Journal of Global Antimicrobial Resistance 17 (2019) 312–315

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Do antimicrobial stewardship programme interventions reduce the rate of and protect against *Clostridium difficile* infection?

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ARTICLE INFO

Article history:
Received 21 August 2018
Received in revised form 10 January 2019
Accepted 11 January 2019
Available online 22 January 2019

Keywords:
Antimicrobial stewardship programme
Clostridium difficile

ABSTRACT

Objectives: Antimicrobial stewardship programmes (ASPs) have often been recommended as a viable solution to minimise the incidence of *Clostridium difficile* infection (CDI), which can be life-threatening. This study aimed to evaluate whether ASP interventions have contributed to reducing CDI rates.
Methods: A retrospective review of ASP interventions issued from January 2013 to April 2014 was performed using data from the ASP database of Singapore General Hospital, a 1600-bed tertiary-care hospital in Singapore. A total of 283 interventions satisfied the inclusion criteria, of which commonly audited antibiotics were piperacillin/tazobactam (41.3%) and carbapenems (54.8%). Comparisons were made at 30 days post-intervention between those with accepted or rejected interventions. The primary outcome was CDI incidence; secondary outcomes included length of hospitalisation post-intervention, 30-day mortality and CDI recurrence rate.
Results: Whilst the median duration of antibiotic therapy was reduced by 2 days (6 days vs. 4 days; $P < 0.001$), acceptance of ASP interventions did not alter primary CDI incidence at 30 days ($P = 0.644$) post-intervention. However, reduced CDI recurrence rates were observed for patients positive for CDI in the accepted patient group compared with the rejected group (0% vs. 37.5%; $P = 0.03$), with no difference in CDI 30-day mortality between the two groups.
Conclusion: Intervention acceptance did not contribute to a significant reduction in CDI incidence but may be associated with lower recurrence rates, although further studies are required.

1. Introduction

Clostridium difficile infection (CDI) can cause potential life-threatening complications and is associated with increased mortality, length of hospital stay and financial costs, posing an economic and clinical burden [1–4]. With recent studies suggesting an increased incidence of CDI, it remains a relevant concern [5]. Antibiotic use has been considered as a major but modifiable risk factor for CDI [6–8]. For instance, Slimings and Riley reported that the risk of hospital- acquired CDI with prior exposure to β-lactam/β-lactamase inhibitors, fluoroquinolones and carbapenems was 1.54 [95% confidence interval (CI) 1.05–2.24], 1.66 (95% CI 1.17–2.35) and 1.84 (95% CI 1.26–2.68), respectively [8]. Furthermore, the risk of CDI increases with increasing cumulative antibiotic exposure (cumulative doses, number of antibiotics and antibiotic days) [9]. Therefore, antimicrobial stewardship programmes (ASPs) that seek to reduce unnecessary antibiotic use have been recommended as a viable method to control the incidence of CDI [10].

The ASP team in Singapore General Hospital (SGH) reviews the hospital-wide use of broad-spectrum antibiotics, including carbapenems, piperacillin/tazobactam (TZP) and intravenous (i.v.) ciprofloxacin. By reducing improper use of these antibiotics, it is hoped to reduce the rate of CDI acquired in the hospital setting. Whilst our previous studies have demonstrated decreases in antibiotic usage and length of hospitalisation in cases where ASP interventions were accepted compared with those where

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https://doi.org/10.1016/j.jgar.2019.01.018
2213-7165/

interventions were rejected, we have yet to determine the impact of the ASP on the CDI incidence and outcomes [11].

The aim of this study was to evaluate whether the ASP interventions have contributed to reducing healthcare-associated (HA) CDI rates.

2. Patients and methods

2.1. Patient population and study design

This was a retrospective cohort study of patients from SGH, a 1600-bed tertiary-care hospital in Singapore, conducted between January 2013 and April 2014. Patients were included in the study if they met the following criteria: (i) received an antibiotic reviewed by the ASP team; (ii) the antibiotic order resulted in an ASP intervention that recommended the discontinuation of an antibiotic owing to absence of infection, narrowing of empirical coverage or de-escalation based on culture results; and (iii) they had at least one *C. difficile* PCR test performed within 30 days of an ASP intervention. Approval from the SingHealth Centralised Institutional Review Board was acquired prior to initiation of this study. Waiver of informed consent was granted in view of the retrospective nature of the study.

2.2. Data collection

Baseline demographics, co-morbidities, microbiological data, antibiotic exposures and intervention data were extracted from electronic medical records, computerised records of the microbiological laboratory and the ASP database. Co-morbidity burden was assessed using the Charlson comorbidity index [12]. Antibiotic exposures in the 30 days prior to the *C. difficile* test date were recorded. All antibiotics were grouped according to antibiotics classes and were measured by days of therapy.

2.3. Description of the antimicrobial stewardship programme

The ASP team comprised clinical microbiologists, infectious diseases (ID) clinical pharmacists and an ID physician. A list of patients who received TZP, meropenem, imipenem, ertapenem or parenteral ciprofloxacin was generated from the pharmacy database daily. The identified cases were subjected to a two-stage prospective audit by the ASP team with prospective and concurrent feedback. For cases with clinical conundrum and complexity, a second review was then performed with the ASP director (ID physician).

Within the first 24 h of an audited antibiotic being prescribed by the primary healthcare team, an audit based on assessment of the

Table 1
Baseline demographics and antibiotic exposure of patients between the antimicrobial stewardship programme (ASP) intervention accepted and rejected groups in Singapore General Hospital.

Characteristic	Intervention rejected ($n = 87$)	Intervention accepted ($n = 196$)	*P*-value
CDI	8 (9.2)	15 (7.7)	0.644
Demographics			
Age (years) [median (range)]	69 (55–79)	66 (56–77)	0.41
Female sex	43 (49.4)	94 (48.0)	0.9
Ward type			0.48
Surgical	11 (12.6)	32 (16.3)	
Medical	76 (87.4)	164 (83.7)	
Charlson comorbidity index [median (range)]	5 (0–12)	5 (5–13)	0.96
Other risk factors			
Previous hospitalisation	47 (54.0)	118 (60.2)	0.36
Previous ICU stay	8 (9.2)	24 (12.2)	0.139
Acid suppression	54 (62.1)	96 (49.0)	0.9
H_2 antagonists	0	7 (3.6)	0.104
Proton pump inhibitors	53 (60.9)	92 (46.9)	0.79
ASP characteristics			
Intervention acceptance			
ASP antibiotic			0.53
Ciprofloxacin	3 (3.4)	8 (4.1)	
Carbapenems	52 (59.8)	103 (52.6)	
Piperacillin/tazobactam	32 (36.8)	85 (43.4)	
Intervention type			0.15
De-escalation/narrowing	29 (33.3)	84 (42.9)	
Discontinuation	58 (66.7)	112 (57.1)	
Duration of ASP antibiotic (days) [median (range)]	6 (4–9)	4 (2–6)	<0.001
Antibiotic use			
Penicillins	3 (3.4)	16 (8.2)	0.2
Duration of penicillins (days) [median (range)]	4 (4–5)	4 (3–5)	0.49
Cephalosporins	29 (33.3)	59 (30.1)	0.58
Duration of cephalosporins (days) [median (range)]	4 (1–10)	3 (1–13)	1.00
β-Lactam/BLIs	71 (81.6)	159 (81.1)	1
Duration of β-lactam/BLIs (days) [median (range)]	8 (1–27)	3 (1–30)	0.08
Carbapenems	30 (34.5)	78 (39.8)	0.43
Duration of carbapenems (days) [median (range)]	7 (2–24)	7 (1–24)	0.772
Macrolides	6 (6.9)	13 (6.6)	1
Duration of macrolides (days) [median (range)]	2 (1–7)	3 (1–30)	1.00
Fluoroquinolones	17 (19.5)	61 (31.1)	0.045
Duration of fluroquinolone (days) [median (range)]	5 (1–31)	7 (1–30)	0.474
Trimethoprim/sulfamethoxazole (SXT)	2 (2.3)	17 (8.7)	0.17
Duration of SXT (days) [median (range)]	28 (4–30)	15.5 (7–24)	0.474
Clindamycin	0 (0.0)	4 (2.0)	0.28
Duration of clindamycin (days) [median (range)]	–	10 (3–14)	N/A
Length of antibiotic therapy (days) [median (range)]	11 (6–17)	9 (4–16.5)	0.37

CDI, *Clostridium difficile* infection; ICU, intensive care unit; BLI, β-lactamase inhibitor; N/A, not applicable.

indication, appropriateness, dose, route of administration and duration of use of the antibiotic would be conducted by the ASP team. For cases where use of the audited antibiotic was found to be inappropriate, a written intervention was issued. Intervention acceptance or rejection was determined by the primary team within 24 h following issuance of the intervention. Antibiotic prescriptions were reviewed on Days 2, 4 and 7 if applicable, with appropriate recommendations to discontinue, dose adjust, change or de-escalate audited antibiotics. In certain cases, requests for ordering additional clinical tests or referrals for review by an ID specialist were also made by the ASP team.

For an antibiotic to be deemed as inappropriately prescribed, one or more of the following criteria needed to be met: (i) based on culture results, a narrower-spectrum antibiotic could be used; (ii) no infection was present (e.g. bacterial colonisation, other causes of fever); (iii) antibiotic use deviated from hospital guidelines without valid reasons; or (iv) dosage, duration of therapy and/or empirical treatment choices were suboptimal based on available guidelines.

2.4. Outcomes

The primary outcome was the rate of primary HA CDI occurring within 30 days of ASP intervention. A patient was classified as having HA CDI if the following criteria were met: (i) a positive CDI test (positive PCR test); (ii) development of diarrhoea (at least three unformed stools over a period of 24 h) lasting for $\geq$2 days; and (iii) hospitalisation for >48 h or had previous hospitalisation within 30 days [13].

The secondary outcomes included length of hospitalisation post-intervention, 30-day mortality post-intervention and CDI 30-day mortality (defined as mortality within 30 days of the *C. difficile* test date) and CDI recurrence rate. CDI recurrence refers to a second CDI episode occurring within 8 weeks after completion of treatment of the initial episode [1].

2.5. Statistical analysis

Continuous data were expressed as mean ± standard deviation (S.D.) for parametric data and median and range for non-parametric data and were analysed using the Wilcoxon rank sum test for non-normally distributed variables. Categorical data were expressed as proportion with percentages and were analysed using the unpaired χ^2 test or Fisher's exact test. All tests were two-tailed and a result was considered to be statistically significant at a *P*-value of <0.05. All analytical data were processed using Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX).

3. Results

During the study period a total of 4530 cases were audited, of which 283 cases received an ASP-audited antibiotic requiring an intervention and had a *C. difficile* test performed (due to presence of diarrhoea) and thus were included in the study. Of these 283 cases, 23 (8.1%) developed HA CDI within 30 days of ASP intervention, and these were their first episodes of HA CDI.

A comparison of the baseline demographics, clinical characteristics, antibiotic exposures and ASP intervention types between the ASP intervention accepted and rejected groups is summarised in Table 1. There were no significant differences in the baseline demographics between intervention accepted and rejected groups. A larger proportion of patients from the intervention accepted group received fluoroquinolones compared with the intervention rejected group [31.1% (61/196) vs. 19.5% (17/87); $P = 0.045$], although the median duration of fluoroquinolone use between the two groups did not differ significantly. The proportion of patients on other antibiotics and the median duration of all antibiotic use between the two groups were not statistically different.

3.1. Primary healthcare-associated C. difficile infection

The development of primary HA CDI occurred in 8 (9.2%) of 87 patients from the intervention rejected group and 15 (7.7%) of 196 patients from the intervention accepted group. There was no statistically significant difference ($P = 0.644$) in the proportion of patients with CDI between the two groups.

3.2. Audited antibiotic duration

The median (range) duration of audited antibiotic use was significantly shorter [4 (2–6) days vs. 6 (4–9) days; $P < 0.001$] in patients with interventions accepted compared with those with interventions rejected.

3.3. 30-day mortality

There was no significant difference in 30-day mortality post-intervention between intervention accepted and rejected groups [16.8% (33/196) vs. 17.2% (15/87); $P = 0.933$]. There was also no significant difference in CDI 30-day mortality (i.e. within 30 days of the *C. difficile* test date) between intervention accepted and rejected groups [20.9% (41/196) vs. 25.3% (22/87); $P = 0.415$].

3.4. Length of hospital stay

Post-intervention length of hospital stay was shorter in the intervention accepted group (mean ± S.D. 21.6 ± 29.48 days vs. 32.59 ± 89 days), but this was not statistically significant ($P = 0.122$). Amongst patients with CDI, the median duration of hospitalisation prior to *C. difficile* test date was significantly longer compared with those without CDI (23 days vs. 12 days; $P < 0.001$).

3.5. C. difficile infection recurrence

None of the 15 patients who had CDI from the intervention accepted group experienced recurrence, whilst 3 of the 8 patients who had CDI from the intervention rejected group experienced recurrence and received oral vancomycin as first-line therapy according to the institutional antibiotic guidelines. The CDI recurrence rate was lower in the ASP intervention accepted group and this was statistically significant (0% vs. 37.5%; $P = 0.03$).

4. Discussion

In this study, 23 patients developed HA CDI within 30 days of ASP intervention. These cases constituted 3.4% of the 672 *C. difficile* PCR-positive tests recorded from 2013–2014. The CDI incidence during this period was 6.1 per 10 000 inpatient days, which was a notable increase from 2012 (4.6 per 10 000 inpatient days), highlighting the need to tackle the rising disease burden, which has been associated with poor patient outcomes and increasing healthcare costs. Many studies have recommended ASPs, which seek to reduce unnecessary antibiotic use, as a viable method to control CDI incidence. Whilst the ASP of SGH has been demonstrated to be safe with a reduction in the duration of audited antibiotic use without an increase in 30-day post-intervention mortality, we did not demonstrate a significant reduction in primary HA CDI in patients with acceptance of ASP interventions.

Despite a significant reduction in the duration of audited antibiotics, this study was unable to demonstrate a statistically significant reduction in the primary CDI incidence rate within

30 days post-intervention in the ASP intervention accepted group. Similar results were obtained in a retrospective study conducted in a 1500-bed acute care academic hospital in Singapore exploring the safety and clinical outcomes of carbapenem de-escalation by their ASP team [14]. As the ASP of SGH in the current study did not include audit of all antibiotics, in particular amoxicillin/clavulanic acid and other anaerobic spectrum active fluoroquinolones, the statistical insignificant reduction of HA CDI finding is not unexpected.

In this study, the proportion of patients with fluoroquinolone use was higher in the intervention accepted group, although the median duration of treatment was comparable. Hence, a potential explanation for the findings would be that increased exposure to fluoroquinolones could have cancelled out any benefit in CDI reduction especially as it could be considered as one of the antibiotic classes with the highest risk of CDI (risk ratio $\geq$5) [15]. Moreover, only i.v., and not oral, ciprofloxacin was audited during the study period. Moving forward, our institution has included the other quinolones for ASP audit in the bid to reduce CDI rates.

An increased duration of hospitalisation has been demonstrated as a risk factor for CDI [16,17]. Whilst the intervention accepted group was observed to have an increasing statistical trend towards shorter post-intervention length of hospital stay, it was noted that the median duration of hospitalisation prior to *C. difficile* test date was longer in patients with CDI (23 days vs. 12 days; $P < 0.001$). The longer length of stay prior to the *C. difficile* test date could have negated potential benefits of reduced *C. difficile* exposure post-intervention.

Recurrence rates were significantly lower for CDI-positive patients within the intervention accepted group compared with the intervention rejected group (0% vs. 37.5%; $P = 0.03$). This finding may be attributed to higher antibiotic discontinuation rates after diagnosis of CDI in the intervention accepted group, since continued treatment with non-*C. difficile* antibiotics after diagnosis of CDI has been associated with a higher recurrence rate (44.4% vs. 12.5%; $P = 0.294$) [18]. The three patients who had recurrent CDI in the rejected group had continued on the audited antibiotics despite the ASP's continuous effort to stop therapy. As demonstrated in a study by Drekonja et al., non-CDI antimicrobial use was associated with a three-fold increase in the odds of CDI recurrence [19]. Interestingly, Watson et al. mentioned that amongst patients who received antibiotics after diagnosis of CDI, those with inappropriate antibiotic use were at higher risk of CDI recurrence after adjusting for covariates compared with those with appropriate antibiotic use, suggesting the potential role of the ASP in lowering CDI recurrence rates [20]. Further studies are warranted to establish the benefit of ASP interventions on reduction in CDI recurrence rates.

Several limitations of this study must be acknowledged. Owing to its retrospective design, data pertaining to outpatient antibiotic use were extracted from SGH medication discharge records. This may not reflect true antibiotic exposure as it does not account for compliance or outpatient antibiotic consumption. Another limitation of the study is the small sample size, which reduces the power of the statistical analysis. Lastly, the study is based on outcomes from a single institution and may not be generalisable to other hospitals.

5. Conclusion

Despite a reduction in the duration of audited antibiotic use, intervention acceptance did not contribute to a significant reduction in primary HA CDI incidence. Whilst there may be an association between intervention acceptance and reduced CDI recurrence rates, further studies will be required to validate this association.

Funding

None.

Competing interests

None declared.

Ethical approval

Ethical approval was obtained from SingHealth Centralised Institutional Review Board [CIRB Ref: 2010/114/E]. Waiver of informed consent was granted in view of the retrospective nature of the study.

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