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CLINICAL THERAPEUTICS

Impact of a Carbapenem Antimicrobial Stewardship Program on Patient Outcomes

Valerie Xue Fen Seah,[a] Rina Yue Ling Ong,[a] Ashley Shi Yuan Lim,[a] Chia Yin Chong,[b,c,d] Natalie Woon Hui Tan,[b,c,d,e] Koh Cheng Thoon[b,c,d]

Department of Pharmacy, KK Women's and Children's Hospital, Singapore[a]; Infectious Disease Service, Department of Pediatrics, KK Women's and Children's Hospital, Singapore[b]; Yong Loo Lin School of Medicine, National University of Singapore, Singapore[c]; Duke-National University of Singapore Medical School, Singapore[d]; Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore[e]

ABSTRACT Antimicrobial stewardship programs (ASPs) aim to improve appropriate antimicrobial use. However, concerns of the negative consequences from accepting ASP interventions exist, particularly when deescalation or discontinuation of broad-spectrum antibiotics is recommended. Hence, we sought to evaluate the impact on clinical outcomes when ASP interventions for inappropriate carbapenem use were accepted or rejected by primary providers. We retrospectively reviewed all carbapenem prescriptions deemed inappropriate according to institutional guidelines with ASP interventions between July 2011 and December 2014. Intervention acceptance and outcomes, including carbapenem utilization, length of stay, hospitalization charges, 30-day readmission, and mortality rates were reviewed. Data were analyzed in two groups, one in which physicians accepted all interventions ("accepted") and one in which interventions were rejected ("rejected"). A total of 158 ASP interventions were made. These included carbapenem discontinuation (35%), change to narrower-spectrum antibiotic (32%), dose optimization (17%), further investigations (including imaging and procalcitonin) (11%), infectious diseases referral (3%), antibiotic discontinuation (other than carbapenem) (1%), and source control (1%). Of 220 unique patients, carbapenem use was inappropriate in 101 (45.9%) patients. A significant reduction in carbapenem utilization was observed in the accepted group versus rejected group (median defined daily doses, 0.224 versus 0.668 per 1,000 patient-days, respectively; $P < 0.001$). There was a significant reduction in 30-day mortality in the accepted (none) versus rejected group (10 deaths, $P = 0.015$), but there were no differences in length of stay, hospitalization charge, or 30-day readmission rates. Hypotension was independently associated with mortality in multivariate analysis (odds ratio, 5.25; 95% confidence interval, 1.34 to 20.6). In our institution, acceptance of carbapenem ASP interventions did not compromise patient safety in terms of clinical outcomes while reducing consumption.

KEYWORDS antimicrobial stewardship, interventions, pediatric, safety

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Address correspondence to Valerie Xue Fen Seah, Valerie.Seah.XF@kkh.com.sg.

Antimicrobial stewardship programs (ASPs) promote the judicious use of antimicrobials, in particular, broad-spectrum antimicrobials, such as carbapenems (1). Multiple studies have demonstrated the effectiveness of ASPs in reducing inappropriate antimicrobial use and hospital antimicrobial expenditures, as well as in reducing rates of antimicrobial resistance among health care-associated pathogens (2–4). In addition, the goals of ASPs extend beyond cost-saving strategies, as patient safety, including improvement in patient care and outcomes, is an integral component of antimicrobial stewardship (5).

The Infectious Disease Society of America has cited an evaluation of the effective-

TABLE 1 Reasons for inappropriate carbapenem use

Reasons for inappropriate use (n = 114)	No.	%
Prolonged duration of use	45	40
Wrong dose	24	21
No indication for use/escalation	26	23
Wrong empirical choice (too broad spectrum)	11	10
Organism susceptible to narrower-spectrum antibiotic	8	7

ness of ASP strategies in specialized populations as a research priority (1). However, concerns that acceptance of ASP interventions may compromise patient safety do exist, particularly where deescalation or discontinuation of broad-spectrum antibiotics is recommended. In addition, few have described the impact of ASP interventions on patient outcomes, in particular, unique populations, such as pediatrics (6–10).

A prospective-review-and-feedback ASP for carbapenems was formally established in a hospital dedicated to pediatrics and women's services (predominantly obstetrics/gynecology) in Singapore (KKH) in July 2011. KKH is an 830-bed tertiary-care hospital and major referral center for pediatrics and obstetrics/gynecology conditions in Singapore, with approximately 20,000 inpatient admissions yearly. This includes general pediatrics and subspecialties, including hemato-oncology, bone marrow transplant, gastroenterology, rheumatology, immunology; neonatal intensive and special care; and high-risk obstetrics, gynecological cancer, and urogynecology services. Hence, we sought to evaluate the impact of ASP interventions on clinical outcomes to address the safety concerns of accepting ASP recommendations in our institution.

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RESULTS

Reasons for inappropriate carbapenem use and intervention acceptance rates. We evaluated a total of 220 unique patients who were prescribed carbapenems and for whom ASP interventions were made between July 2011 and December 2014. Carbapenem use was inappropriate in 101 (46%) patients. Reasons for inappropriate use are described in Table 1. There was more than one reason for inappropriate use in 17 of 101 patients (17%). Multiple interventions might have been made for an individual patient. The main reason for inappropriate use was prolonged duration of use (45 [40%] patients), followed by no indication for use or escalation (26 [23%] patients) and wrong dose (24 [21%] patients).

A total of 158 interventions were made. The interventions recommended and reasons for nonacceptance are described in Table 2. Discontinuation of carbapenems was the main intervention made by our ASP (56 [35%] patients), followed by a change to a narrower-spectrum antibiotic (50 [32%] patients) and optimization of dosing (26 [17%] patients). Intervention acceptance rates were low, at 35.1%, 40%, and 65.4%, respectively. The main reasons for nonacceptance identified include physician's choice (51 [60%] patients) and reluctance to discontinue or deescalate carbapenems, as the patient was still sick (17 [20%] patients) or improving (10 [12%] patients). There were no significant differences in nonacceptance rates between patients in pediatrics and neonatology and those in obstetrics/gynecology (34% versus 31%, respectively; $P = 0.82$).

Patient demographics. There were few significant differences in the baseline characteristics between patients whose prescribers rejected the interventions and those who accepted all interventions. More patients in the group in which prescribers rejected interventions received broad-spectrum antibiotics prior to admission (44% versus 12% for the accepted group, respectively; $P < 0.001$) and prior first ASP review (59% versus 26%, respectively; $P < 0.001$) and presented with hypotension, requiring fluid boluses and/or inotropic support (31% versus 12%, respectively; $P = 0.031$) (Table 3).

TABLE 2 Intervention acceptance rates and reasons for nonacceptance

Intervention or reason for nonacceptance	No. of interventions	%	No. of acceptances	%
Interventions made (n = 158)				
Discontinue carbapenem	56	35	19	34
Change to narrower-spectrum antibiotic	50	32	20	40
Optimize dosing	26	17	17	65
Further investigations (e.g., procalcitonin, imaging, cultures)	17	11	12	71
Discontinue antibiotic (other than carbapenem)	2	1	2	100
Infectious diseases referral	5	3	3	60
Source control (e.g., line removal)	2	1	1	50
Total interventions	158	100	75	48
Reasons for nonacceptance (n = 85)		%		
Physician choice	51	60		
Patient still sick, does not wish to deescalate	17	20		
Patient improving, does not wish to deescalate	10	12		
Awaiting surgery, stay on antibiotic	3	4		
Other reasons[a]	4	5		

[a]Other reasons: patient was afebrile and cultures negative, but the team intended to keep the patient on antibiotics until neutrophils counts improved (n = 3); ASP recommended source (urinary catheter) removal and amikacin for an ESBL *E. coli* urinary tract infection, but the team felt that the patient "failed" amikacin therapy (despite the organism being susceptible to amikacin; n = 1).

Clinical outcomes. A significant reduction in carbapenem consumption in terms of weight and days of therapy was observed between the "accepted" and "rejected" groups (median defined daily doses, 0.224 versus 0.668 per 1,000 patient-days; days of therapy, 0.417 versus 0.764 per 1,000 patient-days, respectively; both $P < 0.001$).

There was a significant reduction in 30-day mortality in the accepted (no mortality) versus rejected group (10 deaths, $P = 0.015$) but not length of stay (median of 26 versus 39 days, respectively; $P = 0.112$), hospitalization charges (median, \$10,843 versus \$17,470, respectively; $P = 0.088$), or 30-day readmission rates (38% versus 52%, respectively; $P = 0.212$) (Table 4). Two patients who received inappropriate carbapenem therapy and rejected ASP interventions to deescalate carbapenems eventually developed infections due to carbapenem-resistant organisms (CROs), while none of the patients in the group in which interventions were accepted developed infections due to CROs.

A multivariate logistic regression performed using mortality as an independent outcome identified that patients with a baseline of hypotension prior to carbapenem initiation had an increased risk of 30-day mortality (odds ratio, 5.2; 95% confidence interval, 1.34 to 20.6; $P = 0.018$), independent of ASP intervention acceptance (Table 5).

DISCUSSION

To the best of our knowledge, this is the first local study that focused on the impact of ASP interventions on patient safety in unique populations (pediatrics and obstetrics/gynecology) in whom the use of carbapenems was considered inappropriate by the ASP team. The interventions recommended by our ASP did not compromise patient safety in terms of clinical outcomes, including length of stay and 30-day readmission rates. There was a significant reduction in 30-day mortality in the accepted intervention group compared to the rejected intervention group, but it was independently associated with patients who had hypotension requiring fluid boluses and/or inotropic support at baseline. In addition, we demonstrated a significant reduction in carbapenem consumption in the group of patients where ASP interventions were accepted.

We recognized that more patients in the rejected group had broad-spectrum antibiotic use prior to hospitalization and were sicker than the accepted group, which might have contributed to the relatively low overall acceptance rate of our ASP interventions. Our intervention acceptance was 48%, despite the efforts of our prospective review-and-feedback strategy, compared to rates of 59% (11) to 89% (6), as reported in studies in which similar ASP strategies were in place. In a tertiary-care adult hospital which also focused on improving carbapenem use (11), acceptance rates for

TABLE 3 Patient demographics and clinical characteristics[a]

Demographic or characteristic[b]	Rejected group ($n = 67$)	Accepted group ($n = 34$)	*P* value
Age (median [range]) (yr)	10.0 (0.01–98.0)	6.3 (0.01–76.0)	0.172
Department			0.129
Pediatrics	56 (84)	29 (85)	0.824
Neonatal	5 (8)	3 (9)	0.811
Obstetrics/gynecology	8 (12)	5 (15)	0.757
Hospitalization in past 30 days	47 (70)	19 (56)	0.154
Broad-spectrum antibiotic use in past 30 days			
Prior admission	29 (43)	4 (12)	<0.001
Prior 1st review	40 (59)	9 (26)	<0.001
Immunocompromised[c]	38 (57)	21 (64)	0.508
Previous ESBL or MDRO colonization and/or infection	29 (43)	11 (32)	0.288
Hypotension requiring fluid boluses and/or inotropes	21 (31)	4 (12)	0.031
Respiratory support	19 (28)	8 (24)	0.203
Oxygen	4 (6)	1 (3)	
Noninvasive ventilation	1 (2)	3 (9)	
Invasive	14 (21)	4 (12)	
Intensive care/high-dependency unit admission	23 (34)	9 (27)	0.422
Febrile neutropenia	27 (40)	13 (38)	0.841
Infection source			0.348
Systemic, culture positive	34 (51)	14 (41)	
Systemic, culture negative	8 (12)	7 (21)	
Gastrointestinal	7 (10)	7 (21)	
Genitourinary	7 (10)	3 (9)	
Respiratory	8 (12)	1 (3)	
Skin and soft tissue	2 (3)	1 (3)	
Multiple infections	1 (2)	0 (0)	
Prophylaxis	0 (0)	1 (3)	
ESBL-resistant organism identified	12 (44)	5 (33)	0.482

[a]Data are presented as number (%), unless otherwise indicated.
[b]ESBL, extended-spectrum beta-lactamase; MDRO, multidrug-resistant organism (resistant to three or more antimicrobial classes).
[c]Immunocompromised includes those undergoing a transplant, who had malignancy/receipt of chemotherapy, or who had immunodeficiency disorders.

stopping and deescalating carbapenems ranged from 30 to 65%, which were similar to our findings, in which the majority of interventions which were rejected were those that pertained to limiting carbapenem use. In addition, similar to Goldman et al.'s evaluation of their pediatric ASP, the primary team was highly likely to disagree with ASP recommendations that focused on the use of broad-spectrum antibiotics, such as carbapenems (odds ratio, 2.8), where stopping of therapy was likely to be recommended (12).

One contributing factor to the low acceptance rate of our ASP interventions could have been the novelty of an ASP in our institution, as prescribers were anecdotally initially concerned about the effectiveness and safety of ASP recommendations for discontinuation or deescalation of carbapenem therapy. This is evidenced in our study, in which the main reason for inappropriate was extended duration of use (40%), where prescribers were reluctant to accept our interventions for carbapenem discontinuation or deescalation, despite a lack of strong evidence to justify its continued use. We observed this especially in patients who were still ill (19%), and surprisingly, even in patients who were improving (12%), as prescribers were often hesitant to "rock the boat" or "change a winning formula" (13). These behaviors were largely driven by common false beliefs that broader-spectrum antibiotics, such as carbapenems, especially at high doses, were perceived to be more effective, as meningitic doses of meropenem were often initiated inappropriately in patients with evidence of neither meningitis nor septic shock, nor in febrile neutropenic patients.

TABLE 4 Clinical outcomes

Outcome[a]	Rejected (n = 67)	Accepted (n = 34)	P value
DDD per 1,000 patient-days (median [range])	0.668 (0.01–11.5)	0.224 (0.002–1.93)	<0.001
DOT per 1,000 patient-days (median [range])	0.764 (0.11–9.19)	0.417 (0.03–2.63)	<0.001
Length of stay (median [range]) (days)	39 (4–599)	26 (6–173)	0.112
Hospitalization charges (median [range])	$17,470 ($1,704–273,356)	$10,843 ($2,556–116,839)	0.088
30-day readmission (no. [%])[b]	29 (52)	13 (38)	0.212
Infection related	7 (13)	3 (9)	0.737
30-day mortality (no. [%])	10 (15)	0 (0)	0.015
Infection related	4 (6)	0 (0)	0.297
Clinical improvement 7 days after initial review (no. [%])	52 (78)	29 (85)	0.360
Clinical improvement at end of carbapenem therapy (no. [%])	58 (87)	31 (91)	0.746
Microbiologic clearance 7 days after 1st positive culture(no. [%])	14 (70)	11 (85)	0.431
Carbapenem-resistant organism within 30 days of start of carbapenem therapy (no. [%])	2 (3)[c]	0 (0)	0.549

[a]DDD, daily defined doses; DOT, days of therapy.
[b]Excluded in-hospitalization mortality.
[c]Organisms identified were *Stenotrophomonas maltophilia* and *Acinetobacter* spp. from blood cultures.

In a study by Metjian et al. (6), an ASP in their institution has been established and well integrated into the institution for 15 years, which could be a major contributing factor to their high intervention acceptance rates of 89%, with up to 96% for interventions to use a narrower-spectrum antibiotic. Also, in-person recommendations to the primary team were potential approaches to improving the acceptance rates for ASP recommendations. This was demonstrated by Di Pentima et al. (7), as their 1-on-1 dialogue between ASP members and medical staff contributed to an increase in compliance rates to their ASP recommendations from 83 to 92% over 3 years. In addition, Hurst et al.'s (14) unique "handshake" approach to stewardship, where in particular, a prospective rounding-based in-person approach to feedback by a pharmacist-physician team was in place resulted in a high intervention acceptance rate of 84%.

Although intervention acceptance intervention rates appear low in this study, we have observed a significant increase in acceptance rates for deescalation of carbapenems from 57% to 83% after 2.5 years of ASP initiation (15). We postulate that this increase in willingness of prescribers to accept ASP recommendations could be due to an increase in awareness of other appropriate narrower-spectrum antimicrobial alternatives through ASP recommendations, along with gradual confidence in our ASP when patients did not appear to do worse after accepting our recommendations. Also,

TABLE 5 Logistic regression analysis of variables associated with 30-day mortality

	Univariate analysis[b]		Multivariate analysis[b]	
Variable[a]	OR	95% CI	OR	95% CI
Previous ESBL-resistant organism or MDRO colonization and/or infection	1.98	0.56 to 6.98	1.7	0.64 to 4.85
Broad-spectrum antibiotic use in past 30 days				
Prior admission	0.58	0.17 to 2.05	0.39	0.05 to 3.12
Prior 1st review	1.39	0.16 to 12.0	1.49	0.132 to 16.9
Immunocompromised[c]	0.35	0.10 to 1.30	0.87	0.25 to 3.05
Hypotension requiring fluid boluses and/or inotropes	7.00	1.85 to 26.5	5.2	1.34 to 20.6
Respiratory support	6.13	1.63 to 23.1	1.28	0.42 to 3.98
Intensive care/high-dependency unit admission	7.33	1.80 to 29.9	2.36	0.25 to 22.7
Febrile neutropenia	0.54	0.13 to 2.16	0.46	0.01 to 29.1
ESBL organism identified	0.33	0.03 to 3.23	0.10	0.03 to 3.52
Intervention nonacceptance	<0.001	<0.001 to >999	<0.001	<0.001 to >999

[a]Forced variables in multivariate model. ESBL, extended-spectrum beta-lactamase; MDRO, multidrug-resistant organism (resistant to three or more antimicrobial classes).
[b]OR, odds ratio; 95% CI, 95% confidence interval.
[c]Immunocompromised includes those undergoing a transplant, who had malignancy/receipt of chemotherapy, or who had immunodeficiency disorders.

similar to the in-person approach by Di Pentima et al. (7) and Hurst et al. (14), we communicated to the primary team via both written and verbal means, which may have contributed to the improvement in our ASP recommendation acceptance rates. It was also encouraging to observe that the appropriateness of carbapenem prescribing improved from 72% pre-ASP implementation to 78% at 2.5 years after ASP implementation, and to 81% in the year 2014.

Our findings in terms of patient safety outcomes were similar to other local studies in adult populations by Teng et al. (11) and Liew et al. (16), where there were no significant differences in terms of mortality and 30-day readmission rates between patients on carbapenems with and without acceptance of ASP. Pitt bacteremia score was a predictor of 30-day mortality in one study (11), similar to our findings where illness severity was a risk factor for mortality. Our study did not demonstrate an association of acceptance of ASP recommendations with a reduction in the duration of hospitalization and infection-related admissions, unlike the study by Lee et al. (10), who demonstrated a decrease in length of stay and a significant reduction in 30-day readmission rates in patients with complex chronic care conditions.

However, it should be noted that we had a large proportion of patients with high acuity, as 32% of our patients required intensive care/high-dependency unit admission and 58% were immunocompromised patients, in comparison to a study by Teng et al. (11), where only 7.7% of patients were in intensive care units (ICUs) and none were hematology-oncology patients. This is an important and encouraging finding, as acceptance of ASP recommendations for carbapenem discontinuation or deescalation in this group of high-acuity patients did not adversely impact patient safety and in fact could safely reduce carbapenem use, as we have demonstrated, in terms of both quantity and duration of therapy.

Our study findings contribute to the paucity of literature evaluating the impact of ASP interventions on clinical outcomes, in particular, specialized populations, such as pediatrics (17). We focused on this particular group of patients (i.e., those with whom carbapenem use was inappropriate), as ASP interventions to limit excessive prescribing would have an intrinsic tendency to be met with higher resistance in order to provide some insights into potential barriers to accepting ASP interventions, particularly in high-acuity settings. In addition, we quantified carbapenem utilization in both defined daily doses (DDDs) and days of therapy (DOTs) per 1,000 patient-days, which would provide useful comparisons with other institutions with similar patient profiles (18, 19).

We acknowledge that there are several assumptions in and limitations to this single-center observational study, where measures of metrics, such as length of stay and mortality, are subject to inherent biases due to secular trends in health care (18). However, these metrics do have their usefulness as a "balancing measure" to assure key stakeholders that ASP interventions do not lead to increased harm or excessive mortality, in particular where efforts are focused on a reduction in excessive prescribing (19). Also, our findings may not be entirely generalizable to other institutions where patient populations, ASP mechanisms, and prescribing practices may differ. However, we hope to be able to address the impact of ASP interventions on compensatory antibiotic use and carbapenem resistance in the future.

Conclusion. Carbapenem ASP interventions did not have an adverse impact on clinical outcomes in our institution. Interventions made by our ASP did not compromise patient safety while decreasing carbapenem utilization, even in high-acuity patients. We also identified specific barriers to intervention acceptance, which are potential targets for future ASP efforts to improve the appropriateness of carbapenem use. More studies on the impact of ASP interventions on patient outcomes in unique populations are necessary, including those on antimicrobial resistance trends.

MATERIALS AND METHODS

Data collection. We retrospectively reviewed all carbapenem ASP interventions made between July 2011 and December 2014 and only included reviews in which carbapenem use was deemed inappropriate according to institutional guidelines in this study (Tables 6 and 7). The details of our ASP have been described in an earlier study (15). In summary, the main strategy adopted by our ASP was a prospective-

TABLE 6 Criteria for appropriate use of carbapenems

Type of therapy	Description[a]
Targeted	For treatment of serious cephalosporin-resistant e.g., ESBL-resistant Gram-negative infections For second-line treatment of Gram-positive/Gram-negative infections in serious penicillin or cephalosporin allergy (e.g., extensive rash, angioedema, or anaphylactic reactions) Ertapenem should only be used as targeted therapy or as deescalation therapy from other broad-spectrum carbapenems when the following criteria are met: (i) for treatment of ertapenem-susceptible Gram-negative bacteria resistant to other beta-lactam antibiotics or/and fluoroquinolones (and not *Pseudomonas* spp.), and/or (ii) if patient is amenable to outpatient i.m./i.v. ertapenem antimicrobial therapy
Empiric	Empirical first-line therapy in severe/overwhelming sepsis (especially multiorgan dysfunction) requiring ventilatory and/or inotropic support for (i) severely ill neutropenic hemato-oncologic patients, (ii) severely ill patients with pneumonia/ARDS who may have suspected infection with *Burkholderia pseudomallei*, (iii) severely ill patients with intra-abdominal sepsis, and (iv) severely ill neonatal patients in intensive care unit with signs of worsening sepsis Empirical second- or third-line therapy for febrile neutropenic patients with strong evidence of cephalosporin-resistant Gram-negative infection: (i) known colonization with cephalosporin-resistant (e.g., ESBL) Gram-negative organisms (e.g., hemato-oncologic patients with mucositis or typhlitis) and (ii) blood culture positive for Gram-negative bacteria before final identification and susceptibility testing
Prophylactic (to discuss with ASP physician/ pharmacist for prophylactic use)	Prophylaxis for major surgical procedures in a patient with serious penicillin and cephalosporin allergy and prophylaxis for major surgical procedures in patients with preexisting infections with cephalosporin-resistant Gram-negative bacteria at the site of surgery

[a]ESBL, extended-spectrum beta-lactamase; i.m., intramuscular; i.v., intravenous; ARDS, acute respiratory distress syndrome.

review-and-feedback approach based on Infectious Diseases Society of America (IDSA) recommendations (1). A list of active carbapenem orders was generated daily on Monday through Friday. Our ASP team, composed of an infectious diseases physician and a full-time pharmacist, assessed the appropriateness of carbapenem use based on our institutional guidelines for the respective clinical condition at initiation to the end of therapy. Our assessment of appropriateness and clear reasons for interventions were conveyed to the primary team via written documentation in case notes and verbal communication.

ASP interventions include (i) discontinuation of carbapenem, (ii) change to a narrower-spectrum antimicrobial, (iii) optimization of dosing, (iv) further investigations (including procalcitonin, imaging, and cultures), (v) infectious diseases referral, (vi) discontinuation of antibiotic (other than a carbapenem), and (vii) source control (e.g., line removal). Intervention acceptance was reviewed by the ASP team the next working day to determine its acceptance or nonacceptance. Reason(s) for nonacceptance were clarified by the ASP physician or the pharmacist with the primary team either via face-to-face or by telephone conversation and documented. There may be more than one intervention made for a patient. Recommendations were reviewed throughout the individual's entire carbapenem course, in particular where new results, such as culture(s) and/or further investigations, such as procalcitonin and imaging, were available.

TABLE 7 Carbapenem dosing guidelines[a]

Carbapenem	Indication	Neonates		Infants/pediatrics		Adults
Meropenem	Sepsis/other (nonmeningitis)	<32 wks GA, <14 days PNA	20 mg/kg of body weight/dose q12h	20 mg/kg/dose q8h		1 g q8h
		<32 wks GA, ≥14 days PNA, or ≥32 wks GA	20 mg/kg/dose q8h			
	Severe, meningitis[b]	<32 wks GA, <14 days PNA	40 mg/kg/dose q12h	40 mg/kg/dose q8h		2 g q8h
		<32 wks GA, ≥14 days PNA, or ≥32 wks GA	40 mg/kg/dose q8h			
Ertapenem	Sepsis/other (nonmeningitis)	NA		15 mg/kg/dose q12h (max single dose, 500 mg)	≤12 yo	1 g q24h

[a]GA, gestation age/postmenstrual age (in weeks); PNA, postnatal age (in days); q12h, every 12 h; q8h, every 8 h; NA, not applicable; q24h, every 24 h.
[b]Severe defined as fulfilling criteria for empirical first-line therapy in severe/overwhelming sepsis (especially multiorgan dysfunction) requiring ventilatory and/or inotropic support for (i) severely ill neutropenic hemato-oncologic patients, (ii) severely ill patients with pneumonia/ARDS who may have suspected infection with *Burkholderia pseudomallei*, (iii) severely ill patients with intra-abdominal sepsis, and (iv) severely ill neonatal patients in intensive care unit with signs of worsening sepsis.

Reasons for nonacceptance of ASP interventions were classified as follows: (i) physician choice, (ii) patient still sick and does not wish to deescalate/discontinue carbapenems, (iii) patient improving and does not wish to deescalate/discontinue carbapenems, (iv) patient awaiting surgery and wants to stay on antibiotic, (v) patient deceased (i.e., before recommendation could be communicated to primary physician), and (vi) other reasons.

Data were analyzed in groups, one in which physicians accepted all interventions (accepted) and one in which physicians rejected interventions (rejected) for individual patients. For instance, if there were multiple reviews for the same patient for the same admission and/or more than one intervention was made, if any intervention was rejected, the patient would be classified in the rejected group.

The characteristics of the patients in both groups, including age, hospitalization, broad-spectrum antibiotic use in the past 30 days, immunocompromised status, severity of illness, hypotension, oxygen requirements, intensive care or high-dependency unit admission, and infection source were documented. We defined broad-spectrum antibiotics as third- and fourth-generation cephalosporins, fluoroquinolones, piperacillin-tazobactam, and carbapenems. Patients were defined as immunocompromised if they were undergoing a transplant, had a malignancy/receipt of chemotherapy, or had an immunodeficiency disorder.

Clinical outcomes, including World Health Organization defined daily doses (DDD) (http://www.whocc.no/atc_ddd_index) and days of therapy (DOT) per 1,000 patient-days, length of stay (days), 30-day all-cause infection-related readmissions and mortality, and clinical improvement at 7 days after initial review and at end of carbapenem therapy were collected. Microbiologic clearance at 7 days after first positive culture (if identified) and emergence of an carbapenem-resistant organism within 30 days after the start of carbapenem exposure were determined as well. Thirty-day readmissions were defined as admissions within 30 days from the date of discharge. Mortality was defined as death occurring during hospitalization or within 30 days of discharge. Infection-related status was determined based on the primary cause of readmission/death, which was based on the patient's discharge and/or death summary.

Carbapenem utilization was extracted from our hospital's electronic medication database, which captured the exact doses ordered and days administered for individual patients. Hospital census data were utilized to calculate carbapenem utilization rates by normalizing the days of therapy to 1,000 patient-days. Individual patients' medical records were reviewed for clinical outcomes data. Individual patient cost data were tabulated from hospitalization charges per day of their stay (ward and treatment fee) in the general ward, high-dependency unit, and/or intensive care unit in U.S. dollars.

Statistical analysis. For univariate analyses, categorical variables were compared using a chi-square test or Fisher's exact test, where appropriate. Continuous variables were compared using a *t* test or Mann-Whitney U test, where appropriate. Variables found to have an association with 30-day mortality ($P < 0.10$) or that were deemed clinically relevant *a priori* were included into a multivariate logistic regression model. Such variables included broad-spectrum antimicrobial use in the past 30 days, immunocompromised status, hypotension, oxygen requirements, intensive care or high-dependency unit admission, febrile neutropenia, intervention nonacceptance, and infection with extended-spectrum beta-lactamase-resistant organisms.

A *P* value was considered statistically significant if <0.05. All statistical analyses were performed using SPSS version 19 (IBM, Armonk, NY, USA).

This study was approved by the SingHealth Centralised Institutional Review Board. A requirement for informed consent was waived, as ASP operations were part of routine clinical practice and quality improvement protocols.

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