Clinical Infectious Diseases

MAJOR ARTICLE

Postprescription Review With Threat of Infectious Disease Consultation and Sustained Reduction in Meropenem Use Over Four Years

Nandita S. Mani,[1] Kristine F. Lan,[1] Rupali Jain,[1,2] Chloe Bryson-Cahn,[1] John B. Lynch,[1] Elizabeth M. Krantz,[3] Andrew Bryan,[4] Catherine Liu,[1,3] Jeannie D. Chan,[1,5] Paul S. Pottinger,[1] and H. Nina Kim[1]

[1]Department of Medicine, Division of Allergy and Infectious Diseases, University of Washington, Seattle, Washington, USA, [2]Department of Pharmacy, University of Washington Medical Center, School of Pharmacy, University of Washington, Seattle, Washington, USA, [3]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA, [4]Department of Laboratory Medicine, University of Washington Medical Center, Seattle, Washington, USA, and [5]Department of Pharmacy, Harborview Medical Center, School of Pharmacy, University of Washington, Seattle, Washington, USA

Background. Following a meropenem shortage, we implemented a postprescription review with feedback (PPRF) in November 2015 with mandatory infectious disease (ID) consultation for all meropenem and imipenem courses > 72 hours. Providers were made aware of the policy via an electronic alert at the time of ordering.

Methods. A retrospective study was conducted at the University of Washington Medical Center (UWMC) and Harborview Medical Center (HMC) to evaluate the impact of the policy on antimicrobial consumption and clinical outcomes pre- and postintervention during a 6-year period. Antimicrobial use was tracked using days of therapy (DOT) per 1000 patient-days, and data were analyzed by an interrupted time series.

Results. There were 4066 and 2552 patients in the pre- and postintervention periods, respectively. Meropenem and imipenem use remained steady until the intervention, when a marked reduction in DOT/1000 patient-days occurred at both hospitals (UWMC: percentage change −72.1% (95% confidence interval [CI] −76.6, −66.9), $P < .001$; HMC: percentage change −43.6% (95% CI −59.9, −20.7), $P = .001$). Notably, although the intervention did not address antibiotic use until 72 hours after initiation, there was a significant decline in meropenem and imipenem initiation ("first starts") in the postintervention period, with a 64.9% reduction (95% CI 58.7, 70.2; $P < .001$) at UWMC and 44.7% reduction (95% CI 28.1, 57.4; $P < .001$) at HMC.

Conclusions. PPRF and mandatory ID consultation for meropenem and imipenem use beyond 72 hours resulted in a significant and sustained reduction in the use of these antibiotics and notably impacted their up-front usage.

Keywords. antimicrobial stewardship; carbapenems.

The primary objective of antimicrobial stewardship programs (ASP) is to optimize individual patient outcomes while simultaneously preserving the effectiveness of antibiotics for future use [1]. In particular, carbapenems are an important target for antimicrobial stewardship, as they are broad-spectrum agents that should be reserved for the treatment of suspected or confirmed multidrug resistant infections [2].

A variety of stewardship approaches have proven to be effective in improving antimicrobial use, costs, and resistance rates. These include educational strategies, formulary restrictions, preprescription authorization (PPA), postprescription review with feedback (PPRF), and computer-assisted decisional support [1, 3, 4]. Passive interventions that nudge or influence providers to make better antibiotic decisions have also proven to be effective, and their flexibility helps to preserve clinician autonomy [5, 6].

PPRF is among the most effective strategies; it allows the prescriber to select an empiric antibiotic regimen of their choice, and after 48–72 hours, the ASP may recommend deescalation or discontinuation of therapy based on evolving clinical and microbiological data [4, 7–11]. PPRF, however, does not directly address inappropriate or unnecessary empiric antibiotics [12]. PPA requires that the clinician receive approval from the ASP prior to the first dose of antibiotic, and while this increases the likelihood of appropriate empiric antibiotic use, it may be resource-intensive for the ASP.

In November 2015, we experienced a critical supply shortage of meropenem at the University of Washington health system and its affiliated hospitals. As a result, we implemented a PPRF policy with mandatory infectious disease (ID) consultation for all meropenem and imipenem orders exceeding 72 hours with the approval of the Pharmacy and Therapeutic Committee. A computer-generated alert (Supplemental Figure) notified the

Received 22 May 2020; editorial decision 13 August 2020; published online 31 August 2020.
Correspondence: N. S. Mani, 1959 NE Pacific St, Box 358061, Seattle, WA 98195 (nsmani@uw.edu).

Clinical Infectious Diseases® 2020;XX(XX):1–6

DOI: 10.1093/cid/ciaa1279

provider of the policy when ordering the antibiotic. After the shortage resolved, the policy was continued for antimicrobial stewardship purposes. We conducted a retrospective longitudinal study to evaluate whether the policy had a sustained effect in reducing meropenem and imipenem consumption.

METHODS

Study Setting

The University of Washington Medical Center (UWMC) is a 570-bed tertiary/quaternary care facility in Seattle, Washington. Harborview Medical Center (HMC) is a 413-bed acute care hospital that serves as a public safety-net hospital, as well as a level 1 trauma and burn center in Seattle, Washington, that is affiliated with UW Medicine.

Prior to the intervention, carbapenems were unrestricted at both institutions, and there was no systematic protocol in place for reviewing carbapenem use. Inappropriate carbapenem use was periodically but not comprehensively identified during microbiology rounds at each hospital, where the ID consult and microbiology teams would meet three times weekly to review patients with new culture data and discuss their antimicrobial regimens. If an inappropriate antibiotic was identified based on culture data, the infectious diseases fellow or antimicrobial stewardship (AMS) pharmacist would contact the primary team to recommend de-escalation. Additionally, the ID teams encouraged the use of carbapenem alternatives when appropriate for patients on their consult services.

In November 2015, due to a critical supply shortage of meropenem, a new policy was implemented across both hospitals requiring ID consultation for meropenem and imipenem use beyond 72 hours, with the exception of patients in the neonatal intensive care unit (NICU) or those with cystic fibrosis. When an inpatient order for meropenem or imipenem was entered, a computer-generated alert displayed, informing the provider that the antibiotic should be reserved for patients with multidrug-resistant infections and that mandatory ID consultation would occur if the antibiotic was continued for >72 hours. The provider could then choose to proceed with the order or cancel the order and select an alternate antibiotic (Supplementary Materials).

Following implementation of the policy, the AMS pharmacist began daily (M–F) and thrice weekly reviews of all inpatients on meropenem and imipenem at UWMC and HMC, respectively. Patients were eligible for PPRF if the antibiotic was initiated and approaching 72 hours; at that time, the pharmacist would call the primary team to suggest deescalation of therapy if it was appropriate based on clinical and microbiological data and to remind the team that ID consultation would be required if the drug were continued beyond 72 hours. If the team did not accept the recommendations, or if deescalation did not seem appropriate, the pharmacist would inform the on-call infectious disease team of the need for consultation. This process has remained in effect as a system-wide policy after the meropenem shortage resolved in May 2016.

Study Design and Outcomes

Our retrospective longitudinal study evaluated meropenem and imipenem utilization in hospitalized patients before and after the policy was implemented. The preintervention period occurred from 1 January 2013 to 14 November 2015; the postintervention period occurred from 15 November 2015 to 31 October 2019. All inpatients were included, with the exception of patients who had cystic fibrosis or received antibiotics in the NICU. Basic demographics including age, sex, and race, as well as clinical comorbidities, were provided for descriptive purposes (Table 1). The latter was extracted using International Classification of Diseases (9th and 10th edition) codes previously validated for Charleson comorbidities [13].

The primary outcome was meropenem and imipenem days of therapy (DOT) per 1000 patient-days. A single DOT was recorded for 1 or more doses of meropenem or imipenem administered to a patient on a given day. Ertapenem DOT were also calculated and served as a control outcome, as the policy did not restrict the use of ertapenem. Secondary outcomes included the following: empiric meropenem and imipenem use, or "first starts," which was defined as at least 1 dose of the antibiotic preceded by a day with no doses; carbapenem duration of therapy (for a given course); annual 30-day mortality and length of stay (LOS) among patients with gram-negative rod (GNR) bacteremia at UWMC; and concurrent antibiotic use trends for cefepime, ceftriaxone, and piperacillin-tazobactam at both hospitals. Multiple first starts of meropenem or imipenem could be included per patient per hospitalization; however, only 1 first start per month was included in our analysis. The subset analysis to assess clinical outcomes focused primarily on patients with GNR bacteremia at UWMC as this hospital serves more immunocompromised patients.

Statistical Analysis

The analysis was conducted under an interrupted time series framework. The implemented PPRF intervention was evaluated using segmented regression models [14]. Level and slope changes were calculated with data summarized by calendar month of the study period from 1 January 2013 to 31 October 2019. The primary outcome, meropenem and imipenem DOT per 1000 patient-days was modeled with a negative binomial distribution. The dependent variable was the days of therapy each month, and the logarithm of the total number of patient-days was included as an offset to normalize the DOT and model the DOT rates. As UWMC and HMC consisted of different patient populations and different initial rates, the medical centers were modeled separately.

Each model included a term for a level change following the intervention and a single linear term for postintervention slope. We tested for autocorrelation by examining patterns in residuals over time and by using the Durbin-Watson test. Despite evidence of slight autocorrelation in the first few weeks of the postintervention period, we did not observe a consistent pattern of autocorrelation later. Ertapenem utilization was also modeled similarly to serve as a control group. Model estimates were exponentiated to compute the incidence rate ratio (IRR) and were presented as the percentage change in rates by computing IRR − 1.

Secondary antibiotic utilization outcomes included meropenem and imipenem first starts and meropenem use duration. The first starts were also modeled with a negative binomial model with the same framework as the primary outcome. Duration of meropenem use was pooled from both medical centers, dichotomized as > 72 hours versus 72 hours or less for each course, and compared between pre- and postintervention using a χ^2 test. We also evaluated duration of therapy as a continuous variable comparing pre- and postintervention using Wilcoxon rank sum.

We evaluated 30-day mortality and hospital length of stay (LOS) as clinical outcomes for GNR bacteremic patients at UWMC. For patients with >1 episode of GNR bacteremia, only the first episode was included in these analyses. Mortality was evaluated using logistic regression, with the intervention (pre/post) period as a main exposure variable, adjusting for age and sex. Patient LOS was fitted with a proportional subdistribution hazards regression model accounting for death as a competing risk for the main outcome of hospital discharge and adjusting for age and sex [15, 16]. All analyses were performed using the R computing environment (version 3.5.1).

RESULTS

Baseline Characteristics of Patients

During the study period, a total of 4066 and 2552 patients were included for analysis in the pre- and postintervention periods, respectively. The 2 groups were similar with regard to baseline demographic and clinical characteristics (Table 1).

Table 1. Patient Demographics

	Pre-intervention n = 4066	Postintervention n = 2552
Sex		
Female	1664 (41)	1031 (40)
Male	2402 (59)	1521 (60)
Age		
< 20	44 (1)	45 (2)
21–30	361 (9)	245 (10)
31–40	434 (11)	306 (12)
41–50	586 (14)	358 (14)
51–60	1029 (25)	594 (23)
61–70	944 (23)	595 (23)
> 70	668 (16)	409 (16)
Race		
Black	311 (8)	224 (9)
Other	753 (19)	429 (17)
White	3002 (74)	1899 (74)
Comorbidities		
Any malignancy	1457 (36)	875 (34)
Cerebrovascular disease	1391 (34)	1176 (46)
Chronic pulmonary disease	1346 (33)	1088 (43)
Congestive heart failure	1478 (36)	894 (35)
Liver disease	291 (7)	213 (8)
Metastatic solid tumor	672 (17)	405 (16)
Myocardial infarction	409 (10)	206 (8)
Peripheral vascular disease	453 (11)	364 (14)
Renal disease	1586 (39)	1063 (42)

Antibiotic Utilization

At HMC, median meropenem and imipenem DOT/1000 patient-days in the pre- and postintervention periods were 26.2 and 9.6, respectively. At UWMC, median meropenem and imipenem DOT/1000 patient days in the pre- and postintervention periods were 49 and 15.1, respectively. Figure 1 displays the results of the interrupted time series analysis.

Meropenem and imipenem DOT at HMC were stable preceding the intervention (percentage change per month −0.56%; 95% CI −1.88, .77; P = .41). Following the intervention, DOT/1000 patient-days decreased by 43.6% (95% CI 20.7, 59.9; P = .001), and there was a sustained decline per month over a 4-year period following the intervention (percentage change −1.19%; 95% CI −1.96, −.41; P = .004).

During the preintervention period, meropenem and imipenem DOT/1000 patient-days at UWMC similarly remained steady (percentage change per month −0.08%; 95% CI −.75, .58; P = .80). After implementation of the intervention, there was a 72.1% (95% CI 66.9, 76.6) immediate reduction in meropenem and imipenem DOT/1000 patient-days indicated by the level change for that initial month postintervention (P < .001). In the 4 years that followed, this level remained largely stable, although a slight gradual increase in meropenem and imipenem DOT/1000 patient-days was observed (percentage change per month 0.51%; 95% CI .1, .92; P = .02). Negative binomial regression estimates of meropenem and imipenem use can be found in the Supplementary Table.

Ertapenem use served as a control because this antibiotic was not specifically targeted by the intervention. There was no significant level or slope change in ertapenem DOT per 1000 patient-days at either institution during these periods of interest (Figure 2).

Antibiotic First Starts

Although our policy was intended to impact meropenem and imipenem use after 72 hours rather than initiation per se, we

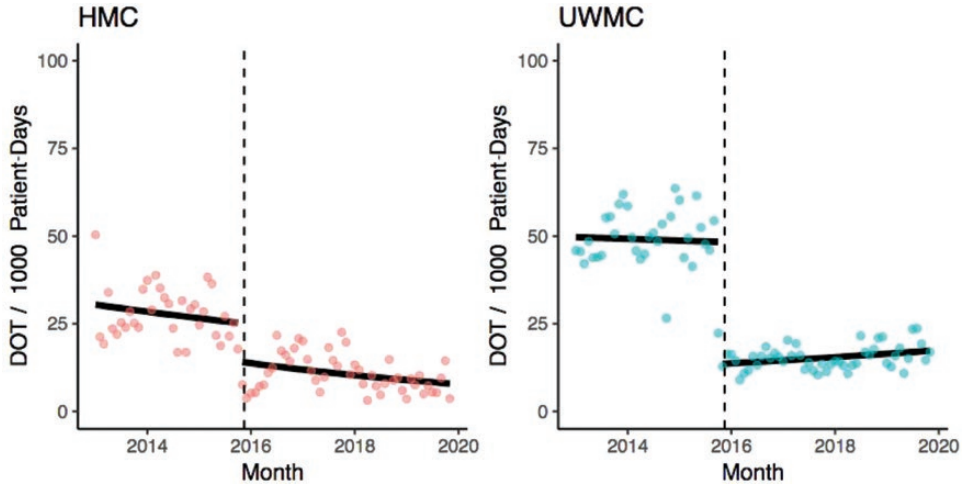

Figure 1. Meropenem and imipenem DOT (January 2013–November 2019). Intervention on 15 November 2015 shown as vertical dashed line. Filled circles represent observed data, and solid lines represent model fits from negative binomial segmented regression model. Abbreviations: DOT, days of therapy; HMC, Harborview Medical Center; UWMC, University of Washington Medical Center.

observed a significant decline in up-front usage of these antibiotics, or "first starts," at both institutions following the intervention. Figure 3 displays the results of the interrupted time series analysis. The intervention was associated with significant decreases in first starts of 64.9% (95% CI 58.7, 70.2; $P < .001$) and 44.7% (95% CI 28.1, 57.4; $P < .001$) at UWMC and HMC, respectively. Median number of first starts/1000 patient-days declined from 8.7 preintervention to 3.5 postintervention at UWMC and from 5.0 to 1.9 at HMC. At HMC, the slope also continued to decline following the intervention (percentage change per month −0.93%; 95% CI −1.56%, −.29%; $P = .006$), and at UWMC there was a nonsignificant increase in slope (percentage change per month 0.3%; 95% CI −.12%, .71%; $P = .17$).

Antibiotic Duration

Using pooled data from both hospitals, the median duration of meropenem decreased from 4 days preintervention to 3 days postintervention ($P < .001$). Prior to the intervention, the majority of meropenem courses were >3 days in duration (2529 of 4755, 53%), whereas postintervention, there was a statistically significant shift toward shorter course durations, with only 1279 of 3105 (41%) of courses lasting >3 days, $P < .001$.

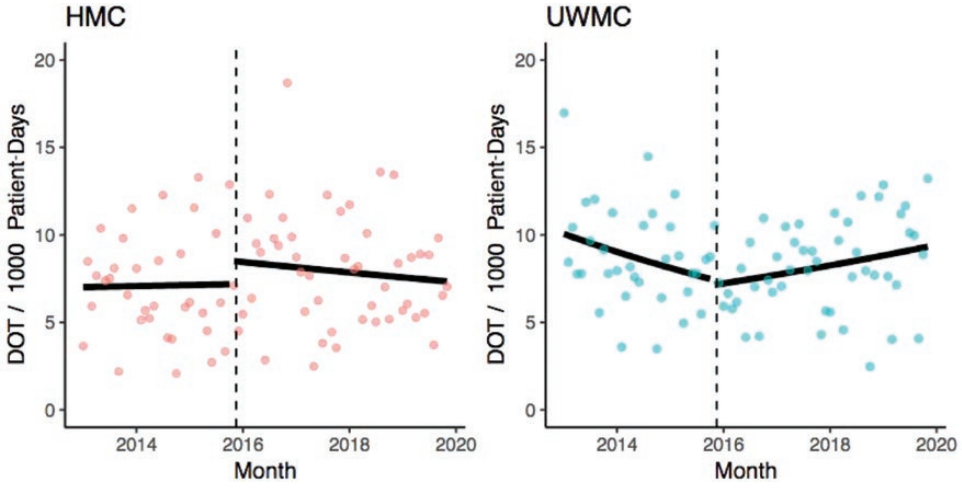

Figure 2. Ertapenem DOT (January 2013–November 2019). Intervention on 15 November 2015 shown as vertical dashed line. Filled circles represent observed data, and solid lines represent model fits from negative binomial segmented regression model. Abbreviations: DOT, days of therapy; HMC, Harborview Medical Center; UWMC, University of Washington Medical Center.

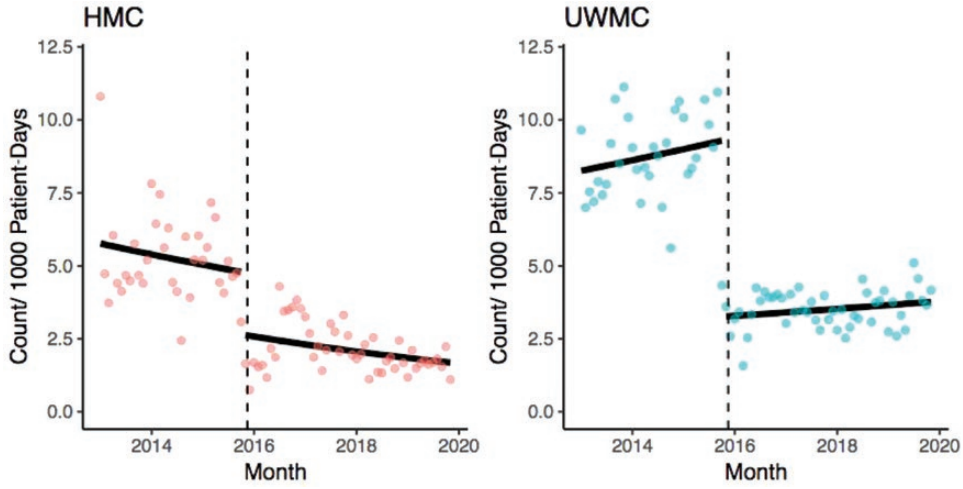

Figure 3. Meropenem and imipenem first starts (January 2013–November 2019). Intervention on 15 November 2015 shown as vertical dashed line. Filled circles represent observed data, and solid lines represent model fits from negative binomial segmented regression model. Abbreviations: DOT, days of therapy; HMC, Harborview Medical Center; UWMC, University of Washington Medical Center.

For meropenem orders > 72 hours, the proportion of courses 6 days or fewer was 54% versus 59% pre- and postintervention, $P < .001$.

Clinical outcomes in GNR bacteremia

Between 1 November 2013 and 15 November 2015 in the preintervention period, 49 (25%) of 200 patients with GNR bacteremia died; between 15 November 2015 and 30 November 2018, 63 (21%) of 307 patients with GNR bacteremia died. We did not find any significant difference in 30-day mortality by intervention period, adjusting for age and sex.

When evaluating hospital length of stay among patients with GNR bacteremia, we found no difference between the pre- and postintervention periods (HR 1.06 95% CI .89, 1.3, $P = .45$), adjusting for age and sex and accounting for in-hospital death as a competing risk.

Antibiotic Use Trends

The use of ceftriaxone, cefepime, and piperacillin/tazobactam was evaluated during the study period in order to assess whether a potential "squeezing the balloon" effect was present, where the restriction of certain antimicrobials may lead to increased use of nonrestricted antimicrobials [17]. These trends are displayed in Supplementary Materials. Interrupted time series analysis was performed on cefepime use and did not suggest a statistically significant difference in the baseline trend towards increased utilization pre- and postintervention (Supplementary Materials). Interrupted time series was not performed on ceftriaxone or piperacillin/tazobactam, as no obvious pattern was detected for these antibiotics during exploratory analysis.

DISCUSSION

The present study describes the impact of a 72-hour PPRF on carbapenem use and clinical outcomes in 2 academic teaching hospitals. We found a significant decline (44–72%) in carbapenem consumption following implementation of this policy and observed this as a sustained effect over a 4-year period postimplementation.

Because our intervention did not restrict initial use of carbapenem therapy, one might assume that any decline in consumption would be due to earlier deescalation and shortened durations of therapy. Indeed, the median duration in therapy did decrease from 4 to 3 days following the intervention, and there was a higher proportion of carbapenem courses >3 days (53%) in the preintervention period compared to the postintervention period (41%). However, the decline in overall days of carbapenem therapy was in large part attributable to declines in meropenem and imipenem initiation ("first starts") in the postintervention period, indicating that the reduced consumption was primarily due to a decline in upfront usage of carbapenems. Although our policy did not place a restriction on initiating carbapenems, when providers placed orders for meropenem or imipenem, they were alerted through the electronic health record to a mandatory ID consultation that would occur after 72 hours of meropenem or imipenem use. We believe that the warning of ID consultation, and the mindset of scarcity and conservation that might have been associated with this threat, may have played a significant role in reducing empiric carbapenem orders and driving down overall carbapenem use.

Our policy of PPRF followed by mandatory ID consultation gave providers autonomy when prescribing empiric antibiotics, however in its ultimate impact, this measure functioned similarly to PPA, in that it reduced inappropriate empiric

carbapenem use [12]. Additionally, it was less resource intensive than PPA for the ASP, as it did not require a physician or pharmacist to be on-call to approve empiric antibiotic orders in real-time.

The switch to carbapenem-sparing regimens did not appear to result in patient harm as measured by short-term mortality or hospital duration. We found no difference in 30-day mortality or hospital LOS between the pre- and postintervention periods among the high-risk subpopulation of patients with GNR bacteremia.

To our knowledge, there have been no studies that have shown a significant impact on empiric antibiotics using a PPRF strategy. Our study shows that PPRF combined with a potential mandatory ID consultation can serve as an impactful yet relatively low-resource intervention that can significantly reduce carbapenem consumption without compromising clinical outcomes.

In traditional PPRF programs, uptake of the ASP's recommendation is not mandatory, as the primary team has to elect to discontinue these antibiotics. Our strategy coupled PPRF with ID consultation to ensure that carbapenem appropriateness was assessed by a specialist external to the primary team. Partnership between ID consult teams and ASPs has been previously shown to improve carbapenem use and infection-related mortality [18].

There are limitations to our study. First, given that prescribers were alerted of the policy at the time of electronic order, our findings may not be generalizable to healthcare systems that do not use computer prescriber order entry. Next, PPRF at Harborview Medical Center was not consistently performed until July 2018. Due to staffing limitations on the ASP team prior to that, meropenem orders were reviewed 3 times per week rather than daily, and the ASP team relied on assistance from primary team pharmacists to enforce the 72-hour policy. This may explain a lower decline in consumption at HMC compared to UWMC, where the policy was more rigorously implemented from the beginning. Finally, as with any observational study, we should be cautious regarding inferring causality. However, the immediacy of this decline, the selected nature of the effect (no impact on ertapenem or other antibiotic usage), and the absence of other competing explanations for this observation, would provide compelling evidence that the policy resulted in the observed changes in meropenem and imipenem use.

CONCLUSION

We observed that PPRF and mandatory ID consultation for meropenem and imipenem after 72 hours resulted in a significant reduction in the use of these drugs, and the effect was sustained over 4 years. This relatively low-resource ASP intervention had a marked effect on empiric carbapenem use in addition to overall carbapenem consumption. It will be important to examine whether our findings can be replicated in other care settings.

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

Acknowledgments. The authors thank the UW Medicine Pharmacy Department and Pharmacy and Therapeutics Subcommittee for supporting this intervention. They thank Dr Anna Wald and the UW Allergy & Infectious Diseases Research Collaboratory for their support.

Financial support. No funding was received for this project.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis **2016**; 62:e51–77.
2. Wilson APR. Sparing carbapenem usage. J Antimicrob Chemother **2017**; 72:2410–7.
3. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev **2017**; 2:CD003543.
4. Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's principles and practice of infectious diseases e-Book. Elsevier Health Sciences, **2019**.
5. Jones M, Butler J, Graber CJ, et al. Think twice: a cognitive perspective of an antibiotic timeout intervention to improve antibiotic use. J Biomed Inform **2017**; 71S:22–31.
6. Meeker D, Knight TK, Friedberg MW, et al. Nudging guideline-concordant antibiotic prescribing: a randomized clinical trial. JAMA Intern Med **2014**; 174:425–31.
7. Abbara S, Pitsch A, Jochmans S, et al. Impact of a multimodal strategy combining a new standard of care and restriction of carbapenems, fluoroquinolones and cephalosporins on antibiotic consumption and resistance of *Pseudomonas aeruginosa* in a French intensive care unit. Int J Antimicrob Agents **2019**; 53:416–22.
8. Tamma PD, Avdic E, Keenan JF, et al. What is the more effective antibiotic stewardship intervention: preprescription authorization or postprescription review with feedback? Clin Infect Dis **2017**; 64:537–43. doi: 10.1093/cid/ciw780.
9. Elligsen M, Walker SA, Pinto R, et al. Audit and feedback to reduce broad-spectrum antibiotic use among intensive care unit patients: a controlled interrupted time series analysis. Infect Control Hosp Epidemiol **2012**; 33:354–61.
10. Honda H, Murakami S, Tagashira Y, et al. Efficacy of a postprescription review of broad-spectrum antimicrobial agents with feedback: a 4-year experience of antimicrobial stewardship at a tertiary care center. Open Forum Infect Dis **2018**; 5:ofy314.
11. Rupali P, Palanikumar P, Shanthamurthy D, et al. Impact of an antimicrobial stewardship intervention in India: evaluation of post-prescription review and feedback as a method of promoting optimal antimicrobial use in the intensive care units of a tertiary-care hospital. Infect Control Hosp Epidemiol **2019**; 40:512–9.
12. Tamma PD, Cosgrove SE. Antimicrobial stewardship. Infect Dis Clin North Am **2011**; 25:245–60.
13. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care **2005**; 43:1130–9.
14. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol **2017**; 46:348–55.
15. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc **1999**; 94:496–509.
16. Brock GN, Barnes C, Ramirez JA, Myers J. How to handle mortality when investigating length of hospital stay and time to clinical stability. BMC Med Res Methodol **2011**; 11:144.
17. Peterson LR. Squeezing the antibiotic balloon: the impact of antimicrobial classes on emerging resistance. Clin Microbiol Infect **2005**; 11(Suppl 5):4–16.
18. Horikoshi Y, Suwa J, Higuchi H, et al. Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality. Int J Infect Dis **2017**; 64:69–73.