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Infection Prevention in Practice

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

Impact of an empiric antimicrobial therapy manual on antimicrobial usage and multidrug resistant organism trends in a large Italian teaching hospital

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ARTICLE INFO

Article history:

Received 16 March 2021

Accepted 11 November 2021

Available online 23 November 2021

Keywords:Antimicrobial stewardship
Multidrug resistant organism
Antibiotics

SUMMARY

Aim: To evaluate the changes in antimicrobial consumption and multidrug-resistant microorganism trends after introducing an empiric antimicrobial therapy manual to support antimicrobial stewardship.

Methods: A 4-year prospective interventional study assessed the effect of introducing an empiric antimicrobial therapy manual in medical and surgical wards during two periods: pre-intervention period (January 2015–May 2017) and post-intervention period (June 2017–December 2019). Outcomes included microorganism trends of bloodstream infections (BSI) for *Klebsiella pneumoniae* carbapenemase-producing bacteria (KPC), extended spectrum beta-lactamase ESBL-*E. coli*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Candida albicans*. Also, *Clostridioides difficile* infection (CDI) episodes were included. Rates were normalised per 1000 patient-days (PD). Antimicrobial consumption was assessed as defined daily dose (DDD)/1000 PD in interrupted time series analysis.

Results: In medical wards, we observed a significant decrease in the consumption of piperacillin-tazobactam and a decrease in the trends of tigecycline and vancomycin consumption. In surgical wards, there was a significant decrease in consumption of fluoroquinolones and piperacillin-tazobactam. This decrease was maintained in trend for all the antimicrobials but was significant for tigecycline only. In medical wards, there was a

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significant reduction of MRSA and *C. albicans*. In surgical wards, we observed a decrease in MRSA, ESBL-*E. coli*, *C. albicans* and CDI. KPC cases decreased by 22.5% in medical wards and 74.3% in surgical wards.

Conclusion: The results suggest that a persuasive educational approach to antimicrobial stewardship, with the introduction of an empiric antimicrobial manual and continuous education, resulted in reductions in both antimicrobial use and healthcare-associated BSI caused by multidrug-resistant organisms. More studies with longer follow up are needed to investigate the effect of antimicrobial stewardship on clinical outcomes.

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Introduction

As reported by the Centers for Disease Control and Prevention (CDC), antimicrobial-resistant organisms cause more than two million infections in the United States annually [1]. A systematic review studying the burden of antimicrobial resistance (AMR) has demonstrated its significant impact on mortality and excess healthcare costs up to \$1 billion per year [2]. These costs highlight the need to improve appropriate antimicrobial use. Therefore, hospitals worldwide have implemented antimicrobial stewardship programs (ASP) led by a multidisciplinary team, to promote systematic actions to improve appropriate antimicrobial use [6].

The Infectious Diseases Society of America (IDSA) has defined antimicrobial stewardship as “parallel interventions that improve and evaluate the proper use of antimicrobials by enhancing the favorable treatment concerning dosage, time of therapy, and administration route” [4]. ASP can reduce antimicrobial consumption by 20–50% promoting improved clinical outcomes through reducing mortality and infection rates caused by multidrug-resistant organisms (MDRo) [5]. Moreover, the benefits of ASP include decreased costs, adverse drug events, including reduced *Clostridioides difficile* infections (CDI) and increased susceptibility rates to targeted antimicrobials [6].

Various ASP have been successfully implemented worldwide [6], with reductions in targeted antimicrobial prescribing. The impact of ASP on MDRo trends is sometimes difficult to evaluate due to the long period of follow-up required to measure outcomes after the implementation of ASP, whether educational or interventional [7]. The aim of this study was to evaluate the change of antimicrobial consumption and its effect on MDRo trends after introducing an empiric antimicrobial therapy manual as part of the ASP at our hospital. We hypothesised that this intervention may help to optimise the use of antimicrobials and consequently reduce MDRo rates over time.

Methods

Study design

A four-year prospective interventional study (2015–2019) aimed to assess the effect of the introduction of an empiric antimicrobial therapy manual in June 2017, on both MDRo trends and antimicrobial consumption. The study was conducted at City of Health and Sciences, Molinette Hospital, which is a 1200-bed tertiary care teaching hospital in Turin, Italy.

Outcome measures were the change in level and linear trend of antimicrobial consumption, CDI rates and MDRo in blood cultures. Outcomes were evaluated in medical and surgical wards in two periods: the pre-intervention period (January 2015–May 2017) and post-intervention period (June 2017–December 2019).

The study was approved by the local ethical committee of City of Health and Science Protocol N° 0029333.

Intervention: the manual of empiric antimicrobial therapy

The manual was introduced to improve the appropriateness of empiric antimicrobial therapy in patients admitted to internal medicine and surgical wards (general surgery and urology). Surgical antimicrobial prophylaxis recommendations were detailed in a separate manual. The antimicrobial therapy manual covered the primary choice antimicrobials for treatment and detailed alternatives for patients with allergy to penicillin. Guidelines were provided for neutropenic and non-neutropenic patients and for various infections comprising respiratory and urinary tract, abdomen, skin and soft tissue, bone and joint, central nervous system and cardiac. In addition, the manual addressed other infections including sepsis, invasive fungal infections, endocarditis prophylaxis and catheter-related infections. Dosing, route and duration was specified for each infection.

When the manual was introduced, on-site education sessions were provided on different wards by infectious diseases physicians and healthcare workers from other disciplines who were involved in the study. These comprised mostly physicians and nurses. Follow-up meetings were conducted once a month rotating between the different medical and surgical wards, for approximately three months after the manual introduction.

Local antimicrobial susceptibility patterns and in-hospital broad spectrum antimicrobial consumption data were reviewed before preparing the manual. A multidisciplinary team led by infectious diseases specialists and one internal medicine specialist together with microbiologists, infection prevention and control practitioners, pharmacists and hospital management provided the recommendation for the development of the manual, which was developed by means of programmed meetings within the hospital as a part of continuous education in medicine (ECM programs in Italy). The manual was made available on the hospital intranet. Several educational meetings with nurses and medical doctors had been organised during the release of the manual to help promote the use of the manual. No restrictive policy on antimicrobial prescribing was applied.

Outcomes

Antimicrobial consumption was measured as defined daily dose per 1000 patient days (DDD/1000 PD). The antimicrobials investigated were piperacillin-tazobactam, third-generation cephalosporins, fluoroquinolones, carbapenems, tigecycline and vancomycin.

Microorganism trends included positive blood cultures for *K. pneumoniae* carbapenemase-producing (KPC) bacteria, extended-spectrum beta-lactamase (ESBL) *E. coli*, methicillin-resistant *S. aureus* (MRSA) and *Candida albicans*. In addition, CDI episodes were measured and rates were normalised per 1000 PD.

Carbapenemase-production was detected by the phenotypic modified Hodge test and defined or confirmed by the combination disk test (MAST, UK; Rosco, Denmark) until 2018; later immunochromatographic lateral flow tests (ICT) were used for rapid detection and typing of carbapenemases.

Hospital-acquired bloodstream infections (BSIs) were defined as those diagnosed from blood cultures obtained ≥ 48 h after hospital admission. Patients with a further positive blood culture of the same microorganism were considered a unique episode of BSI unless the sample was obtained less than two weeks after the last positive blood culture. The identification of microorganisms in blood cultures and the determination of resistance to antimicrobials were performed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Statistical analysis

Trends in antimicrobial consumption in medical and surgical wards, calculated monthly as Daily Defined Doses (DDD)/1000 Patient Days (PD), were investigated over a period of four years (2015–2019) using segmented regression analysis of an interrupted time series, with change in consumption, change in trend and pre-existing trend estimations between pre-intervention and intervention period. The breakpoint was set on June 1st 2017. Appropriate tests were run to check autocorrelation (ACF and pACF plots) and seasonality (Weber and Ollech test) [8]. A 12 month wide rolling mean was then performed, and all regression models were run on the smoothed data. Software R was used to manage data and to perform the analysis [9].

Interrupted time series analysis was inapplicable for MDRO analysis because of the scarce episodes of BSI. As a result, chi-square test using SPSS was performed and the percent change was calculated to compare the incidence rates pre- and post-intervention. Additionally, MDRO rates were normalised per 1000 PD.

Results

Antimicrobial consumption

In medical wards, we observed a significant decrease in consumption of piperacillin-tazobactam (-33.29 , $P < 0.001$). A significant decrease in the trends of consumption was identified for tigecycline and vancomycin ($P < 0.001$) (Table I). Carbapenems and vancomycin use increased early after the intervention, but the post intervention trends were still decreasing significantly ($P = 0.002$ and $P < 0.001$, respectively) (Figure 1).

In surgical wards, there was a significant decrease in consumption of fluoroquinolones, tigecycline, and piperacillin-tazobactam (-17.4 , -2.6 , and -32.0 DDD/1000 PD, respectively). This decrease was maintained in trend for all the antimicrobials but was significant for tigecycline only.

Table I

Antimicrobial consumption trends in interrupted time series analysis

Ward	Estimate	SE	95% CI	P-value
Medical wards				
<i>Carbapenems</i>				
Change in level	11.95	1.96	8.0; 15.91	<0.001
Trend	-0.59	0.1	-0.8; -0.39	<0.001
Change in trend	0.45	0.14	0.17; 0.73	0.002
<i>3rd generation cephalosporins</i>				
Change in level	17.7	3.61	10.43; 24.98	<0.001
Trend	0.03	0.19	-0.35; 0.40	0.879
Change in trend	0.79	0.26	0.27; 1.3	<0.001
<i>Fluoroquinolones</i>				
Change in level	9.68	2.47	4.7; 14.65	<0.001
Trend	-1.39	0.13	-1.64; -1.13	<0.001
Change in trend	-0.07	0.17	-0.42; 0.28	0.685
<i>Vancomycin</i>				
Change in level	2.36	0.5	1.35; 3.36	<0.001
Trend	0.19	0.03	0.14; 0.25	<0.001
Change in trend	-0.24	0.04	-0.3; -0.16	<0.001
<i>Tigecycline</i>				
Change in level	0.68	0.24	0.2; 1.15	0.007
Trend	0.01	0.01	-0.01; 0.04	0.306
Change in trend	-0.1	0.02	-0.14; -0.07	<0.001
<i>Piperacillin- tazobactam</i>				
Change in level	-33.29	5.17	-43.69; -22.89	<0.001
Trend	0.26	0.27	-0.28; 0.79	0.335
Change in trend	0.31	0.37	-0.43; 1.04	0.406
Surgery				
<i>Carbapenems</i>				
Change in level	25.67	6.13	13.33; 38.01	<0.001
Trend	-1.33	0.32	-1.96; -0.69	<0.001
Change in trend	1.12	0.43	0.25; 1.99	0.013
<i>3rd generation cephalosporins</i>				
Change in level	13.14	2.5	8.1; 18.17	<0.001
Trend	-0.52	0.13	-0.78; -0.26	<0.001
Change in trend	-0.04	0.18	-0.4; 0.32	0.823
<i>Fluoroquinolones</i>				
Change in level	-17.46	4.42	-26.37; -8.55	<0.001
Trend	-0.89	0.23	-1.35; -0.43	<0.001
Change in trend	0.47	0.31	-0.16; 1.09	0.142
<i>Vancomycin</i>				
Change in level	0.96	0.69	-0.44; 2.36	0.173
Trend	-0.31	0.04	-0.38; -0.24	<0.001
Change in trend	0.62	0.05	0.53; 0.72	<0.001
<i>Tigecycline</i>				
Change in level	-2.65	0.79	-4.24; -1.06	0.002
Trend	0.02	0.04	-0.06; 0.1	0.567
Change in trend	-0.26	0.06	-0.37; -0.15	<0.001
<i>Piperacillin-tazobactam</i>				
Change in level	-32.03	6.62	-45.35; -18.7	<0.001
Trend	1.65	0.34	0.97; 2.34	<0.001
Change in trend	-0.18	0.47	-1.12; 0.76	0.705

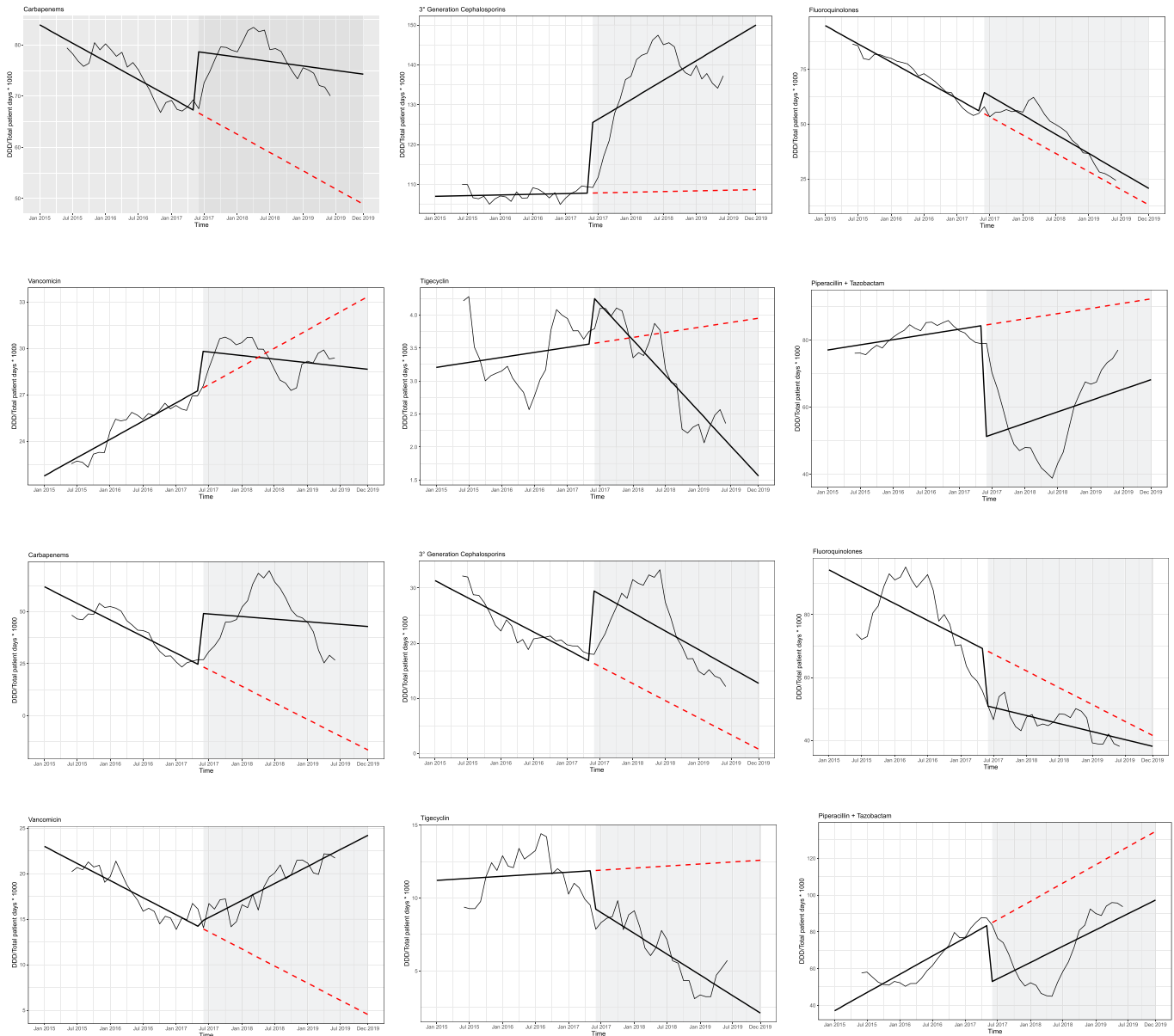


Figure 1. Trends in antimicrobial consumption in medical and surgical wards.

Microorganism trends

From January 2015 through December 2019, a total of 1449 BSI episodes were reported. Among MDRo, the most common microorganisms isolated in blood cultures were ESBL-*E. coli* (N=494, 34%), MRSA (N=255, 18%) and KPC (N=129, 9%), *C. albicans* (N=93,6%). CDI episodes comprised N=478, 33% (Table II).

In medical wards, there was a significant reduction in MRSA cases (−39.0%, 2.57 episodes/1000 PD, $P = 0.032$). *C. albicans* cases decreased by −43.7% (0.7 episodes/1000 PD) in the post-intervention period. In contrast, there was an increase in the rate of ESBL-*E. coli* cases (+1.5%, 6.22 episodes/1000 PD, $P = 0.001$).

Similarly, in surgical wards, we observed a decrease in MRSA cases (−45.6%, 0.51 episodes/1000 PD) and ESBL-*E. coli* cases (−17.9%, 2.05 episodes/1000 PD) after intervention. In

addition, we observed a decrease in *C. albicans* cases (−24.7%, 0.81 episodes/1000 PD) and in CDI cases (−9%, 1.1 episodes/1000 PD). For KPC, the overall cases decreased by 22.5% in medical wards and 74.3% in surgical wards in the post-intervention period.

Discussion

Several studies have shown the impact of ASP on appropriate antimicrobial use. ASP can reduce broad-spectrum antimicrobial usage and the incidence of multidrug resistant microorganism trends in the long term [10–12]. This study implemented a manual for empiric antimicrobial therapy with strengthened education and training on appropriate antimicrobial use without applying any restrictive measure for antimicrobial prescribing. Our study shows the potential for

Table II
Microorganism distribution pre- and post-intervention

MDR	Total N (%)	Pre-intervention N (%)	Post-intervention N (%)	P-value*	Pre-isolates /1,000 PD	Post-isolates /1,000 PD	Percentage change
KPC	129 (8.9)	78 (5.3)	51 (3.5)	0.125	1.60	1.00	-37.5
Medicine	99 (6.8)	54 (3.7)	45 (3)	0.763	1.60	1.20	-22.5
Surgery	30 (2.1)	24 (1.6)	6 (0.4)	0.019	1.71	0.40	-74.3
ESBL- <i>E. coli</i>	494 (34.1)	236 (16.2)	258 (17.9)	0.001	4.80	5.20	+8.3
Medicine	431 (29.7)	201 (13.8)	230 (15.9)	0.001	6.12	6.22	+1.5
Surgery	63 (4.3)	35 (2.3)	28 (1.9)	0.262	2.50	2.05	-17.9
MRSA	255 (17.6)	153 (10.5)	102 (7)	0.035	3.10	2.00	-35.5
Medicine	234 (16.1)	139 (9.5)	95 (6.6)	0.032	4.24	2.57	-39.0
Surgery	21 (1.4)	14 (0.9)	7 (0.4)	0.573	1.00	0.51	-45.6
<i>C. albicans</i>	93 (6.4)	56 (3.8)	37 (2.6)	0.217	1.10	0.70	-36.4
Medicine	67 (4.6)	41 (2.8)	26 (1.8)	0.172	1.25	0.70	-43.7
Surgery	26 (1.8)	15 (1.0)	11 (0.8)	0.703	1.07	0.81	-24.7
CDI	478 (33)	260 (17.9)	218 (15.1)	0.849	5.20	4.40	-15.4
Medicine	446 (30.8)	243 (16.7)	203 (14.1)	0.466	7.40	5.40	-25.8
Surgery	32 (2.2)	17 (1.1)	15 (1.1)	0.308	1.21	1.10	-9.4
Total	1449 (100)	783 (54)	666 (46)	**	15.70	13.37	-14.8
Medicine	1277(88)	678 (46.7)	599 (41.3)	**	20.6	16.2	-21.3
Surgery	172 (11.9)	105 (7.2)	67 (4.7)	**	7.4	4.9	-33.7

*Chi-square test. **No statistics are computed because MDRO is a constant.

educational interventions to optimise antimicrobial use of a particular antimicrobial and to result in a significant reduction of BSIs caused by MDRO in both surgical and medical wards with sustained improvements over time. The reduction of MDRO is of considerable importance, especially in regards of CRE, since in Italy the spread of CRE is widely reported. Of note, we observed significant reduction in KPC-BSI which is important in respect to its high incidence nationally.

One of the main aims of the manual was reducing inappropriate carbapenem use. We successfully observed decreasing trends in carbapenems in both medical and surgical wards. Along with the reduction in carbapenem consumption, there was no significant change in the trend for piperacillin-tazobactam consumption. This may be due to the fact that the carbapenem-sparing approach was used in the setting of non-ESBL high-risk patients where piperacillin-tazobactam was a suitable option. In the setting of ESBL infections, the introduction of a new antimicrobial into clinical practice during the study period, ceftolozane-tazobactam, may have played a role in the reduction of carbapenem use. In addition, for carbapenem-resistant organisms, the introduction of another new antimicrobial, ceftazidime-avibactam, may have reduced the use of combination treatment with carbapenems and tigecycline.

The manual aimed to reduce the use of fluoroquinolones as first-line therapy, using it only in patients allergic to beta-lactams. We observed a decrease in fluoroquinolone use in both medical and surgical wards. Although, we did not investigate the appropriateness of empiric therapy, the reduction of fluoroquinolones, especially as prophylaxis in surgery, can be considered as an improvement in ASP due to the high prevalence of fluoroquinolone-resistant organisms in our hospital. Moreover, fluoroquinolones have been consistently associated with significant adverse events, increasing risk of CDI, ESBL-producing *Enterobacteriales*, and MRSA infections [12]. In parallel, we observed a downward trend in CDI and MRSA along with fluoroquinolone reduction.

It is well-known that the reduced use of some antimicrobial classes may result in increased resistance to others, pictured as “squeezing the balloon effect” [13]. In our setting, we observed increased vancomycin use in surgical wards and cephalosporins in medical wards because they were used as de-escalation or alternative antimicrobials for carbapenems and fluoroquinolones. This also could reflect our high ESBL-*E. coli* rates. We did not check for resistance to these antimicrobials due to the short period of the study. A longer period of time is needed to confirm the effect of antimicrobial cycling on resistance.

Our results cannot be attributed to the introduction of the manual alone, and are likely to reflect the effects of other educational interventions including infection control and appropriate isolation practices. Our data showed a sharp decrease after the intervention which was not maintained over time. These findings emphasise the need for continuous education as a tool of ASP to sustain improvements. Education for prescribing physicians is the first step in ASP but it must be followed by other interventions such as audit, feedback and pharmacist engagement [14]. In addition, compliance with infection control measures such as hand and environment hygiene and appropriate isolation procedures should be implemented along with reducing antimicrobial exposure [15].

The strength of this study is that it well reflects the real-world setting in a large Italian hospital. In addition, it reports some long-term analysis with MDRO trends which is hard to measure in ASP. The limitations of the study included the single-setting and retrospective nature of the study. Confounders were infection control measures and behavioural changes of physicians that could not be fully controlled. The impact of new antimicrobials on overall consumption was not investigated because they were recently introduced during the study period. We did not audit the appropriateness of antimicrobial therapy and the post-intervention period was not long enough to demonstrate if the improvements were sustained long term.

Conclusions

The results of this study suggest that a persuasive educational approach to antimicrobial stewardship with an empiric antimicrobial therapy manual and continuous education sessions, was effective in reducing antimicrobial use and hospital-acquired infections BSIs. Further studies are required to investigate the impact of ASP on clinical outcomes.

Credit author statement

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Conflict of interest statement

The authors have no conflicts to declare.

Funding

No funding was received for this work.

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