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Brief Report

Effect of carbapenem restriction on prescribing trends for immunocompromised wards at an academic medical center

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The recently described proportion of carbapenem consumption metric was used to assess the effectiveness of formulary restriction for carbapenems for 2 units housing predominantly immunocompromised patients at a large academic medical center. Interrupted time series analysis revealed a significant decrease in meropenem use for hematology-oncology and bone marrow transplant units after restriction.

Patients suffering from hematologic malignancies are particularly vulnerable to bacterial and fungal infections secondary to the immunocompromise that may occur as a direct result of cancer or from cancer treatment. An accelerating incidence of infections due to multidrug resistant bacteria has been noted in the transplant and hematology-oncology (HO) literature; in particular, carbapenem-resistant Enterobacteriaceae and multidrug resistant *Pseudomonas Aeruginosa* pose a rapidly increasing threat.[1-5] Carbapenem-resistant Enterobacteriaceae bacteremia in patients with hematologic malignancies is associated with mortality rates as high as 73%.[6]

To minimize the development of carbapenem resistance, piperacillin-tazobactam (PT) and cefepime are preferred for empirical treatment of neutropenic fever for many hematology patients.[7,8] However, carbapenem overuse remains common. A recent study noted that 18% of patients with neutropenic fever received initial carbapenem therapy despite institutional guidelines recommending alternative therapy.[9]

The Virginia Commonwealth University Health System (VCUHS) is an 865-bed urban tertiary care facility that has had an antimicrobial stewardship program in place for approximately 20 years. Our stewardship program has a longstanding formulary restriction and preauthorization (FRPA) program in place. The recently described proportion of carbapenem consumption (PoCC) is a novel metric used by our staff to evaluate the relative use of cefepime, PT, and carbapenems in a variety of clinical settings.[10] It is calculated as:

$$\frac{\text{Carbapenem days of therapy (DOT) per 1,000 patient-days}}{\text{(Carbapenem + PT + Cefepime) DOT per 1,000 patient-days}}$$

Equation 1–PoCC calculation

Meropenem (the primary carbapenem used within VCUHS; all other carbapenems have been subject to longstanding restriction) was added to our restricted formulary, and, thus, became subject to our existing FRPA protocol for all adult wards beginning in February 2018. This policy change allowed us to directly study the effects of FRPA on carbapenem prescribing trends using the PoCC metric for units serving immunocompromised patients. These units were also subject to postantibiotic order review with provider feedback during the study period.

METHODS

Antimicrobial use within the VCUHS bone marrow transplant (BMT) and HO units were available in days of therapy (DOT) per 1,000 patient-days from August 2012 through August 2018. Monthly total patient-days by unit were available beginning in January 2013 through August 2018. Patient-days data were used to calculate total

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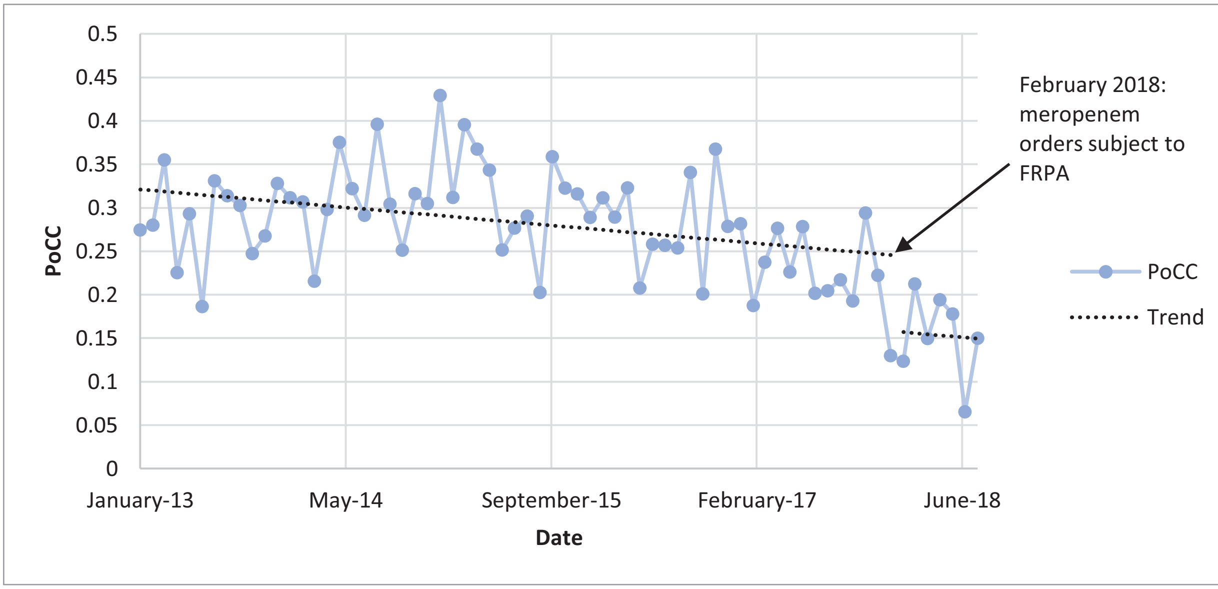

Fig 1. PoCC with superimposed interrupted time series trend. *FRPA*, formulary restriction and preauthorization; *PoCC*, proportion of carbapenem consumption.

DOT for each antimicrobial for both the BMT and HO units, allowing us to sum both DOT values and calculate DOT per 1,000 patient-days for the combined BMT + HO units. DOT for meropenem, PT, and cefepime were used to calculate monthly PoCC for the BMT unit, HO unit, and the combined BMT + HO units.

These data were analyzed using interrupted time series (ITS) analysis, an ordinary least squares regression that models PoCC as a function of time trend (number of months since the beginning of the analysis period) and a binary ITS variable indicating the date meropenem orders became subject to FRPA at our institution. Meropenem, cefepime, and PT were analyzed separately using a similar ITS regression.

Data were available for the BMT and HO units separately beginning in August 2012. Patient-days data by ward, available beginning January 2013, were needed to calculate the aggregated DOT per 1,000 patient-days for the combined wards. Therefore, analysis for the individual HO and BMT units were based on data spanning August 2012 through August 2018, whereas aggregated analysis for both immunocompromised units combined were based on data spanning January 2013 through August 2018. Analysis was carried out using SAS software version 9.4 (SAS Institute, Cary, NC). This study was approved by Virginia Commonwealth University's institutional review board.

RESULTS

ITS analysis of the PoCC trend for the combined BMT and HO units demonstrated a significant reduction in the PoCC postintervention, driven primarily by a reduction in meropenem use across both units. PT use also increased by a statistically significant margin for the BMT unit. (Fig 1 and Table 1)

Our analysis suggests that adding meropenem to our FRPA protocol reduced the PoCC for our immunocompromised units by .09 (a 30.9% decrease compared with the average PoCC preintervention), driven primarily by a reduction in meropenem use of 54 DOT per 1,000 patient days (42.4% of average preintervention use). ITS analysis also indicated that PT use increased by nearly 36 DOT per 1,000 patient-days (96.2% of average preintervention use) in the BMT unit.

Table 1
ITS regression results for PoCC and its components for immunocompromised units

Ward	Analysis	ITS	*P* value-ITS
Combined BMT and HO	PoCC	−0.09	.001
	Meropenem	−54.18	.001
	Cefepime	−35.23	.103
	PT	15.51	.320
BMT	PoCC	−0.12	.003
	Meropenem	−48.34	.011
	Cefepime	−25.45	.279
	PT	35.73	.001
HO	PoCC	−0.09	.028
	Meropenem	−35.35	.011
	Cefepime	−4.44	.793
	PT	6.45	.700

BMT, bone marrow transplant; *HO*, hematology-oncology; *ITS*, interrupted time series; *PoCC*, proportion of carbapenem consumption; *PT*, piperacillin-tazobactam.

DISCUSSION

Our ITS analysis revealed that FRPA significantly reduced relative meropenem use for HO and BMT patients at our medical center. The change in PoCC score was driven primarily by a reduction in meropenem use, although we also saw an increase in PT use postintervention as well. Clinicians appear to be responding as intended to the FRPA intervention, using PT and other relatively narrower-spectrum drugs instead of carbapenems.

Our study has several limitations. Although the majority of patients on our HO unit have either hematologic or solid organ malignancies, infrequently a patient without malignancy will board on this unit. Additionally, this is a single-center study and, as such, results may not extrapolate to other settings.

CONCLUSIONS

Our analysis provides strong evidence supporting the effectiveness of FRPA in reducing carbapenem use within immunocompromised populations. To our knowledge, this is the first description of the PoCC metric as applied to immunocompromised patients and adds to the body of literature examining the impact of FRPA. We believe these data will be useful to other institutions designing carbapenem restriction strategies.

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