Impact of an antimicrobial stewardship program on healthcare-associated *Clostridium difficile* rates at a community-based teaching hospital

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Abstract

We conducted a pre-intervention/post-intervention study to assess the rate of healthcare-associated *Clostridium difficile* infections (HA-CDI) before and after the implementation of an antimicrobial stewardship program (ASP). Upon implementation of our ASP, the usage of targeted antimicrobials, including ceftriaxone, clindamycin, fluoroquinolones and carbapenem antibiotics, were significantly reduced. There was also a significant reduction in HA-CDI/1000 patient-days following ASP implementation (0.84 vs. 0.28; $P = 0.035$).

Keywords

Antimicrobial stewardship, healthcare-associated infections, *Clostridium difficile*, healthcare-associated *Clostridium difficile*, antimicrobial resistance, infection control, infection prevention, infectious diseases, nosocomial infection

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Background

Clostridium difficile has the ability to cause life-threatening diarrhoea and is strongly associated with recent antibiotic and healthcare exposures. It is now the most common pathogen among healthcare-associated infections in the United States, accounting for 12.1% of such infections, and results in significant mortality and healthcare costs (Magill et al., 2014). In 2013, the CDC reported there to be 250,000 *C. difficile* infections (CDI) per year requiring hospitalisations or affecting already hospitalised patients, as well as 14,000 deaths per year (CDC, 2013). Healthcare costs related to CDI have been estimated to be as much as \$4.8 billion for acute care facilities alone (Lessa et al., 2015).

CDI occur almost exclusively in patients that have previously been exposed to antibiotics (CDC, 2013). Certain antibiotics have been associated with higher rates of CDI, including ceftriaxone, clindamycin and fluoroquinolones (Gerding, 2004; Muto et al., 2005). Efforts to reduce exposure to these and other antibiotics with high rates of CDI have been explored by antimicrobial stewardship programs (ASPs). A recent meta-analysis showed a significant protective effect between ASPs and CDI incidence in a random effects model (Feazel et al., 2014). When stratified by

intervention type, a significant reduction in CDI was found for restrictive ASPs, such as complete removal of drug or prior approval requirement.

At our institution, our ASP developed a multi-phase initiative including provider education, syndrome-specific initiatives, drug tier restriction, and prospective audit and feedback. We evaluated the effect of this bundled approach on high-risk antimicrobial usage and healthcare-associated CDI (HA-CDI).

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Table 1. List of restricted antibiotics during the intervention periods.

Tier 1 antibiotics	Tier 2 antibiotics
Amikacin	Cefepime
Aztreonam	Ceftriaxone
Carbapenems	Clindamycin
Ceftaroline	Fluoroquinolones
Daptomycin	Piperacillin-tazobactam
Linezolid	Vancomycin (oral)
Polymyxins	
Tigecycline	
Non-formulary agents	

Tier 1 agents required ASP approval and an ID consultation for usage.
Tier 2 agents underwent prospective audit and feedback.

Methods

We conducted a retrospective, pre-intervention/post-intervention study to assess the impact of ASP implementation on the incidence of HA-CDI. Our institution, The Western Pennsylvania Hospital (WPH), is a 317-bed community-based teaching hospital with nearly 6800 inpatient admissions annually. Our WPH ASP was established in September 2015 and consists of a 0.5 full-time equivalent (FTE) Infectious Diseases attending physician and a 1.0 FTE Infectious Diseases clinical pharmacy specialist. Before our ASP go-live date, a series of educational lectures were delivered by the ASP Infectious Diseases attending physician to the Internal Medicine residency, Internal Medicine faculty, Division of Hospitalist Medicine, Division of Infectious Diseases, Division of Pulmonary and Critical Care Medicine, Department of Emergency Medicine, Department of Surgery, Department of Pharmacy, and Department of Infection Prevention and Control. As for the daily operations of our ASP, prior authorisation is required for Tier 1 restricted antimicrobial agents seven days per week (see Table 1). Use of all Tier 1 agents requires prior ASP approval. The ASP pager is answered between 08:00 and 17:00. Calling clinicians are expected to provide a rationale for the use of the restricted agent. If an agent is approved by the ASP team, the subsequent placement of a formal Infectious Disease consultation is also required. Tier 1 restricted agents ordered between 17:00 and 08:00 are reviewed before noon the following morning, and doses are dispensed until the ASP team is able to evaluate the following day. Prospective audit with real-time intervention and feedback is performed Monday through Friday for our Tier 2 restricted agents by an ASP team member. The ASP team contacts the primary team via telephone call or secure text page with recommendations for an alternative agent, if use

is deemed inappropriate. Additionally, ASP team members provide the primary team with intravenous to oral conversion and duration of therapy recommendations. Furthermore, upon the go-live, our ASP introduced syndrome-specific initiatives for skin and soft-tissue infections and lower respiratory tract infections utilising procalcitonin-guidance (Walsh et al., 2017; Walsh et al., in press). An ASP team member performs prospective audit with real-time intervention and feedback Monday through Friday to ensure compliance with our clinical decision-making pathways for these two disease states. Since our ASP go-live, intensive educational efforts were continued including dissemination of a yearly antimicrobial guide, creation of additional clinical decision-making algorithms, distribution of monthly ASP newsletters and regular lectures to medical staff and house staff.

The primary objective was to evaluate the impact of implementation of our ASP on HA-CDI/1000 patient-days in hospitalised adult patients by comparing incidence in two time periods: (1) pre-intervention: 1 January 2015 – 31 August 2015; and (2) post-intervention: 1 September 2015 – 31 December 2016. This time period was selected due to the CDC/NHSN HA-CDI definition change in January 2015 (CDC, 2017). CDI was diagnosed using real-time polymerase chain reaction throughout the entire study. The secondary objective was to determine the impact of implementation of our ASP on utilisation of targeted antibiotics in two time periods: (1) pre-intervention 1 January 2013 – 31 August 2015; and (2) post-intervention: 1 September 2015 – 31 December 2016. Exempt status was granted by the Allegheny Health Network institutional review board. A review of the Infection Prevention and Control database for all patients diagnosed with HA-CDI based upon CDC/NHSN criteria was performed (CDC, 2017). Days of therapy per 1000 patient-days for Tier 1 and Tier 2 targeted antibiotics were electronically extracted by Quality Intelligence from the Electronic Health Record utilising administration data.

A Wilcoxon rank test was performed to evaluate for differences in HA-CDI rates as well as use of targeted antibiotics between the time periods. All patients aged ≥ 18 years admitted to WPH during the defined study period were included. Patients were excluded if they were admitted to the following units: Neonatal Intensive Care, Labor and Delivery, Post-Partum and Bone Marrow/Stem Cell Transplant.

Results

A total of 19,264 and 75,600 patient-days were analysed in the HA-CDI and targeted antibiotic pre-intervention study periods, respectively. In the post-intervention period, a total of 42,610 patient-days were analysed. There was a significant reduction in HA-CDI/1000 patient-days in the post-intervention period (0.84 vs. 0.28; $P = 0.035$). A significant reduction in the utilisation of ceftriaxone, clindamycin,

Table 2. HA-CDI rates and antibiotic receipt per 1000 patient-days.

Variable	Pre-intervention (8 months)	Post-intervention (16 months)	P value
HA-CDI	0.84 ± 0.7	0.28 ± 0.22	0.035
	Pre-intervention (32 months)	Post-intervention (16 months)	P value
Ceftriaxone	58.0 ± 8.3	49.5 ± 8.1	0.002
Fluoroquinolones	63.8 ± 14.2	51.5 ± 9.7	0.006
Clindamycin	37.5 ± 7.5	29.6 ± 7.9	0.001
Carbapenems	14.4 ± 7.8	10.2 ± 8.1	0.044
Aztreonam, cefepime, ceftaroline, piperacillin-tazobactam	109.9 ± 25	114.8 ± 23.7	0.615
Tigecycline, linezolid, daptomycin	11.5 ± 6.5	5.7 ± 4.6	0.002

HA-CDI rates are reported in HA-CDI/1000 patient-days ± standard deviation. Antibiotic receipt is reported in days of therapy per 1000 patient-days ± standard deviation. Bold values are statistically significant, $P < 0.05$.

fluoroquinolones, carbapenems and the grouped category of tigecycline, linezolid and daptomycin was demonstrated (see Table 2). Utilisation of the group that included aztreonam, cefepime, ceftaroline and piperacillin-tazobactam was not significantly affected.

Discussion

Implementation of our ASP interventions was associated with a significant reduction in HA-CDI incidence as well as the usage of multiple antibiotic classes, particularly those associated with higher rates of CDI (Gerding, 2004; Muto et al., 2005). These interventions were not associated with a reduction in the antibiotic group that contained cefepime and piperacillin-tazobactam. The most likely explanation is that these agents were commonly recommended by our ASP as alternatives to carbapenems and fluoroquinolones. Despite these recommendations, we did not see an overall increase in usage of this group. This highlights the importance of an ASP to not just reduce certain high-risk antibiotics by replacing them with another class, but to reduce the overutilisation of antibiotics as a whole.

Another strength of this study is that it outlines a successful framework for ASP implementation in a community-based teaching hospital. Prior studies have demonstrated ASPs' ability to reduce the risk of CDI, particularly by restrictive policies (Feazel et al., 2014). Along with drug restriction, we implemented a comprehensive ASP that included prospective audit and feedback, syndrome-specific initiatives and intensive education. As our study incorporated different ASP interventions, it is difficult to say which one had the most impact. Of note, no other interventions aimed at reducing HA-CDI rates were implemented during the time period captured in this study.

There are a few limitations to our study. First, our pre-intervention period for antibiotic receipt was longer than our

HA-CDI rates, as a result of the CDC/NHSN definition change for HA-CDI that took place in January 2015 (CDC, 2017). Starting in January 2015, only a positive stool test for *C. difficile* was required to diagnose CDI, as clinical parameters were removed. We excluded HA-CDI data before 2015 due to the expected increase in hospital standardised infection ratios as a consequence of the definition change (CDC, 2015). Second, we did not control for any other variables that may have had an impact on HA-CDI rates. As no other HA-CDI reduction interventions took place at our institution during the study period, we feel that this rate reduction was primarily a result of our antibiotic reduction.

In conclusion, the implementation of a robust ASP was associated with significant reductions in incidence of HA-CDI and targeted antibiotic utilisation at our community-based teaching hospital.

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