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Brief Report

Antimicrobial stewardship program achieved marked decrease in *Clostridium difficile* infections in a Veterans Hospital

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Clostridium (or Clostridioides) difficile infection (CDI) is a common side effect of antimicrobial therapy and is increasingly linked with health care-associated transmissions. Antimicrobial stewardship programs (ASP) have demonstrated success in decreasing in-hospital CDI cases. We implemented an ASP targeting inappropriate or unnecessary use of all antibiotics especially empiric piperacillin-tazobactam and fluoroquinolone use. Concurrently, we monitored all health-care associated CDI. Our CDI cases were markedly decreased after initiation of our ASP.

Clostridium (or Clostridioides) difficile infection (CDI) is a common side effect of antimicrobial therapy and is increasingly linked with health-care associated transmissions. Antimicrobial stewardship programs (ASP) have demonstrated success in combating CDI, primarily through antibiotic restrictive strategies on cephalosporins (CEF), clindamycin, and fluoroquinolones (FQ).[1,2] Piperacillin/tazobactam (PTZ) is one of the most frequently utilized broad-spectrum antimicrobials for empirical gram-negative bacterial coverage (including Pseudomonas and anaerobes) for hospitalized patients.[3] PTZ along with vancomycin is currently the most common empiric antibiotic combination for "virtually everything" in US hospitals, making stewardship of PTZ challenging.[4] In 2014, there was a national shortage of PTZ. Cunha reported an unexpected benefit from PTZ shortage in their institution: Appropriate antibiotic prescribing and more importantly, decreased *C. difficile* infection rates.[4] Gross et al, however, reviewed antibiotic utilization in 88 hospitals for 2 years, including the year of the national PTZ shortage, and found mixed results: Hospitals without increased high-risk antibiotic use ([clindamycin, FQ, CEF, carbapenems, aztreonam and ampicillin/sulbactam [AMS]) showed lower CDI rates while those with increased use of high-risk antibiotics had greater CDI rates.[5] An ASP was initiated in our institution in 2016. We describe the effects of our ASP on antibiotic prescribing and CDI rates before and after the program implementation.

METHODS

Northport Veterans Affairs Medical Center provides a hospital-based acute care – 100 bed capacity—for US Veterans. ASP was initiated in 2016. The team consists of 2 infectious diseases full time physicians, rotating infectious diseases fellows, an infection control nurse, and a pharmacist. This report addresses CDI rates and antibiotic utilization in acute care setting. Case definitions for hospital acquired CDI were based on Centers for Disease Control and Prevention (CDC) criteria and a positive *C. difficile* test. Cepheid Xpert *C. difficile* Assay (Cepheid, Sunnyvale California) – a rapid diagnostic real-time polymerase chain reaction (PCR) test for the detection *C. difficile's* toxin B gene sequences – was used from 2011 to October 2016; from November 2016 to February 2019 Xpert *C. difficile*/Epi (Cepheid, Sunnyvale CA) was utilized with the ability to detect and differentiate the epidemic strain of *C. difficile* (027/NAP1/BI).

We compared the antimicrobial utilization by days of therapy/1,000 patient days of antibiotics using the program BI Office, (Pyramid Analytics, Kirkland, WA). Specifically, we compared cephalosporins, FQs PTZ, meropenem, cefepime, clindamycin from 2011 to 2015 (pre-ASP implementation) to 2016-February 2019 (post-ASP implementation). Members of the infection control team, with each new

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case of CDI, provided education to the relevant medical and nursing teams, reinforcing proper handwashing practices and isolation precautions. The infection control team monthly assesses, reviews new hospital acquired CDI cases and reports to national database within the Veterans Affairs. The ASP team reviews electronically all requests for restricted antibiotics. Restricted antibiotics include intravenous (IV) and oral FQ, fourth generation cephalosporins, carbapenems, monobactams, vancomycin, PTZ, AMS, daptomycin, dalbavancin, doxycycline, linezolid, antivirals/antiretrovirals, and antifungals. The ASP team often offered infectious diseases consultation for complex cases, thus assisting in antibiotic choice and duration of therapy. Frequencies and *P* values via T-test were calculated by using Microsoft Excel programs.

RESULTS

There were 21,330 (3,806 in intensive care units) total admissions from March 1, 2011 to February 28, 2019. Since the initiation of ASP in 2016, 4,021 antibiotic approvals were requested and 483 were denied. There has been a statistically significant decrease in PTZ use between pre- and postimplementation of ASP, with the quarterly median of PTZ-days of therapy/1,000 patient days being 248 versus 146, P: <0.001; FQ use 118 versus 84 P: 0.006; vancomycin use: 250 versus 233 P:0.012 (Fig 1, Table 1) Comparing pre-and-post ASP implementation, there has been a decrease in CDI median annual rate 20 cases versus 6 P: 0.0005 and recurrent CDI total cases 26 versus 1 (Fig 2). Meropenem use increased 20 versus 60 $P < 0.001$, as did cefepime 117 versus 208 $P < 0.001$, ceftriaxone 24 versus 67 $P < 0.001$, and cefazolin 59 versus 79 *P*: 0.0027. No significant change in clindamycin use was noted, 37 versus 35 *P*: 0.391. Of the 483 denied requests, 144 were for PTZ, 43 for vancomycin, 156 for FQ (95 ciprofloxacin, 55 levofloxacin, 6 moxifloxacin). Infectious diseases consultations increased during the years of ASP: Annual median number of consults; 199 (pre-ASP) versus 351 (post-ASP), *P*: 0.017.

Table 1
Antibiotic utilization between the study periods

Antibiotic	2011-2015	2016-2019	*P* value
Piperacillin/tazobactam	248*	146	0.00002
Fluoroquinolones	118	84	0.006
Meropenem	20	60	<0.001
Cefepime	117	208	<0.001
Ceftriaxone	24	67	<0.001
Cefazolin	59	79	0.0027
Clindamycin	37	35	0.391

*Note: Year divided in quarters; Median antibiotic usage by days of therapy/1,000 patient days per quarter.

DISCUSSION

Our ASP achieved a marked decrease in CDI. This is due to significant alteration in antibiotic utilization. We believe this was achieved as a result of a significant decrease in both FQ and PTZ use. Clindamycin utilization remained the same and carbapenem, cefepime, and ceftriaxone utilization increased, yet, this did not lead to higher CDI rates in our institution. King et al analyzed the impact of PTZ shortage in their hospital and showed a 21.8% decrease in CDI with impressive increases in use of meropenem (96%), Cefepime (97.9%); ceftriaxone usage also increased, 30.1%, while FQ usage remained unaltered.[6] This finding of increasing cephalosporin usage – but not linked to increased CDI rates – likely supports multifactorial factors for the mitigation of CDI rates in the above institutions. Our observed changes in antibiotic utilization may not have been solely due to antibiotic denials. Bui et al, in their study, showed that ASP that targeted only high-cost, broad-spectrum antimicrobials missed opportunities to reduce CDI due to overuse of unaudited low-cost and often unnecessary antimicrobials.[7] The increase of infectious diseases consultations likely led to a decrease of prolonged or inappropriately prescribed antibiotics. This was a strategic goal of our ASP, to make the infectious diseases team

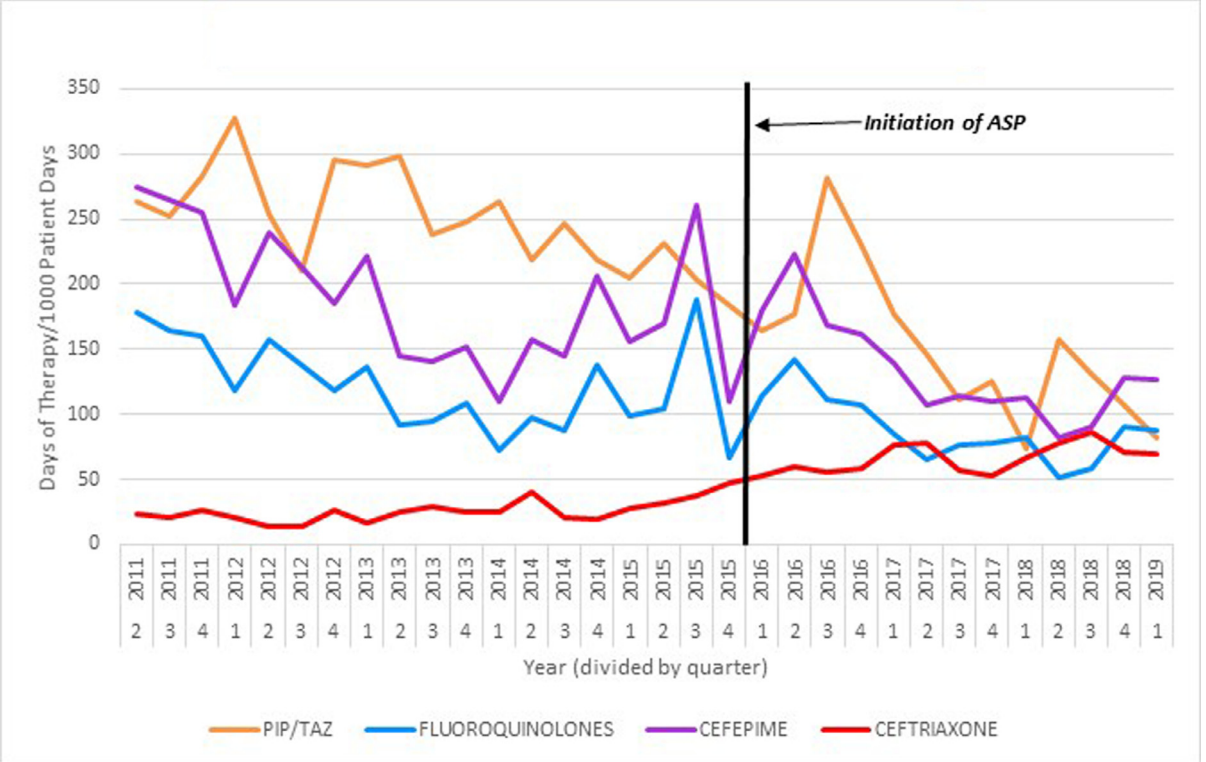
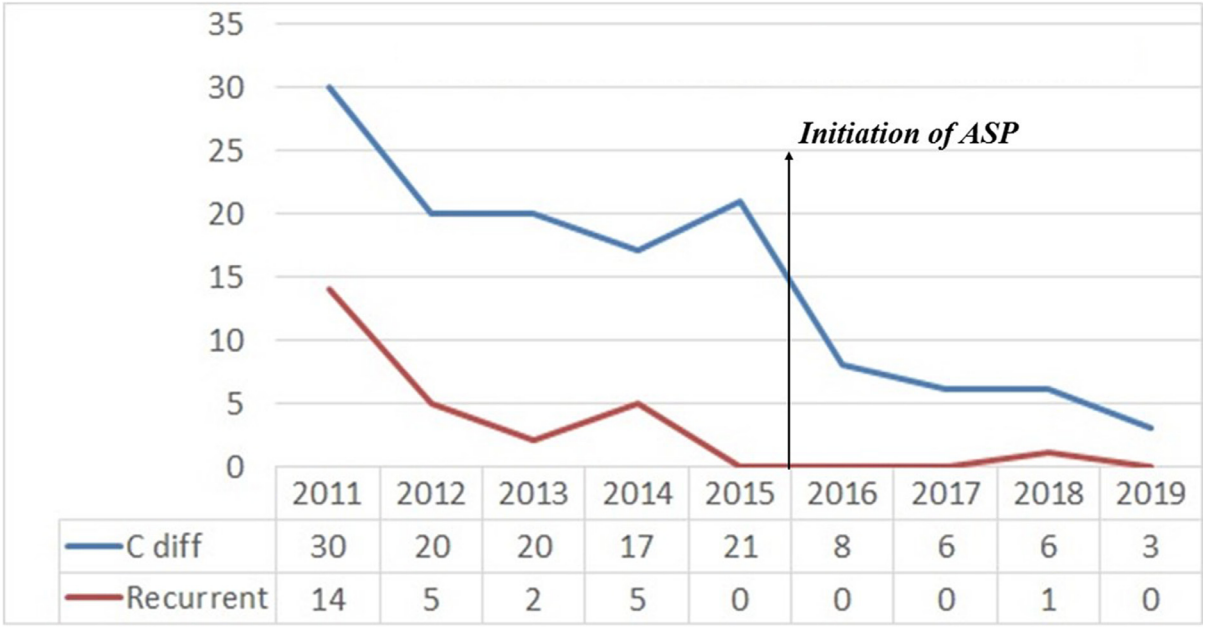


Fig 1. Antimicrobial use: Days of therapy/1,000 days 2011-2019.



	2011	2012	2013	2014	2015	2016	2017	2018	2019
C diff	30	20	20	17	21	8	6	6	3
Recurrent	14	5	2	5	0	0	0	1	0

Fig 2. *Clostridium difficile* infections 2011-2019.

more accessible, more "hands on", as close to hospital admission as possible, in providing guidance on how, where, and when to appropriate use (or stop) antibiotics. Our institution is affiliated with a university medical center, and many young physicians in training are rotating in our wards throughout the year. Interaction of our ASP team and residents led to important review of ASP concepts, allowed time for questions and better understanding of the goals of antimicrobial stewardship in general, thus, aiding in a lifetime style of proper antibiotic prescribing practice. One of the most common denials of antibiotic therapy from our ASP was for asymptomatic bacteriuria or pyuria. We believe this was one of the important teaching points delivered to residents and consequently had an impact in appropriate prescribing of antibiotics. Also, the ASP team noted that vancomycin plus PTZ was the most trusted combination for treatment of healthcare acquired pneumonia before the initiation of the program. Utilizing the negative results of the rapid molecular typing tests via polymerase chain reaction (PCR) for methicillin resistant *Staphylococcus aureous* (MRSA) on admission nares swabs, the ASP team guided the practitioners to discontinue vancomycin. This led to decreased utilization of vancomycin. Equally important was the ASP team's education against universal empiric use of PTZ for treating for healthcare-acquired pneumonia, thus providing alternative options based upon case by case review; other options included AMS (especially for aspiration pneumonia), cefepime (if no anaerobic coverage is needed), or escalation to meropenem when pretest probability for extended spectrum beta lactamase (ESBL) producing organisms was high. Successful use of a narrow-spectrum antibiotic policy reinforced by feedback of antibiotic usage and leading to decrease in CDI rates has been reported previously.[8] Recently, a decrease of CDI rates was reported in 15 facilities in California utilizing on site collaboration between infection control, antimicrobial stewardship teams, and hospital administrators, nurses, pharmacists, quality control professionals through interactive learning and discussion sessions.[9] Similarly our success in decreasing our CDI rates, could not have been accomplished without a collective and collaborative team approach between, ASP, infection control, nursing, residents, and our colleagues.

CONCLUSIONS

Implementation of ASP in healthcare facilities can be challenging and requires a multidisciplinary approach and collaboration. One of the goals of successful ASP interventions is to achieve a decrease in hospital acquired CDI. Targeting and liming FQ and PTZ use in the hospital setting can help attain this primary ASP goal.

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