ORIGINAL ARTICLE

Outcomes of intrahospital antimicrobial stewardship programs related to prevention of *Clostridium difficile* infection outbreaks

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ABSTRACT

Aim To synthesize evidence about the influence of individual antimicrobial stewardship programs (ASP) related to the prevention of *Clostridium difficile* (*C. difficile*) infection on primary and secondary outcomes.

Methods Relevant databases such as Medline, PUBMED, COCHRANE library and EBSCO were searched from 1 April to 27 April 2017. Additional studies were reached by the manual search for original articles in relevant journals. We included all randomized controlled, quasi-experimental and observational studies, published in the English language from 2007 onward, that evaluated effectiveness of ASP in preventing and controlling *C. difficile* associated disease (CDAD) among adult inpatients.

Results Implementation of ASP interventions was associated with CDAD incidence reduction in 62.5% studies, but no significant differences were reported for the duration of hospitalization, readmission and mortality rate. Improvements in prescribing patterns (decreased antimicrobial use or increased rational use) and microbial outcomes (decreased rates of selected antimicrobial-resistant bacteria) were reported. Evidence on the effects of ASP is mainly limited to the results of studies low in methodological quality with great heterogeneity of outcomes, interventions, and units in which CDAD incidence data were reported.

Conclusion Despite the low strength of evidence of reviewed studies, consistency of findings suggest the positive impact of antimicrobial stewardship programs on the prevention and control of nosocomial CDAD. The significance of this problem imposes randomized control trial use as the best instrument to provide high-quality evidence. Further studies need to systematically analyse changes in all antibiotic use and its outcomes.

Key words: Antimicrobial Stewardship Program, clostridium infections, disease outbreaks, prevention

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INTRODUCTION

Clostridium difficile (*C. difficile*) is a Gram-positive, anaerobic bacterium sensitive in vegetative form, which can survive for a long period of time in an external environment (1). It is the well-established causative agent of nosocomial diarrhoea (1,2). In addition to asymptomatic *carrying*, *C. difficile* toxin-producing strains (A, BI Binary toxin) can cause different clinical manifestations (ranging from mild diarrhoea to pseudomembranous colitis and toxic megacolon) in individuals with risk factors such as older adults in hospitals and in long-term care facilities. *Clostridium difficile–associated disease* (CDAD) has become an increasingly prevalent problem with pronounced hospitalization costs and adverse outcomes (3,4).

According to a study conducted in 2013 in 482 hospitals from 20 European countries, incidence rates for hospital-acquired CDAD ranged from 0.7 to 28.7, while the average incidence rate was 7 per 10.000 hospital discharges (5).United States' hospitals reported approximately 453.000 cases of hospital-acquired diarrhea associated with *C. difficile* in 2011.The estimated number of first recurrences was 83.000 and the estimated number of deaths 29.300. The incidence was higher among females, Caucasians and persons older than 65 years of age (6). The CDAD was more frequently diagnosed in internal medicine and long-term care wards (7).

Over 90% of nosocomial CDAD occurs during or after a broad-spectrum antibiotic therapy, (second and third generation cephalosporins, fluoroquinolone and clindamycin). Therefore, antimicrobial stewardship programs (ASPs) could be the most effective methods for the prevention and suppression of CDAD in the hospital setting (8).These programs focus on the adequate antibiotics use and the microbial resistance reduction (9).Their implementation can be achieved through several types of interventions. Restrictive interventions involve rigorously limiting the choice of healthcare workers in prescribing antibiotics to patients. Persuasive interventions are mainly focused on counselling health workers to change their existing attitudes and practices related to prescribing. Structural interventions refer to locating the source of the problem and altering it through individual, organizational and environmental levels (10).

The previous systematic review found low-quality evidence that ASPs could improve prescribing policy and microbial outcomes without significant adverse effects on patient outcomes and healthcare expenditures. Very little is known what would be the most cost-effective programs for rationalizing antibiotic use at hospitals and healthcare systems level (11).

The aim of this systematic review was to synthesize evidence about the impact of individual antimicrobial stewardship programs (ASP) related to the prevention of *C. difficile* infection on primary and secondary outcomes.

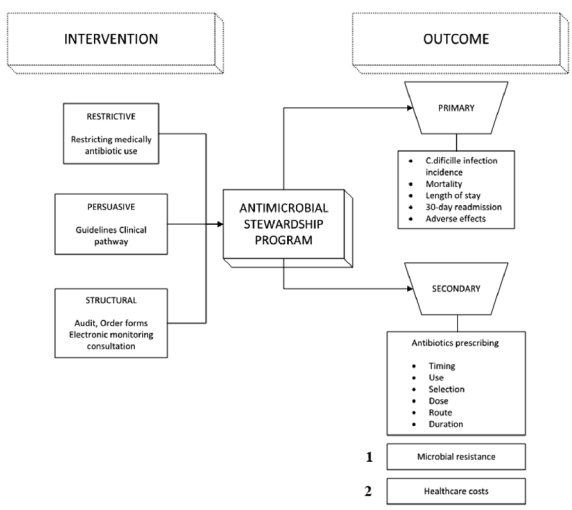

Figure 1. Conceptual framework of antimicrobial stewardship program

MATERIALS AND METHODS

Selection criteria

The conceptual framework for content analysis illustrated interventions and outcomes of ASP (Figure 1). The ASP was defined as a continuing procedure in a health care institution to optimize antimicrobial use among patients in the hospital setting, improve patient outcomes, reduce antimicrobial resistance and provide cost-effective treatment. The effective inpatient ASPs are associated with the key, coordinated specific interventions and aimed at improving the practice of prescribing antibiotics either by increasing effective or by reducing unnecessary treatment. The restrictive interventional techniques included banning or restricting medically important *antibiotics* use in hospital and obtaining the approval of clinical pharmacologist or infective disease

specialists before administering an antibiotic. The persuasive interventional techniques considered guidelines, clinical pathway development, and education. The structural interventions were prospective audit and intervention, antimicrobial order forms, electronic monitoring system for prescribing therapy to hospitalized patients, maintaining e-mail consultation or using modern rapid laboratory tests (10,13).

The outcome variables included in this paper were patient-centred or primary (incidence of *C. difficile* infection, mortality, duration of hospitalization, adverse effects) and secondary outcomes (antibiotic prescribing, microbial resistance and healthcare costs).

The first three authors discussed and reached an agreement about the selection criteria. All randomized, control, quasi-experimental, controlled clinical trial, controlled before/after study and observational studies from 2007 onward, with available abstracts and data on the effectiveness of ASPs in preventing and controlling *C. difficile* infection outbreaks among adult hospitalized patients, were included. In addition to adult hospitalized patients, all health workers licensed to prescribe antibiotics to hospitalized patients are considered research participants. Full-text language was limited to English. The researchers (authors) applied no restrictions on the country.

The studies carried out in nursing home or long-term care settings involving only the elderly or paediatric population, describing an intervention with no assessment of the effect of the intervention and analysing antimicrobials for medical or surgical prophylaxis or the impact of antibiotic rationing programs on outcomes that were not associated with the incidence of CDAD, were excluded.

Search strategy

Key words and Medical Subject Headings (MeSH) used for research strategy were: *C. difficile* pseudomembranous colitis; antibiotic/antimicrobial; stewardship/ restriction/ guideline/ policy; prevention and control; hospital setting. Medline, PUBMED, COCHRANE library and EBSCO were searched from 27 April to 1 April 2017. A combination of terms was adapted to each database; Boolean AND/OR operators used to establish the logical relations among concepts. Additional relevant studies were identified according to the correspondence of the title with the question of systematic review. The authors performed the manual search for original studies in relevant journals (International Journal of Epidemiology, The Journal of Clinical Epidemiology, Journal of Hospital Infection, Antimicrobial Resistance and Infection Control).

Study selection

The first two authors independently identified and screened the articles against the inclusion and exclusion criteria. The content analysis was conducted on articles that met inclusion criteria. The authors discussed the results, and, in case of disagreement, the opinion of a third author was considered for the final decision.

Data extraction and analysis

Secondary synthesis involved abstraction of data and appraisal of their quality. Second author extracted data from each full-text article using data extraction forms. Extracted data focused on: study characteristics (region, intervention, design, hospital type description), patient outcomes (*C. difficile* infection, mortality, duration of hospitalization, morbidity, adverse effects), microbial outcomes (resistance), prescribing outcomes (use, selection, duration), and costs. The first, third or fourth author checked if extracted data fitting the descriptions of the outcomes. The quality of the studies being reported was assessed using the Best Evidence Medical Education (BEME) Collaboration Guide (14). The first three authors independently scored on a BEME scale of 1–5 for the strength of the findings as follows: Grade 1: No clear conclusions can be drawn; not significant; Grade 2: Results ambiguous, but there appears to be a trend; Grade 3: Conclusions can probably be based on the results; Grade 4: Results are clear and very likely to be true; Grade 5: Results are unequivocal.

The authors sought external comments from other experts in ASPs (SS and DBL) on their ideas and work, who also conducted BEME grading process and scrutiny of final reports.

Meta-analysis was not possible due to the heterogeneity of measured outcomes, methods, instruments, quality of methodology and statistical analysis of included studies. Analysis and synthesis of results were provided using narrative

synthesis (15). For each study, description, study design, sample, outcomes and statistical test and results were reported.

RESULTS

The initial database and manual search identified 857 articles. Following de-duplication, 719 articles were excluded. After the screening of titles and abstracts, additional 47 articles were excluded. Ninety-one articles were retrieved for full-text review. Systematic reviews, studies with poorly defined outcomes and interventions (grade 1 and 2) were further removed. Twenty-four studies were selected for data extraction and analysis (Figure 2).

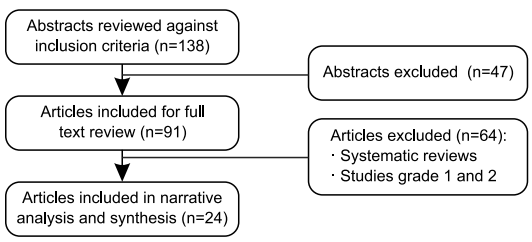

Figure 2. Flow diagram of articles selection process

Study characteristics

Majority of the studies (54%) were published in the USA (9, 17-24) and Canada (25-28). Five studies were carried out in the UK (29-33), one in Sweden (34), one in Germany (35), one in Austria (36) and one in Spain (37). The remaining two (8.5%) were conducted in Mexico (38) and Taiwan (39).

Eleven studies (45.8 %) were interrupted time series, and the same number of the studies also had the pre-post design. Due to the lack of randomization, these studies were more susceptible to bias and a lower degree of quality compared to the randomized experimental design. High-quality quasi-experimental design (controlled) had three studies (17,20,28). Only two studies (8.3%) were randomized controlled (26,37).

All quasi-experimental studies without the control group were grade 3, and randomized control grade 4.

Type of interventions

In twenty studies (80%), the impact of intervention implementation was only investigated in one hospital, while 20% of the studies were conducted in multiple hospital settings. Authors included all hospital wards in eighteen studies.

Eight studies investigated the impact of only one intervention, respectively, two examined the application of restrictive interventions (32, 38) and four studies of the persuasive intervention (17-19, 25,27,28,34,37). Sixteen studies analysed the effects of the implementation of combined programs, of which nine studies referred to a combination of restrictive and persuasive interventions (20-22, 29,30,31,33,35,36). One study included all three interventions (23).

Aims of intervention

In three studies (12.5%), the aim was to analyse the impact of the intervention on *C. difficile* infection incidence (21,32,38). In addition to CDI incidence analysis, eighteen studies (75%) evaluated antibiotics administration, and eight studies (33.3%) the impact of the interventions on financial aspects, mainly hospital costs associated with the use of antibiotics (9, 17-19, 22,24,27,37). Four studies addressed the evaluation of secondary outcomes (9,22,28,37). Seven studies analysed the effect of intervention on the incidence of several hospital infections caused by multi-resistant agents (9,23,26,28,30,34,39).

Primary (patient) outcomes

Incidence of CDAD decreased in 15 of the 24 extracted studies (62.5%) (9,18,21, 23-25, 28-33, 36-38). Both of the studies implementing restrictive interventions solemnly, recorded a CDAD incidence reduction (32,38), while 50% of the studies using persuasive intervention (18,25,28,37) detected the same impact. Implementation of combined interventions has yielded heterogeneous results (21,29,31,33,36).

No differences were reported for readmission and mortality rate (26-28, 34,37). In one study, length of hospitalization was reduced (26).

Secondary outcomes

ASPs decreased the use of targeted antibiotics in 17 studies and overall antimicrobial use in 4 studies (22.2%). Majority of the studies included the administration of high-risk antibiotics such as the second and third generation of cephalosporin, fluoroquinolones, and clindamycin. Eight studies reported cost outcomes with seven founding decreased drug costs (9, 17-19, 22,27,37).

Table 1. Summary of articles reporting outcomes of antimicrobial stewardship program related to *Clostridium difficile* infection prevention

Author/ year	Study design	Location	Duration	Intervention	Outcome	Findings	Grade
Aldeyab, 2012 (29)	Quasi-experimental study using interrupted time series	Medium-sized hospital United Kingdom	6,5 years; (4/2,5 years)	RESTRICTIVE: Restriction of high-risk antibiotics (second generation cephalosporins, third-generation cephalosporins, fluoroquinolones and clindamycin) Medium-risk antibiotics monitoring PERSUASIVE: The exemption forms were assessed by the Antimicrobial Management	Primary: 1)CDI incidence Secondary: 1)antibiotic use	- CDI incidence rate decreased by 0.0047/100 bed-days per month - reduction in the use of high-risk antibiotics	3
Beaulac, 2016 (24)	Uninterrupted time-series analysis	General hospital USA	4 years; (12/36 months)	STRUCTURAL: Medical records were reviewed specifically for appropriateness of antimicrobial selection and duration, sufficient monitoring for adverse events, and documentation of follow-up Mail consultation	Primary: 1) CDI incidence Secondary: 1) overall antimicrobial consumption 2) specific antimicrobial group consumption	-significant decrease in monthly CDI cases/1,000 patient day -a decrease in usage of anti-CDI antibiotics by 50.4 DDD/1,000 patient day per month	3
Borde, 2015 (35)	Quasi-experimental study using interrupted time series	Community-based 200-bed hospital Germany	38 months; (26/12 months)	RESTRICTIVE: Reduction of cephalosporin and fluoroquinolone consumption within 1 year. PERSUASIVE: Daily rounds on the interdisciplinary intensive care unit Internal guidelines	Primary: 1)CDI incidence Secondary: 1)use of antimicrobial agents	- no significant effect was noted for CDI incidence rates. -cephalosporin use decreased by 33 %, - fluoroquinolone use decreased by 31 %,	3
Bouza, 2007 (37)	Randomized controlled study	Large teaching institution Spain	2 years	PERSUASIVE: Additional education	Primary - C. difficile–associated diarrhoea - days receiving mechanical ventilation -days of fever Secondary: 1) antibiotic administration 2) costs of antimicrobial agents	Fewer days of fever Fewer days of antibiotic administration Decreased antibiotic consumption, Less C. difficile–associated diarrhoea Lower costs of antimicrobial agents Fewer days receiving mechanical ventilation No statistically significant differences in the rate of mortality at discharge from the hospital	4
Chan, 2011 (39)	Quasi-experimental study using interrupted time series	1 university hospital Taiwan	3 years	RESTRICTIVE: Prescribers should obtain approval from ID physicians to prescribe restricted agents in order to avoid inappropriate use STRUCTURAL: -introducing hospital-wide computerised antimicrobial approval system (HCAAS)	Primary: 1) mortality rates 2) incidence of C. difficile infection. Secondary: 1) restricted antimicrobial usage 2) antimicrobial susceptibility profile	- The rate of C. difficile infections unchanged. - the rate of meticillin resistant Staphylococcus aureus started to decline -third- and fourth-generation cephalosporins, fluoroquinolones and glycopeptides use decreased - carbapenems use increased.-	3
Cook, 2011 (23)	Quasi-experimental study using interrupted time series	Tertiary-care teaching hospital	5 years	RESTRICTIVE: Restricted antimicrobial agents required prior approval by the infectious diseases clinicians. Controlled antimicrobial agents could be prescribed without infectious diseases approval, but the appropriateness of their use was reviewed by the antimicrobial stewardship programme after 48 h of use PERSUASIVE: Walk-rounded STRUCTURAL: Patient charts reviewed Introducing electronic medical record (EMR)	Primary: 1) rates of C.difficile cases (number of isolates per 10 000 PD) 2) rates of nosocomial MRSA, -rates of quinolone-resistant P. aeruginosa (QRPA), 3) rates of carbapenem-resistant P. aeruginosa (CRPA) and C Secondary: 1) antimicrobial drug use (DDD/1000 PD)	- Nosocomial CDI rates decreased by 42.6% and then increased to near baseline levels following implementation of more sensitive testing for detection of CDI - sustained reductions in both antimicrobial use and drug-resistant organisms	3
Cruz - Rodrigez, 2014 (38)	Quasi-experimental design; Before-and-after study	The orthopaedics ward unit in teaching hospital Mexico	23 months (7/16 months)	RESTRICTIVE: Pharmacy restriction of clindamycin	Primary: 1) CDI incidence	-reduction of 88% in CDI -reduction of 84% for all-cause diarrhoea - Clindamycin was reduced 92.61% without an increase in other antibiotic	3
Dancer, 2013 (30)	Quasi-experimental study using interrupted time series	District general hospital in a rural area United Kingdom	25 months (9/16 months)	PERSUASIVE: Educational programme encouraging prescribers to reduce consumption of cephalosporins and quinolones RESTRICTIVE: Microbiological authorisation suppressed release of cephalosporins and quinolones on ward reports unless no other agents were available Ad hoc discussion	Primary: 1) surveillance of all cases of C. difficile, MRSA and ESBL-producing coliforms Secondary: 1) monthly consumption of antibiotics	- Hospital-acquisition rates for C. difficile reduced by 77% - Monthly consumption of ceftriaxone and ciprofloxacin significantly reduced	3

Elligsen, 2012 (28)	Prospective, controlled interrupted time series.	Single tertiary care centre with 3 intensive care units Canada	24 months; (12/12 months)	PERSUASIVE: Antimicrobial optimization were communicated to the critical care team STRUCTURAL A formal review of all critical care patients on their third or tenth day of broad-spectrum antibiotic therapy	Primary: 1) nosocomial C. difficile infections 2) length of stay 3) mortality. Secondary: 1) broad-spectrum antibiotic use (days of therapy per 1000 patient-days 2) overall antibiotic use 3) gram-negative bacterial susceptibility, ,	- The incidence of nosocomial C. difficile infections decreased - The mean monthly broad-spectrum antibiotic use decreased to 503 days of therapy per 1,000 PD - Overall gram negative susceptibility increased - length of stay and mortality did not change	3
Jenkins, 2015 (22)	Quasi-expe-rimental, interrupted-time series study	525-bed public safety-net hospital USA	6 years andi 3 months; (36 months/39 months)	RESTRICTIVE: Formulary restriction Automatic intravenous to oral transitions Pre-authorization requirement for selected antibiotic PERSUASIVE: Once-weekly presence of an ID attending and ID pharmacist at multidisciplinary surgical intensive care unit rounds. Post-prescription review with real-time feedback to prescribers Local guidelines for common infection	Primary: 1) hospital-onset C. difficile infection, and other patient-centred measures 2) length of hospital stay 3) in-hospital mortality 4) 30-day hospital readmissions Secondary: 1) antibacterial and antipseudomonal use in days of therapy (DOT) per 1000 PD 2) antimicrobial costs - resistance,	-few apparent changes in C. difficile infection and other primary outcomes -total antibacterial and antipseudomonal use declined - antibiotic expenditures declined markedly - variable changes in antimicrobial resistance	3
Leung, 2011 (27)	Quasi-experi-mental design; Study before-after	490-bed commu-nity teaching hospital Canada	6 months (pilot and post-pilot phase)	STRUCTURAL: Prospective audit and feedback	Primary: 1) frequency of nosocomially acquired C. difficile infection 2) mortality rate Secondary: 1) expenditures 2) utilization of antimicrobials	- CDI rate was lower than, but not significantly different from previous rate - no differences in mortality rate -utilization of broad-spectrum antipseudomonal antimicrobial agents was also lower - reduction in the cost of antimicrobial drug for 36.2%	3
Nowak, 2012 (9)	Study before-after	Teaching hospital USA	7 years and 8 months; (4 years/3 years and 8 months)	PERSUASIVE: Educational comments STRUCTURAL: Introducing electronic system Chart review	Primary: 1) rates of infections due to common nosocomial 2) patient survival 3) length of stay 4) mortality rate 5) 30-days readmisson Secondary: 1) annual antimicrobial expenditures	- rates of nosocomial infections involving Clostridium difficile, decreased after ASP implementation -significant differences in other primary outcomes were not found -antimicrobial expenditures reduction	3
Nuila, 2008 (21)	Quasi-experi-mental before-and-after study	One teaching hospital USA	4 years; (36/12 months)	RESTRICTIVE: Approval from ID physician PERSUASIVE: Education	Primary: 1) CDI incidence (number of case/1000 OBD)	- 47,2% CDAC reduction	3
Ostrowsky, 2014 (20)	A multicentre controlled before-and-after intervention comparative study	Ten medical cen-tres in the greater New York region USA	20 months	RESTRICTIVE: Restriction of target antibiotic use in one hospital Comprehensive restriction in 3 hospitals PERSUASIVE: Educational meeting in 6 hospitals Additional education in 3 hospitals	Primary 1) monthly CDI rates Secondary: Prescribing 1) total antibiotic usage 2) total target antibiotic usage 3) total nontarget antibiotic usage 4) usage for each individual target antibiotic/class	-No statistically significant decreases in aggregate hospital-onset CDI betwe-en intervention and nonintervention groups - Total target antibiotic use significantly decreased when measured by days of therapy and number of courses - Intravenous moxifloxacin and oral ciprofloxacin use showed significant reduction	3
Palmay, 2014 (26)	Stepped-Wedge Randomized Trial	1 hospital 6 inpatient services: general internal medicine, nephro-logy, cardiology, general surgery/ trauma, orthopa-edic surgery, and neurosurgery Canada	2 years	PERSUASIVE: Education Advising STRUCTURAL: Integrated antibiotic stewardship software system Chart review	Primary: 1) nosocomial C. difficile infections measured as the number of cases per 1000 patient-days 2) length of stay 3)all-cause in-hospital mortality. Secondary: 1) the number of days of therapy -nontargeted and total antimicrobial utilization 2) costs of antimicrobial therapy	- no significant change in targeted antibiotic use among all admitted patients - no change in the incidence of C. difficile - no change in cost - no change in mortality rate - decreased median length of stay	4

Price, 2010 (31)	Quasi-experimental study using interrupted time series	Teaching hospital providing acute secondary care services USA	27 months; (12/15 months)	PERSUASIVE: Guideline distribution RESTRICTIVE: A new antibiotic policy restricting the use of cephalosporins and quinolones	Primary: 1) number of CDI cases Secondary: 2) targeted antibiotic use (DDD/1000 OBD)	- reduced level of cephalosporin and quinolone use (22.0% and 38.7%, respectively, both p <0.001) - significant increase in the rate of CDI reduction	3
Storey, 2010 (19)	Study before-after	Community hospital	20 months; (7/13 months)	PERSUASIVE: Medical staff committee meetings Continuing medical education conference STRUCTURAL: Non-binding written recommendations placed in the record using a communication form Audit of medical records of inpatients	Primary: 1) CDI incidence Secondary: 1) use of all antimicrobial agents per 100 admissions 2) antimicrobial cost were per patient-day	- CDI incidence rate for the medical-surgical service was 3.7 during the baseline period and 9.2 during the intervention period -16% reduction in mean monthly antimicrobial use - 25% reduction in cost per patient-day	3
Schön, 2011 (34)	Quasi-experimental design; Study before-after	3 different hospitals Sweden	27 months (12/15 months)	PERSUASIVE: Standardized guidelines for empirical antibiotic therapy in hospitals recommending increased usage of benzylpenicillin and decreased usage of cephalosporins and fluoroquinolones	Primary: 1) CDI incidence 2) mortality in Staphylococcus aureus bacteraemia Secondary: 1) prescribing	- No change was found in mortality in Staphylococcus aureus bacteraemia or the incidence of C. difficile infection. -Significant decrease in total cefotaxime and cefuroxime usage	3
Sarma, 2015 (32)	Quasi-experimental study using interrupted time series	The study analysed 'post-48 hour' in two large acute hospitals United Kingdom	60 months	RESTRICTIVE: Prohibited use of restricted antimicrobials unless approved by a microbiologist.	Primary: 1) CDI incidence	Reduction in CDI rate	3
Talpeart, 2011 (33)	Retrospective, quasi-experimental study using interrupted time series	Adult medical and surgical wards in an acute general hospital. United Kingdom	24 months; (12/12 months)	PERSUASIVE: Regular ward rounds five times a week to optimize adherence to revised antibiotic guidelines Teaching sessions, Face-to-face discussions Provision of pocket-size guideline RESTRICTIVE: Removing antibiotics considered as 'high risk' from ward stocks in order to reduce their availability.	Primary: 1) number of CDI cases per month Secondary: 1) prescribing target antibiotics (DDD/ 1000 OBD)	There was a significant decrease in CDI following the intervention Significant reduction in the use of fluoroquinolones and cephalosporins. There was no significant change in total antibiotic, clindamycin, amoxicillin or co-amoxiclav use.	3
Valiquette, 2012 (25)	Interrupted time-series analysis	Secondary/ tertiary-care hospital located at 2 distinct sites Canada	38 months	PERSUASIVE: Staff education STRUCTURAL: Restrict isolation for patients with diarrhoea The use of dedicated equipment with disposable rectal thermometers,	Primary: 1) CDAD incidence Secondary: 2) prescribing total and target antibiotics	- Antimicrobial stewardship program was followed by Pa marked reduction in incidence - total antibiotic consumption decreased by 23% -targeted antibiotic consumption decreased by 54%	3
Wenisch, 2014 (36)	Quasi-experimental design; Study before-after	1 large community teaching hospital; Austria	12 months; (5/7 months)	PERSUASIVE: Education about CDAD Guidelines RESTRICTIVE: Formal restriction of moxifloksacin use	Primary: 1) CDAD incidence Secondary: -prescribing 1) Moxifloxacin use 2) Total antibiotic use	Immediate decrease in CDI rates for 46% Moxifloxacin use was reduced from a mean of 1,038 109 DDD per month (period 1) to 42 10 DDD per month (period 2) Total antibiotic use was not affected	3
Yam, 2012 (18)	Quasi-experimental design; Study before-after	1 rural, general Hospital USA	13 months	PERSUASIVE: The implementation of a pharmacy-directed antimicrobial stewardship program involving the use of telemedicine technology	Primary: CDAD incidence Secondary: Annual antibiotic costs	The rate of nosocomial Clostridium difficile infection decreased A decrease in annual antibiotic costs	3
Yu, 2014 (17)	Quasi-experimental design; Controlled before-after study	Two ASP sites and three similar sites within the same health system not included in the ASP initiative USA	12 month	PERSUASIVE: Additional professional education	Primary: CDAD incidence Secondary: 1) prescribing -target antibiotic use (DDD/1000 OBD) 2) costs	-The rate of C. difficile infections unchanged. The utilization of all classes of antibiotics decreased and antimicrobial costs per 1000 patient-days decreased	3

Following implementation of ASPs, several studies recorded decreased rates of selected antimicrobial-resistant bacteria.

Statistically significant reduction in the incidence of MRSA-induced infections was observed in 4 of 6 studies (66.7%) (9,23,30,39).

DISCUSION

Summary of main findings and comparison with previous reviews

This systematic review found low-level evidence that ASPs may be associated with the reduction in the incidence of *C. difficile* infection. None of the reviewed studies achieved grade 5 of the BEME's strength of findings nor directly comparedone intervention with another. The results included in the report corroborate previously published systematic reviews (10,11).

A statistically significant decline in CDAD incidence was observed in all studies using solemnly restrictive interventions and several studies combining restrictive with persuasive or structural interventions. Majority of studies evaluated an effect on prescribing, microbial resistance or hospital cost rather than an impact on the mortality and clinical outcomes. Rationalization of antibiotic prescribing was not accompanied by increased mortality, duration of hospitalization, CDAD outbreaks and hospital costs. The data on specific elements, sustainability and scalability are lacking.

Evidence on the effects of ASPs is principally limited to the results of quasi-experimental studies. This study design is used to compare the effectiveness of alternative interventions and aims to analyse causal relationship between the intervention applied and the possible outcomes in situations when randomization cannot be performed (40). Due to the non-randomized distribution of the respondents in the groups and uneven distribution of outcome variables, the risk of interpretation bias and number of hypotheses observing causality increase. Inadequate control of confounding variables could be partially overcome by multivariate regression, while the only efficient way of controlling nonresponsive variables remains to apply randomization (40). The risk of bias could be minimized by a good design of quasi-experimental research involving control group and time series with multiplicity measurements in the non-intervention and intervention period (41).

The rigor of research on the ASPs has been previously reported as weak, especially in regard to limited quality of studies and heterogeneity of outcomes, interventions and units in which CDAD incidence data were reported. Current research shows that quality of studies is still weak even though research instruments and strategies have been growing rapidly in the past decade. Antimicrobial stewardship interventions are seen as opportunities to reflect on prescribing patterns, to decrease uncertainty, conduct audit and facilitate patient-oriented care (42,43).

Despite aforementioned methodological problems and differences in the design of the reviewed studies, the overall consistency of findings supports the hypothesis that antimicrobial stewardship programs could have the positive impact on the prevention of nosocomial *C. difficile* infection outbreaks.

Strengths and limitation

This systematic review was conducted following PRISMA guidelines and integrated the major databases for epidemiological research. The search strategy included only the English language, so we possibly missed some relevant articles in other languages. The inclusion of the articles was largely based on publication in electronic journals and important printed articles may be omitted. It was not possible to carry out meta-analysis as study designs, tools, outcomes assessed, and the nature of reported results was diverse. Uncharacterized or unreported characteristics of the study setting might have influenced interventions effectiveness and generalized applicability of findings.

Implication for practice and research

Antimicrobial treatment is continuously developing; newer antibiotics are marketing (43). Antibiotic resistance is increasing and becoming a major public health crisis. The single strategy could not have resolved the problem because resistance has the multifactorial background (44). Integrating ASP into patient safety procedures will help bring new support and useful actions, while research on its implementation and outcomes will provide a roadmap for hospitals management and

healthcare systems. A system for evaluating the effectiveness of the implemented ASP and antibiotic monitoring should be integrally involved in the infection control activities of every hospital. The factors to be addressed are CDI prevention programs, hospital pharmacies, microbiology laboratories, hospital staff, continuous medical education, electronic medical record systems, training and certification.

The benefits, hindering factors, adverse effect, sustainability, and costs-effectiveness of ASPs should be the focus of future research. Randomized control trial is the most reasonable instrument to provide high-quality evidence. Further studies need to systematically analyse changes in total antibiotic use and patient-centred outcomes.

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TRANSPARENCY DECLARATION

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