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Evaluation of the potential impact of a carbapenem de-escalation program in an academic healthcare system

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Summary The primary objective of this analysis was to evaluate group 2 carbapenem usage and to model the impact that a formalized de-escalation protocol to ertapenem could potentially have on group 2 carbapenem usage in the hope of alleviating the selective pressure on *Acinetobacter* and *Pseudomonas*. This analysis was conducted in three hospitals within the Detroit Medical Center in 2009. Patients were considered candidates for de-escalation of carbapenem therapy when a group 2 carbapenem was utilized to treat Enterobacteriaceae, such as extended spectrum β-lactamase (ESBL)-producing organisms, or if cultures were negative in non-intensive care unit (ICU) patients. In total, 179 patients (28%) and 1074 patient-days (29%) were deemed eligible for de-escalation according to our pre-defined criteria. We concluded that preferential utilization of ertapenem in appropriate patients warranting carbapenem therapy has the potential to significantly decrease group 2 carbapenem usage at our institution.

Introduction

Resistance to group 2 carbapenems, such as meropenem, imipenem, and doripenem, among *Acinetobacter baumannii* and *Pseudomonas aeruginosa* poses a significant therapeutic

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challenge. Often, the only remaining therapeutic options are tigecycline (for *Acinetobacter* and not *Pseudomonas*) or colistin-based regimens, which are associated with suboptimal outcomes and high rates of toxicity [1—3]. Ertapenem is a group 1 carbapenem that retains good *in vitro* activity against Enterobacteriaceae, including extended spectrum β-lactamase-producers (ESBLs) and ampC hyperproducers [4], but has no appreciable activity against *A. baumannii* or *P. aeruginosa*. Because of this lack of activity against non-lactose-fermenting Gram-negative organisms, there is a potential benefit, in terms of antimicrobial resistance, of using ertapenem in place of group 2 carbapenems to reduce the selective antimicrobial pressure. Recent studies have reported that the susceptibility of *P. aeruginosa* to imipenem remained stable [5—7] and, in some cases, even improved [8] after the introduction of ertapenem into hospital formularies. However, it is important to note that direct causality between ertapenem introduction and the improved susceptibilities in *P. aeruginosa* should not be assumed, as increases or decreases in susceptibility are multifactorial. Despite this caveat, evidence suggests that, at the very least, introduction of ertapenem does not negatively affect imipenem susceptibility in *P. aeruginosa*.

The aims of this study were to analyze the utilization of group 2 carbapenems in a large tertiary healthcare system to identify patients in whom de-escalation from group 2 carbapenem to ertapenem would have been appropriate and to model the potential impact of a formalized carbapenem de-escalation program on carbapenem utilization.

Materials and methods

A retrospective analysis of all carbapenem use at three hospitals within the Detroit Medical Center (DMC) in 2009 was performed. The DMC is a university-affiliated eight-hospital tertiary healthcare system with more than 2200 inpatient beds in metropolitan Detroit. For the purposes of these analyses, only patients at Detroit Receiving Hospital, Harper University Hospital, and Sinai-Grace Hospital were included. These three hospitals have a total of 1180 beds. The pharmacy database was queried to identify all patients at these institutions who received any carbapenem in the 2009 calendar year. The medical records for these patients were then accessed, and a standardized data collection form was utilized to extract the patient demographics, comorbid conditions, intensive care unit (ICU) status, relevant laboratory values, indications for carbapenem therapy, microbiological results, and the doses and durations of therapy.

The charts of the patients who received group 2 carbapenems were analyzed to determine whether de-escalation to ertapenem therapy would have been appropriate. De-escalation was considered appropriate if the patient was receiving therapy for infections due to an ESBL, an ampC-producing organism, or other carbapenem-susceptible Enterobacteriaceae or if the culture was negative and the patient continued to receive therapy; additionally, the patient had to be located on the general medical floor. Patients were deemed ineligible for de-escalation to ertapenem if *P. aeruginosa*, *A. baumannii*, or penicillin-susceptible *Enterococcus* spp. were recovered, if the cultures were negative and they resided in the ICU (as many clinicians desire activity against *P. aeruginosa* in an ICU setting even if cultures are negative) if they received carbapenem therapy for $\leq$72 h following culture, or if the patient had cystic fibrosis, central nervous system infection, febrile neutropenia, osteomyelitis, or infection due to *Nocardia* spp. If patients met the eligibility criteria for de-escalation to ertapenem, the initial 72 h of group 2 carbapenem therapy after culture were considered appropriate, as cultures are often finalized after 72 h.

Analysis was performed to assess the impact that a carbapenem de-escalation program would have on the amounts of group 2 carbapenem and ertapenem utilized during the study period.

Results

Carbapenem utilization

A total of 557 patients received meropenem during the study period, accounting for 3601 patient-days of therapy. Imipenem was used in 42 patients for a total of 223 patient-days, while ertapenem was utilized in 156 patients for 829 patient-days of therapy.

Analysis of group 2 carbapenem usage

Tables 1 and 2 show detailed breakdowns of the group 2 carbapenem usage and cases where de-escalation to ertapenem would have been appropriate (n = 1074 patient-days, 28% of total usage) or inappropriate (n = 2232 patient-days, 58% of total usage). For patients in whom de-escalation therapy would have been appropriate, the first 72 h of the group 2 carbapenem therapy after culture was considered appropriate, and this time accounted for the remaining 528 patient-days (14%) of usage.

Table 1 Incidences of group 2 usage where de-escalation to ertapenem would have been inappropriate.

Indication	Patients	Patient-days
A. baumannii or *P. aeruginosa* coverage needed[a]	134	1152 (32%)
ICU patient	56	483 (12%)
Received agent for ≤72 h	217	451 (12%)
Cystic fibrosis patient	6	48 (1%)
Central nervous system infection	4	40 (1%)
Nocardia infection	2	31 (1%)
Febrile neutropenia	2	20 (1%)
Osteomyelitis	1	7 (0.2%)
Total	423	2232 (58%)

[a] Also included scenarios in which carbapenem therapy + enterococcal activity was needed.

Table 2 Incidences of group 2 usage when de-escalation to ertapenem would have been appropriate.

Indication	Patients	Patient-days
Infection due to ESBL, ampC hyperproducer, or more susceptible Enterobacteriaceae	101	59 (16%)
Cultures (−), non-ICU patient	75	476 (12%)
Total	176	1074 (28%)

For patients in whom de-escalation therapy would have been appropriate, the first 72 h of group 2 carbapenem therapy after culture were considered appropriate (528 patient-days, 14%).

The two most common indications resulting in continued group 2 usage where de-escalation would not have been appropriate were the need for *A. baumannii*, *P. aeruginosa*, or *E. faecalis* coverage based on the culture results (32% of the total group 2 carbapenem usage) and negative cultures recovered from patients in the ICU (12% of the total usage). Based on our predefined criteria, 176 (29%) patients could have been de-escalated from group 2 carbapenem to ertapenem, and 1074 (28%) days of group 2 carbapenem usage could have been spared.

Discussion

Carbapenem resistance in *Pseudomonas* and *Acinetobacter* is a growing problem and is recognized as a major public health threat [9]. Although rates of carbapenem resistance among *Pseudomonas* spp. have remained stable, a marked increase was noted in carbapenem resistance among *Acinetobacter baumannii* over the past 5 years at the DMC [10]. Strategies to decrease group 2 carbapenem use and to reduce selective antimicrobial pressure on *Pseudomonas* and *A. baumannii* have been explored.

This analysis revealed that more than 1000 patient-days of group 2 carbapenem use during a 12-month period (approximately 30% of carbapenem use) in our health system could have been avoided if a de-escalation program had been in place to use ertapenem in place of group 2 carbapenems in appropriate clinical scenarios. This type of drastic reduction has the potential to significantly alleviate some of the selective pressure on *A. baumannii* and *P. aeruginosa*. Based on these findings, our institution has since implemented this de-escalation protocol.

There are important limitations of this analysis that warrant mentioning. The major limitation of our analysis is that some might disagree with the criteria used to determine the appropriate and inappropriate de-escalation opportunities; however, it would be easy to modify this analysis with criteria that others might consider more appropriate. Another important limitation is that we did not analyze the impact of such a program on antimicrobial costs. As imipenem-cilistatin and meropenem are now both generic, while ertapenem remains branded, there might be significant antibiotic cost increases associated with such a switch. Depending on the formulary preferred group 2 carbapenem and the institution's dosing strategy for that agent, ertapenem can be anywhere from $20-$40 more expensive per day. Therefore, if 1074 days of group 2 carbapenem therapy were switched to ertapenem, antibiotic costs might increase by $21,480—$42,960 for an institution. However, these costs might be offset by reductions in the frequency of Gram-negative bacilli infections that are resistant to group 2 carbapenems. While cost is not the primary driver of stewardship programs, it would still need to be taken into consideration. Finally, this model assumes that stewardship programs would be able to de-escalate all eligible patients, and it is likely that prescribers would not be willing to de-escalate in some instances.

This study reports a simple and organized approach that an institution can follow to assess the opportunities for optimizing carbapenem utilization and limiting unnecessary group 2 carbapenem usage. The implementation of a formalized carbapenem de-escalation program has the potential

to significantly reduce unnecessary utilization of group 2 carbapenems and, therefore, to potentially limit the emergence of carbapenem resistance.

Conflict of interest

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Competing interests: None declared.
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