of 1 to 5 (1 being *least likely*; 5 being *most likely*) was used in the assessment of factors deterring empiric carbapenem use. These items included alternative recommendation by pharmacists, need for ID approval, spectrum of activity being too broad for given indication, risk for antibiotic resistance development, and presence of drug-drug interactions.

Multiple-choice questions were utilized to assess provider knowledge of penicillin drug allergy and beta-lactam cross reactivity rates, resistance rates according to the institutional antibiogram, and evidence regarding treatment of infections caused by extended-spectrum beta-lactamase (ESBL)–producing Enterobacteriaceae.

Statistical Methods

Descriptive statistics were performed using Microsoft Excel (Microsoft, Redmond, Washington). Likert-type scale responses are reported using the weighted average score ranging from 1 to 5 as previously described. Multiple-choice answers were stratified both by level of training and by the cohort as a whole and are reported as percentages. A discrimination index was calculated for multiple-choice questions to evaluate whether questions were suitable to differentiate between respondents who were knowledgeable on subject matter and those who were not.

Results

The survey was distributed to 416 active provider email accounts and achieved an overall response rate of 22.8% ($n = 95$). The average time for respondents to complete the survey was 3 minutes. Provider demographics are reported in Table 1. Overall, respondents were well distributed across all levels of training ranging from postgraduate year 1 through attending physician with primary roles in internal medicine and surgery. The majority ($n = 71$; 74.7%) of respondents reported that 25% or less of their duty hours were in an ICU setting.

The importance of various factors influencing empiric carbapenem prescription is shown in Figure 1a. Providers who responded to the survey identified that suspected pathogens at the site of infection, presence of drug allergies, history of MDR organisms, severity of illness, type of infection, and local resistance rates were the factors bearing the largest impact on the empiric use of carbapenems. The likelihood of various factors deterring empiric carbapenem use based on provider opinion is shown in Figure 1b. Providers viewed alternative recommendations provided by pharmacists as the most likely factor for using an alternative agent, followed by the presence of drug-drug interactions, spectrum of activity being too broad, concern for the risk of antibiotic resistance development, and need for ID approval.

Table 1. Demographics of Survey Respondents.

Demographics	n (%)
Level of training	
PGY-1	17 (17.9)
PGY-2	26 (27.4)
PGY-3	19 (20.0)
PGY-4, PGY-5, or fellow	14 (14.7)
Attending physician	19 (20.0)
Practice area(s)	
Internal medicine	68 (71.6)
General surgery	14 (14.7)
Emergency medicine	9 (9.5)
Orthopedic	2 (2.1)
Infectious diseases	2 (2.1)
Neurology	1 (1.1)
Pulmonary critical care	1 (1.1)
Physical medicine and rehabilitation	1 (1.1)
Time caring for patients in ICU	
0%	14 (14.7)
1%-25%	57 (60.0)
26%-50%	18 (18.9)
51%-75%	3 (3.2)
76%-100%	3 (3.2)
Average weekly use of carbapenems	
0 patients	44 (46.3)
1-5 patients	46 (48.4)
6-10 patients	5 (5.3)

Note. Respondents were permitted to select multiple practice areas. PGY = postgraduate year; ICU = intensive care unit.

Answers to multiple-choice questions assessing baseline therapeutic knowledge are shown in Table 2. In assessing provider knowledge of penicillin allergy and beta-lactam cross reactivity, 51.5% of providers correctly selected that carbapenems and advanced-generation cephalosporins have similar and low (ie, $\leq 1\%$) rates of cross reactivity.^{5,6} Based on these responses, approximately one-third of providers favored the use of carbapenems over other beta-lactams in the setting of a penicillin allergy.

According to the institutional antibiogram, susceptibility rates of *Pseudomonas aeruginosa* to cefepime, piperacillin-tazobactam, and meropenem are 94%, 87%, and 85%, respectively. Aztreonam susceptibilities are not routinely performed. The institutional antibiogram is widely accessible through the electronic medical record. Overall, 29.5% of respondents correctly identified cefepime as the drug with the highest percentage of susceptible *P aeruginosa* isolates at our institution. Nearly one-fifth (18.9%) of providers selected meropenem as having the greatest susceptibility rate for *P aeruginosa*, which is incorrect based on the institutional antibiogram.

Finally, familiarity with comparative efficacy data between carbapenems and beta-lactam/beta-lactamase

inhibitors (BLBLIs) for the treatment of bacteremia due to ESBL-producing Enterobacteriaceae from low inoculum sources of infection was assessed. Although carbapenems remain the mainstay of treatment for severe ESBL infections, recent literature suggests similar outcomes when BLBLIs are utilized for the treatment of bacteremia due to ESBL-producing Enterobacteriaceae from low inoculum sources of infection.⁷ However, more than half (52.6%) of providers considered carbapenems to be superior to piperacillin-tazobactam in this setting. Knowledge deficits in each of these 3 areas were apparent across all levels of training. The discrimination index for multiple-choice questions 1, 2, and 3 were 0.57, 0.37, and 0.44, respectively, indicating a reasonably good to very good discrimination index for each question.⁸

Discussion

This is the first study we are aware of investigating factors that influence empiric carbapenem prescribing in acute care hospitals. This study not only illustrates the factors considered most important to providers when prescribing carbapenems empirically but also highlights misconceptions stemming from knowledge deficits that may lead to unnecessary prescribing. A previous systematic review evaluating antibiotic prescribing in long-term care facilities (LTCFs) identified that misconceptions and knowledge deficits among providers played a significant role in antibiotic prescribing.⁹ However, this study was specific to the LTCF context and not specific for factors influencing carbapenem use, and thus, may not be generalizable as such.

At our institution, providers indicated that the factor most strongly influencing their decision to prescribe a carbapenem empirically was the suspected pathogens at the site of infection. Because it was not directly assessed, we cannot draw conclusions as to which pathogens providers are targeting when choosing to prescribe carbapenems empirically. However, it is logical to assume that a carbapenem would be employed in scenarios where MDR bacteria including *P aeruginosa* and ESBL-producing Enterobacteriaceae are suspected, and knowledge pertaining to empiric coverage and treatment of these pathogens was objectively assessed by the survey.

A significant proportion of providers did not correctly identify the antimicrobial agent providing the greatest likelihood of susceptibility for *P aeruginosa* at our institution. Nearly 1 out of every 5 providers chose meropenem as the agent with greatest susceptibility rate for *P aeruginosa* despite having poorer susceptibility rates compared with cefepime and piperacillin-tazobactam. This suggests an unjustified preference for carbapenems among these providers, presumably based on the perception that carbapenems possess greater broad-spectrum activity or because providers may be unfamiliar with how to access or interpret the institutional antibiogram. In addition, more than half of respondents appeared to be unfamiliar with

Figure 1. Factors influencing and deterring carbapenem use among providers.

Note. Figure 1a represents factors influencing carbapenem prescription in order of most important to least important. Figure 1b represents factors deterring carbapenem use in order of most likely to least likely. MDR = multidrug resistant; rec. = recommendation; ID = infectious disease service.

Table 2. Multiple-Choice Survey Questions and Answers.

Answer choice	PGY-1	PGY-2	PGY-3	PGY-4, 5, or fellow	Attending physician	Overall
Question 1. Which of the following statements is correct regarding penicillin drug allergy and beta-lactam cross reactivity?						
All carbapenems and cephalosporins have similar rates of cross reactivity	17.0%	11.5%	5.4%	35.7%	15.8%	17.0%
<i>Carbapenems and advanced-generation cephalosporins have low (i.e. ≤1%) rates of cross reactivity</i>	<i>51.1%</i>	<i>53.9%</i>	<i>66.7%</i>	<i>35.7%</i>	<i>52.6%</i>	<i>51.1%</i>
Carbapenems do not pose a risk for cross reactivity	9.6%	7.7%	5.6%	7.2%	10.5%	9.6%
Carbapenems have a lower likelihood of cross reactivity than cefepime	22.3%	26.9%	22.3%	21.4%	21.1%	22.3%
Question 2. Based on the institutional antibiogram, which of the following antibiotics is <i>P aeruginosa</i> most likely to be susceptible to?						
Piperacillin-tazobactam	47.4%	42.3%	47.4%	50.0%	42.1%	47.4%
Cefepime	29.5%	23.1%	36.8%	42.9%	36.8%	29.5%
Aztreonam	4.2%	3.9%	5.3%	0.0%	5.3%	4.2%
Meropenem	18.9%	30.7%	10.5%	7.1%	15.8%	18.9%
Question 3. True or false. Beta-lactam/beta-lactamase inhibitors (i.e. piperacillin-tazobactam) are inferior to carbapenems to treat bloodstream infections caused by ESBL-producing Enterobacteriaceae from low inoculum sources of infection (i.e. urinary, biliary).						
<i>True</i>	<i>52.6%</i>	<i>57.7%</i>	<i>52.6%</i>	<i>64.3%</i>	<i>36.8%</i>	<i>52.6%</i>
<i>False</i>	<i>47.4%</i>	<i>42.3%</i>	<i>47.4%</i>	<i>35.7%</i>	<i>63.2%</i>	<i>47.4%</i>

Note. Correct responses for each question denoted by italicized font. PGY = postgraduate year; ESBL = extended-spectrum beta-lactamase.

evidence supporting the use of BLBLIs in the treatment of infections caused by ESBL-producing Enterobacteriaceae, despite evidence showing BLBLIs to be an equally efficacious, carbapenem-sparing option for the treatment of these infections in certain scenarios.⁷ Based on these results, providers may have an underappreciation of the value of local susceptibility rates when choosing to use a carbapenem, and misconceptions in both of these areas may contribute to carbapenem overutilization.

Another finding of this survey is that despite the presence of drug allergies being identified as one of the most important factors considered when prescribing a carbapenem, only about half of respondents selected that there is an equal (albeit low) likelihood for patients with a history of an immediate hypersensitivity reaction to penicillin to also have an allergic reaction to a carbapenem or advanced-generation cephalosporin. Nearly one-quarter of respondents suggested that carbapenems pose a lower risk of cross reactivity than

cefepime, and nearly 10% suggested no risk of cross reactivity with carbapenems at all. The presence of penicillin allergy has been shown to be a significant contributor to carbapenem use,¹⁰ and misconceptions about the potential for cross reactivity appear to result in carbapenems being prescribed when cephalosporins are a viable alternative at our institution. An opportunity exists for hospital pharmacists to address this misconception through provider education and clarification of penicillin drug allergies.

Hospital pharmacists play a unique role in antimicrobial stewardship programs (ASPs) and have been shown to be effective in improving antimicrobial utilization.¹¹ Because of the potential negative consequences of carbapenem overconsumption, these agents are often targeted by ASPs to limit their overutilization. Encouragingly, we found that recommendations from pharmacists to use an alternative agent had the greatest likelihood of deterring the empiric use of carbapenems, and indicates that hospital pharmacists may be a key resource to reduce unnecessary carbapenem use. Given this finding, we plan to provide institution-wide education in conjunction with the antimicrobial stewardship team to address misconceptions identified in this survey. Education for providers will be in the format of a 1-time educational handout and 5-item quiz made available through the institution's Blackboard Learn (Blackboard, Washington, DC) subscription. Similarly, a pharmacy-specific education will be made available to reinforce concepts covered by the survey and instances in which patient-specific interventions are warranted to curb unnecessary carbapenem prescribing according to institutional guidelines.

This study is not without limitations. Due to the response rate of 22.8%, a significant risk of nonresponse bias may be introduced into the results. However, web-based surveys of health care providers often yield response rates of <20%.¹² As such, the response rate yielded by this study is unlikely to affect internal validity, but generalizability to other contexts may be affected. In addition, this survey was single-centered in nature, which may also contribute to lack of generalizability to other contexts, including other health care delivery systems and geographic areas with higher rates of MDR organisms. As such, we encourage other institutions to perform similar assessments of carbapenem use to identify specific areas for pharmacist intervention and education at their respective institutions.

In conclusion, a variety of factors appears to influence provider decisions to prescribe carbapenems empirically. Provider misconceptions regarding several factors appear to contribute to unnecessary use of carbapenems. Recommendations from pharmacists to use alternative antibiotics, however, may be a valuable deterrent to using carbapenems inappropriately. An opportunity exists for hospital pharmacists to improve the prescribing patterns of carbapenems by correcting provider misconceptions through education, and providing patient-specific recommendations for alternative agents when appropriate.

Authors' Note

Preliminary results of these materials have been presented in poster format at the Vizient University Health System Consortium Pharmacy Network Meeting Resident Poster Session in Orlando, Florida, on December 2, 2017.

Declaration of Conflicting Interests

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