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Discontinuation of antibiotic therapy within 24 hours of treatment initiation for patients with no clinical evidence of bacterial infection: a 5-year safety and outcome study from Singapore General Hospital Antimicrobial Stewardship Program

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ABSTRACT

Background: Overprescribing antibiotics for patients with no bacterial infection is of growing global concern. It is important for timely Antimicrobial Stewardship Program (ASP) intervention to discontinue antibiotics for patients whose symptoms can be explained by non-infective causes, and without availability of bacterial cultures and susceptibilities reports. This study aimed to evaluate clinical outcomes and safety of early ASP review in these patients.

Methods: A retrospective review of the ASP database (January 2010 to December 2014) was conducted to identify patients for whom ASP recommended discontinuation of empiric antibiotics within 24 hours of prescribing. Demographics were collected. Clinical outcomes – duration of therapy, length of hospital stay (LOS), infection-related readmissions, and all-cause mortality – were compared between interventions accepted and rejected groups. Continuous data were analysed via unpaired Student's *t*-test. Categorical data were analysed using χ^2 test or Fisher's exact test, as appropriate.

Results: The ASP team recommended 794 interventions (overall acceptance rate of 72.9%, 579 of 794). There were no significant between-group differences in underlying demographics, and Charlson comorbidity index score. However, the interventions acceptance group had significantly shorter duration of therapy by 2.61 days (2.72 ± 3.04 vs. 5.33 ± 2.54 days; $P < 0.01$) and LOS by 7.41 days (7.98 ± 13.14 vs. 15.39 ± 22.62 days; $P < 0.01$), with estimated cost savings of SGD10 817 per patient. There were no significant between-group differences in 14-day mortality and readmission rates.

Conclusion: Prompt ASP interventions at Singapore General Hospital were associated with significant reductions in duration of therapy and LOS, with cost savings. It was demonstrated that it is safe to discontinue antibiotics within 24 hours of prescribing for patients with no evidence of bacterial infections.

1. Introduction

Increasingly, worldwide emergence of antimicrobial resistance has become a threat to patient safety in the healthcare setting, both locally and globally. In the last two decades, infectious diseases caused by antibiotic-resistant bacteria have posed a challenge to healthcare providers, as once-effective antibiotics are slowly losing their therapeutic efficacy, thus jeopardising patient safety. This is compounded by the decline in the development of new antibiotics [1–3]. The relationship between antimicrobial use and antimicrobial resistance is complex, but a growing body of data strongly suggest that higher levels of antimicrobial usage are associated with increased levels of antimicrobial resistance [4]. Inappropriate use (misuse or sub-optimal use) of antibiotics are among the key factors contributing to antimicrobial resistance [5–8].

Similarly, in local settings, there is an increasing trend of inappropriate and immoderate prescription of antimicrobial agents in clinical practice [8]. Often, antibiotics are prescribed for patients with viral infections or in situations where the use of antibiotics were not indicated. In an attempt to control the phenomenon of increasing antimicrobial resistance, Antimicrobial Stewardship

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Programs (ASPs) have been implemented in various countries, especially in developed countries. Several studies have shown that ASPs can effectively reduce antibiotic use, cost of care, and antimicrobial resistance rates [9–13].

Most ASPs, which are using the mechanism of prospective audit and feedback review, tend to audit at day 3 or later, after microbiological cultures are available to intervene where relevant. These ASPs do not stop unnecessary use of empiric antibiotics. Stopping unnecessary antibiotics earlier may reduce ecological pressure, but the safety of such intervention has not been studied. To curb overusage and misuse of antibiotics it is important for prompt ASP review within 24 hours of prescribing and to remind physicians to discontinue the use of antibiotics in these patients. It was hypothesised that discontinuing antibiotics for patients with no evidence of bacterial infections, within 24 hours of prescribing, is safe and does not compromise patient safety. This study aimed to evaluate the safety of and cost savings associated with these early ASP interventions.

2. Methods

2.1. Study design and setting

This was a single-centre, retrospective study conducted at Singapore General Hospital (SGH), which is Singapore's largest acute-tertiary care hospital with a capacity of 1785 beds. A review of the ASP database was conducted between January 2010 and December 2014. All patients were reviewed in whom the institution's ASP recommended discontinuation of empiric use of antibiotics within 24 hours of prescribing. All relevant demographics, including Charlson comorbidity index scores, were collected. Patients were classified into two groups: (i) those whose primary physicians accepted ASP interventions (accepted group); and (ii) those whose primary physicians rejected ASP interventions (rejected group).

2.2. Data collection and outcomes

The ASP recommendation to discontinue use of empiric antibiotics was made within 24 hours of antibiotic prescription. Compliance with or rejection of ASP recommendations was followed up as part of the workflow. For the purpose of this study the following clinical outcomes were compared between the accepted and rejected groups for evaluating safety of the ASP interventions: duration of antibiotic therapy, post ASP interventional length of stay (PLOS), 14-day infection-related readmissions, and 14-day all-cause mortality. This study also estimated the cost savings associated with any reduction in LOS and duration of therapy observed. Hospital bills for these patients were estimated from Ministry of Health (MOH), Singapore [14] and were compared between the accepted and rejected groups. For patients whose physicians had accepted ASP interventions (accepted group), any re-initiation of antibiotics within 72 hours was documented. The assumption was that for any other antibiotic course that was prescribed beyond 72 hours post ASP intervention, it would be a new episode of sepsis unrelated to the initial ASP assessment. For patients whose physicians had rejected ASP interventions (rejected group), any escalation of antibiotics within 72 hours and reasons for antibiotic escalation were also documented.

2.3. Definitions

Fourteen-day all-cause mortality was defined as death within 14 days from the date of ASP audit. Fourteen-day infection-related readmissions were defined as admissions due to infective causes within 14 days of the date of discharge. The PLOS was defined as the duration of hospital stay starting from the date of ASP intervention to the date of patient discharge. Duration of antibiotic therapy was defined as the length of audited antibiotic use in days.

2.4. Statistical methods

The IBM SPSS Statistics (version 20) was used for all statistical calculations. Data were expressed as mean ± standard deviation for continuous variables, and unpaired Student's *t*-test was performed to determine between-group differences in mean values. For the duration of antibiotic therapy and the PLOS, data were expressed as median values with range and compared with the Mann-Whitney U test. For categorical variables, data were presented as number and percentage, and were analysed using χ^2 test or Fisher's exact test, as appropriate.

2.5. Description of the Antimicrobial Stewardship Program

The ASP team, consisting of an Infectious Disease (ID) physician and ID clinical pharmacists, drew up new antibiotic guidelines for empirical treatment of common infections. Evidence for these guidelines was drawn from published guidelines by the Infectious Diseases Society of America (IDSA) and the British Society for Antimicrobial Chemotherapy (BSAC), and was adapted to SGH's microbial susceptibility patterns. These guidelines were approved by the institution's Pharmacy and Therapeutics (P and T) Committee and endorsed by the Medical Board before they were uploaded on the institution's intranet [10].

All patients who received carbapenems, cefepime, piperacillin/tazobactam, or parenteral ciprofloxacin were identified from the pharmacy database on a daily basis and subjected to the two-stage prospective audit, with immediate and concurrent feedback (Figure 1). These broad-spectrum antibiotics were selected for audit due to their increasing trends of prescription at SGH [15]. For the first stage of review, trained ID clinical pharmacists assessed the appropriateness of prescribed antibiotics and made therapeutic recommendations to optimise drug choices and dosing. The appropriateness of antibiotics was assessed based on compliance with the institution's guidelines. The ASP pharmacists evaluated and recorded the dose, route of administration, and intended duration for audited antibiotics. The cases in which initial evaluation did not reveal evidence of bacterial infection were brought up within 24 hours of prescription for thorough discussion and evaluation with an ID physician. Audited antibiotics were considered to be inappropriately prescribed if there was no evidence of bacterial infection present (i.e. bacterial colonisation or an alternative explanation for the fever). In such situations, the ASP team issued an intervention note, suggesting that the primary team discontinue the use of empiric antibiotics. The ASP team would follow up on the patient with an intervention note. In situations where the primary team did not follow ASP recommendations, the ASP pharmacist contacted the primary physician about the reasons for rejection. The ID physician was informed of these rejected interventions and spoke with the primary physician to discuss the patient and address their concerns. The ASP frequently recommends using procalcitonin (PCT) levels to guide decisions to initiate antibiotics for patients with suspected bacterial infections and having PCT levels of > 0.5 ng/mL, or to discontinue antibiotics for patients with low suspicion of bacterial infections when PCT levels are < 0.5 ng/mL or serial PCT levels show a decreasing trend.

2.6. Ethics

The study protocol was approved by the Singhealth Centralized Institutional Review Board (CIRB Ref: 2010/114/E). Informed

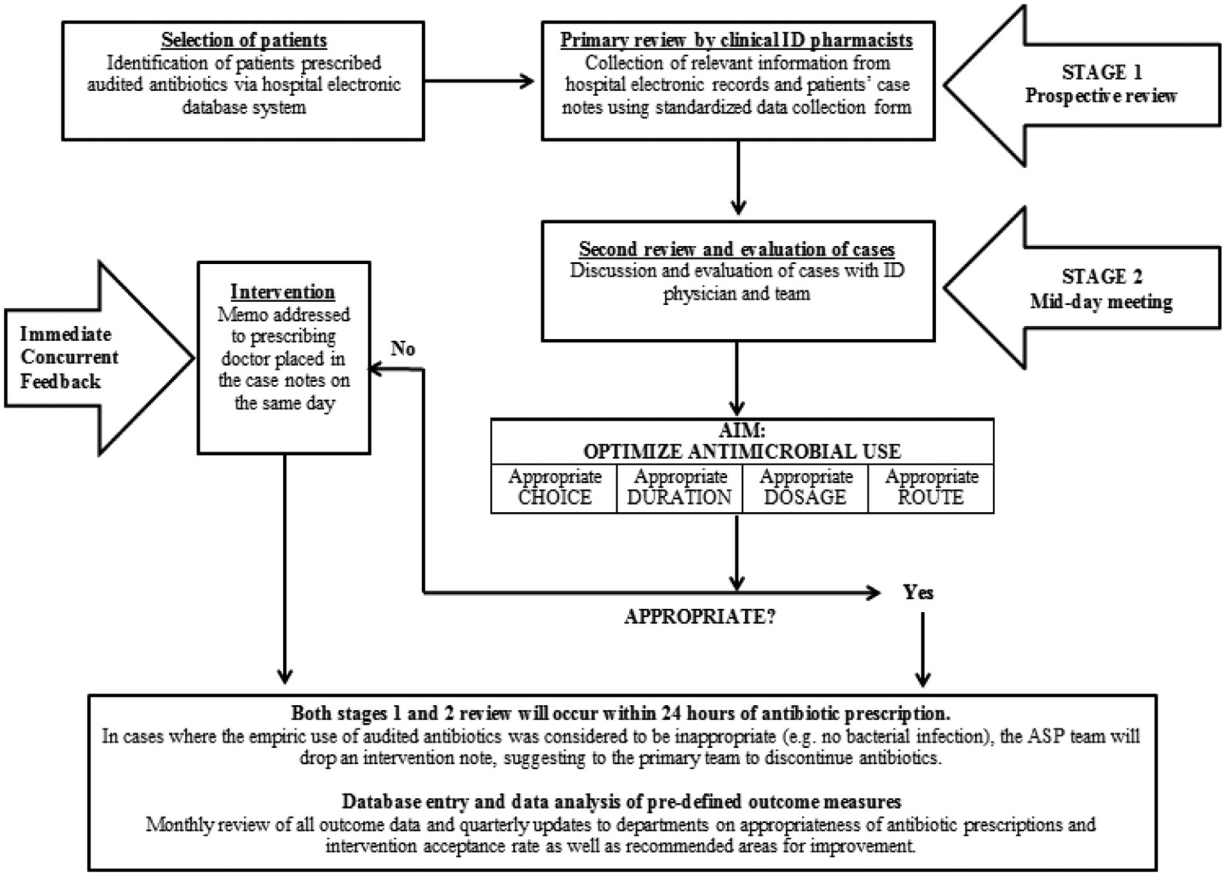

Figure 1. Schematic diagram of the Antimicrobial Stewardship Program prospective audit with immediate concurrent feedback workflow.

consent was not obtained from individual patients, as the operations of ASP constituted routine quality improvement practice, and only anonymised data were analysed.

3. Results

3.1. Interventions

Between January 2010 and December 2014, the ASP team reviewed and recommended 794 interventions to discontinue the use of empiric antibiotics within 24 hours of prescribing, with an overall acceptance rate of 72.9% (579 of 794). Of these 794 cases, 703 (88.5%) were from medical disciplines while the rest were admitted under surgical disciplines. The top three disciplines with highest acceptance rates of ASP interventions were from medical disciplines: internal medicine (80.2%), medical oncology (73.7%), and renal medicine (70.8%). Of these patient cases: 259 had single febrile episodes (32.6%) with no other localising symptoms of sepsis; 203 had malignant/central fever (25.6%); 156 had viral infections (19.6%); 96 had drug-related fever (12.1%); 68 had clinical symptoms that were more suggestive of fluid overload (8.6%); and 12 developed fever secondary to gout flare (1.5%). The differences in the proportions of the various interventions between the accepted and rejected groups were not statistically significant (Table 1). One patient may have one or more of the above-mentioned alternative diagnoses. The most common reasons for rejection were: (i) physician's personal preference to keep audited antibiotics (61.9%, 133 of 215); (ii) physician does not want to de-escalate as patient is improving (16.3%, 35 of 215); and (iii) physician does not want to change antibiotic therapy due to pending cultures (10.2%, 22 of 215).

There were no statistically significant between-group differences in terms of age, gender, Charlson comorbidity index scores, and previous hospitalisation within 3 months, except for previous antibiotic use within 3 months ($P = 0.04$). Of the 579 patients in the accepted group, 340 (58.7%) had previous antibiotic use within the preceding 3 months, while 144 (67.0%) of 215 in the rejected group had previous antibiotic use within the preceding 3 months (Table 2).

Table 1
Reasons for Antimicrobial Stewardship Program recommendations to discontinue empiric antibiotics.

Reasons for Antimicrobial Stewardship Program recommendations to discontinue empiric antibiotics	Proportion of all interventions (%)	Accepted group (n = 579)	Rejected group (n = 215)	*P*-value
Isolated febrile episodes	32.6	187 (32.3%)	72 (33.5%)	0.67
Malignant/central fever	25.6	142 (24.5%)	61 (28.4%)	0.27
Viral infection	19.6	122 (21.1%)	34 (15.8%)	0.10
Drug-related fever	12.1	69 (11.9%)	27 (12.6%)	0.90
Clinical symptoms suggestive of fluid overload	8.6	49 (8.5%)	19 (8.8%)	0.87
Possible gout flare	1.5	10 (1.7%)	2 (0.9%)	0.41

Table 2
Patient demographics.

Demographics	Accepted group (n = 579)	Rejected group (n = 215)	*P*-value
Mean age, years	69.3	70.1	0.50
Male gender	272 (47.0)	108 (50.2)	0.42
Previous hospitalisation within 3 months	384 (66.3)	127 (59.1)	0.07
Previous antibiotic use within 3 months^	340 (58.7)	144 (67.0)	0.04*
Charlson comorbidity scores			
1–2	103	43	
3–4	120	37	
≥ 5	356	135	0.919
Median [IQR]	5 [3–7]†	5 [3–7]†	
	Accepted group (n = 429)	Rejected group (n = 155)	*P*-value
Mean procalcitonin level (ng/mL)	0.18 ± 0.04#	0.16 ± 0.03#	0.07

‡Data are n (%) unless otherwise stated
Mean ± standard deviation
* Statistically significant ($P < 0.05$)
^ Prior to current admission

Table 3
Distribution of audited antibiotics.

Antibiotic	Accepted group (n = 579)	Rejected group (n = 215)
Piperacillin-tazobactam	463 (80.0%)	153 (71.2%)
Meropenem	60 (10.4%)	26 (12.1%)
Ciprofloxacin	28 (4.8%)	14 (6.5%)
Ertapenem	18 (3.0%)	16 (7.4%)
Imipenem	5 (0.9%)	3 (1.4%)
Cefepime	5 (0.9%)	3 (1.4%)

3.2. Distribution of audited antibiotics

The most commonly audited antibiotic was piperacillin-tazobactam (80% in accepted group, 71.2% in rejected group). The distribution of audited antibiotics between the two groups is presented in Table 3.

3.3. Duration of therapy

The mean duration of antibiotic use was significantly shorter by 2.61 days ($P < 0.01$) in the accepted group (2.72 ± 3.04 days) compared with the rejected group (5.33 ± 2.54 days) (Table 4).

3.4. Post Antimicrobial Stewardship Program interventional length of stay and cost savings

The PLOS was significantly shorter by 7.41 days ($P < 0.01$) in the accepted group (7.98 ± 13.14 days) than in the rejected group (15.39 ± 22.62 days) (Table 4). The average cost of stay per day was estimated to be SGD1422. Hence, the estimated cost savings for patients who accepted ASP interventions was SGD10 817 per patient case [16].

3.5. Fourteen-day all-cause mortality

Of the 579 patients in the accepted group, 18 (3.1%) died from all-cause mortality within 14 days of ASP intervention, while 12 (5.6%) of 215 patients in the rejected group died within 14 days of ASP intervention ($P = 0.10$).

3.6. Fourteen-day infection-related readmissions

Of the 731 surviving patients, 38 of 543 patients (7.0%) in the accepted group and 18 of 188 patients (9.6%) in the rejected group were readmitted for infection-related causes ($P = 0.25$) (Table 4). None of these patients had re-infections with the same bacteria at the same site.

3.7. Mean procalcitonin levels

Of the patient cases who received ASP interventions, 155 of 215 (72.1%) in the rejected group and 429 of 579 (74.1%) in the accepted group had serum procalcitonin performed at time of antibiotic initiation. The mean procalcitonin level in the accepted group (0.18 ± 0.04 ng/mL) was similar to that in the rejected group (0.16 ± 0.03 ng/mL). The difference was not statistically significant ($P = 0.07$) (Table 2).

3.8. Follow- up after Antimicrobial Stewardship Program intervention

Of 579 patients in the accepted group, five (1.0%) were re-initiated on antibiotics within 72 hours of intervention acceptance.

Table 4
Impact of Antimicrobial Stewardship Program interventions on the selected outcomes for patients with no bacterial infection.

Outcomes	Accepted group (n = 579)	Rejected group (n = 215)	*P*-value
Duration of therapy (days) [Mean ± SD]	2.72 ± 3.04	5.33 ± 2.54	< 0.01*
Length of stay post Antimicrobial Stewardship Program intervention (days) [Mean ± SD]	7.98 ± 13.14	15.39 ± 22.62	< 0.01*
14-day all-cause mortality	18 (3.1)	12 (5.6)	0.10
	Accepted group (n = 543)	Rejected group (n = 188)	*P*-value
14-day readmission due to infection	38 (7.0)	18 (9.6)	0.25

SD, standard deviation
‡Data are n (%) unless otherwise stated
* Statistically significant ($P < 0.05$)

They were prescribed antibiotics because they had a further febrile episode, despite normal procalcitonin levels (< 0.5 ng/mL) and decreasing C-reactive protein trend. Four of these five patients received 3 days of antibiotics until the repeated septic work-up cultures were available as negative. One patient received a total of 7 days of levofloxacin. There was no difference in the 14-day all-cause mortality and 14-day infection-related readmission in these five patients.

Of the 215 patients in the rejected group, 11 (5.1%) had antibiotic escalation within 72 hours post intervention rejection. The majority of them (10 of 11) had escalation of antibiotics in response to another febrile episode, despite normal inflammatory markers and that alternative explanations were available to account for the febrile episodes. The last patient had an episode of desaturation, which was later improved with the initiation of diuretics.

4. Discussion

The ASP program was pioneered at SGH in 2006. Since then, the adoption of a prospective audit and feedback system has seen the ASP acceptance rates increasing from the initial approximate 70% to a recent sustained acceptance rate of near 90%. This study showed that prompt ASP interventions in SGH were associated with significant reductions in duration of antibiotic therapy and PLOS with cost savings, without compromising patient safety. A recent study by Cai et al. reported a high prevalence rate of 25.5% for unspecified sepsis (the most common type of hospital-acquired infection) in a recent point prevalence study of hospital-acquired infections in Singapore. It was also found that 86% had a fever but not hypotension or oliguria [17]. In addition, a large number of patients in these Singapore acute-care hospitals were also prescribed antibiotics for fever in the absence of other symptoms, which represents a target for intervention to reduce unnecessary antibiotic prescriptions since fever can also arise due to non-infectious inflammatory causes. Effective ASP mechanism incorporating individualised education is needed to counteract this.

Prior authorisation by infectious disease physicians for initiation and continuation of broad-spectrum antibiotics, and/or immediate prospective audit and feedback system have been commonly employed as part of stewardship efforts globally [18]. An immediate prospective audit and feedback system have proved to be promising, as it was previously shown that early ASP review and intervention within 48 hours of antibiotic prescription is safe and beneficial to patients [19]. In general, most institutions would prefer a lapse of ≥ 72 hours of antibiotic prescription before reviewing. This approach allows clinical information, such as bacterial culture results, to be made available before any interventions. However, the current study demonstrated that prompt ASP review and intervention to discontinue antibiotics within 24 hours of prescribing, without waiting for bacterial culture and susceptibilities results to be available, is safe and beneficial. Patients invariably received antibiotics upon admission to the hospital and physicians often did not revisit the need for the antibiotic, even after preliminary investigations results were available. This study showed that many of these patients did not even have an infection to begin with, and prospective audit and feedback within 24 hours of antibiotic prescribing may work best in this instance.

Of the 794 interventions made between January 2010 and December 2014, the three most common reasons for ASP recommendation to discontinue empiric antibiotics in these patients within 24 hours of antibiotic prescription were identified as: isolated fever episodes (usually at a maximum temperature of 37.5–38.5°C) with no localising symptoms of sepsis (32.6%), malignant or central fever (25.6%) and viral infection (19.6%). The other reasons are presented in Table 1. More often than not, antibiotics were prescribed in response to febrile episodes, resulting in septic workup to determine the cause for fever. The ASP interventions to discontinue empiric antibiotic use within 24 hours of prescription resulted in significant reductions in mean duration of antibiotic use and PLOS in the accepted group, without compromising patients' safety. Patients in the rejected group had longer length of hospital stays after rejection of the intervention, which was likely attributed to the need for completion of antibiotic therapy as an inpatient. While it may be argued that the patients in the rejected group were likely more ill and hence the reluctance to discontinue the use of antibiotics, no significant between-group differences were found in the baseline characteristics and Charlson comorbidity scores. Notably, even in the five patients in the accepted group who were restarted on antibiotics again within 72 hours, the reason was still fever, despite normal inflammatory markers. In the 11 patients who had antibiotic escalation within 72 hours of intervention rejection, the reason for antibiotic escalation was again due to repeated febrile episodes, even though the patient remained clinically stable, had normal inflammatory markers and, more importantly, alternative explanations were available to account for the febrile episodes. It appeared that the doctors often prescribe antibiotics in response to fever, like a knee-jerk reaction, when they should actually systematically clinically workup for each patient and consider other sources of fever too.

Procalcitonin is a biomarker that is used for differentiating bacterial from non-infectious systemic inflammatory response syndrome, and has been widely used at SGH as one of the inflammatory markers during each septic workup [20–21]. The use of procalcitonin, in addition to an established ASP, has shown to significantly reduce antibiotic exposure and adverse outcomes [22]. The ASP team has incorporated using normal procalcitonin levels (i.e. < 0.5 ng/mL) as part of clinical assessment to reinforce antibiotic therapy discontinuation to the prescribers. This is especially so in situations where no further sources of sepsis can be found, and a concurrent non-infectious reason (e.g. malignant fever or viral infection) are available to explain febrile episodes [23–24]. This study showed that the mean procalcitonin level in the accepted group (0.18 ± 0.04 ng/mL) was not statistically significant to that of the rejected group (0.16 ± 0.03 ng/mL). This supports the fact that the study cohort, whom the ASP intervened to discontinue empiric antibiotics within 24 hours of prescribing, was not likely to have a bacterial infection.

As this study involved a relatively large sample of patients admitted under various specialties, the results may be applied to a variety of healthcare settings worldwide. However, the retrospective nature of this study limited the amount of information regarding differences in severity of diseases and/or presence of comorbidities that may potentially affect outcomes. While it found no significant between-group differences in the baseline demographics and Charlson comorbidity scores, this did not measure the degree of acute illness. Patients were assigned to the two groups based on physicians' acceptance or rejection of ASP recommendations. As such, it is likely that the patients in the rejected group were more ill, resulting in the physicians wanting to persist with antibiotic therapy. Such selection bias was a limitation to the retrospective nature of this study. Nevertheless, the results remain valid because antibiotic discontinuation within 24 hours in the accepted group alone is already impactful and important. In fact, discontinuing antibiotics within 24 hours in the 'accepted' group was associated with shorter duration of therapy and LOS. In addition, there was no difference demonstrated in patient safety outcomes, such as 14-day mortality and 30-day readmission, between the accepted and rejected groups. The outcomes of this study were limited to the audit of the various broad-spectrum antibiotics listed above.

Further studies should be conducted to understand the prescribing habits of physicians, determine if the physicians need to

be educated on evaluating for infections, and further streamline the ASP program to address inappropriate antimicrobial prescribing and curb growing antimicrobial resistance.

5. Conclusions

Interventions recommended by the ASP to discontinue antibiotics within 24 hours of prescribing at SGH were associated with significant reductions in duration of antibiotic therapy and LOS, without increasing 14-day all-cause mortality and infection-related admissions. ASPs should consider early intervention in selected low-risk patients with no evidence of bacterial infection.

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Competing Interests

No conflict of interest for all authors.

Ethical Approval

The study protocol was approved by the Singhealth Centralized Institutional Review Board (CIRB Ref: 2010/114/E).

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