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Antimicrobial Original Research Paper

Effect of a "handshake" stewardship program versus a formulary restriction policy on High-End antibiotic use, expenditure, antibiotic resistance, and patient outcome

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ABSTRACT

This study reports the effect of implementing an antibiotic stewardship program (ASP) based on the "handshake" strategy for 2 years on multiple endpoints compared with that in a preceding period when an antimicrobial restriction policy was only applied in the absence of a complete program in a tertiary-care Lebanese hospital. The studied endpoints were broad-spectrum antibiotic consumption, antibiotic expenditure, nosocomial bacteremia incidence rate, and patient outcome.

An interrupted time series analysis was undertaken to assess the changes in the trend (ΔT) and level (ΔL) of the aforementioned endpoints among adult inpatients before (October 2013 to September 2015) and after the introduction of the ASP (October 2016 to September 2018).

After the implementation of the "handshake" ASP, marked changes were observed in the consumption of broad-spectrum antibiotics. The mean use density levels for imipenem and meropenem decreased by 13.72% ($P = 0.017$), coupled with a decreasing rate of prescription (ΔT = −24.83 defined daily dose [DDD]/1,000 patient days [PD]/month; $P = 0.02$). Tigecycline use significantly decreased in level by 69.19% ($P < 0.0001$) and in trend (ΔT = −25.63 DDD/1,000 PD/month; $P < 0.0001$). A reduction in the use of colistin was also documented but did not reach statistical significance (ΔL = −8.71%, $P = 0.56$; ΔT = −5.51 DDD/1,000 PD/month = −5.5; $P = 0.67$). Antibiotic costs decreased by 24.6% after ASP implementation ($P < 0.0001$), and there was a distinct change from an increasing rate to a decreasing rate of expenditure (ΔT = −12.19 US dollars/PD/month; $P = 0.002$). The incidence rate of nosocomial bacteremia caused by carbapenem-resistant gram-negative bacteria (CRGNB) decreased by 34.84% ($P = 0.13$) coupled with a decreasing trend (ΔT = −0.23 cases/1,000 PD/month, $P = 0.08$). Specifically, a noticeable reduction in the incidence rate of bacteremia due to carbapenem-resistant *Acinetobacter baumannii* was documented (ΔL = −54.34%, $P = 0.01$; ΔT = −0.24 cases/1000 PD/month, $P = 0.01$). Regarding patient outcome, all-cause mortality rates did not increase in level or in rate (ΔL = −3.55%, $P = 0.59$; ΔT = −0.29 deaths/1000 PD/month, $P = 0.6$). The length of stay and 7-day readmission rate remained stable between the two periods.

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In conclusion, the "handshake" ASP succeeded in controlling the prescription rates of antibiotics and in decreasing the nosocomial bacteremia rates caused by CRGNB without compromising patient outcome in our facility. It also had an economic effect in reducing antibiotic costs compared with the previous restriction policy on antimicrobial dispensing.

Keywords: Handshake antibiotic stewardship; prospective audit and feedback; antibiotic consumption; nosocomial bacteremia; carbapenem-resistant Gram-negative bacteria; expenditure; mortality, length of stay; 7-day readmission rate; patient outcome; Lebanon

Introduction

During the past two decades, the world has witnessed an increase in antimicrobial resistance (AMR), which is propagated by the overuse and misuse of antibiotics.[1,2] This increase in AMR was observed in Lebanon during the last 10 years and has become a growing concern in light of limited resources.[3–5] A rising incidence of infections caused by extensively drug-resistant bacteria such as carbapenem-resistant *Acinetobacter baumannii* (CRAB) was documented in hospitals across the country,[3,4,6] in addition to the acquisition of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and carbapenem-resistant Enterobacteriaceae.[7,8] These serious and difficult-to-treat infections are managed using high-end antibiotic combinations or new antibiotics that are not readily available in all Lebanese hospitals.

In Lebanon, where a national surveillance system that monitors antibiotic consumption is not available, little is known about inpatient antibiotic prescription patterns.[9] In 2012, a cross-sectional study involving 27 nonteaching hospitals revealed that antibiotic use density was higher than what was reported from European hospitals at that time.[10] In most Lebanese healthcare institutions, inpatient antibiotic use is controlled solely by applying institutional formulary restriction policies, which is insufficient to reduce the prevalence of AMR.[11] Consequently, adopting evidence-based and multidisciplinary antimicrobial stewardship programs (ASPs) has become a necessity because these programs aim to improve antimicrobial prescriptions without compromising patient outcome. Recent literature demonstrates the progress in several key strategies used to achieve this aim.[12,13] These programs have been advocated by international organizations concerned by AMR such as the World Health Organisation (WHO) to extend the life expectancy of what is still active in the antimicrobial armamentarium. In 2019, the Lebanese Ministry of Public Health developed a National Action Plan with the support of the WHO to fight AMR, and one of its core objectives is to optimize antibiotic use in hospitals by establishing ASPs.

Our facility, namely, Makassed General Hospital (MGH), is an academic teaching hospital and tertiary-care referral center in Beirut and has followed an anti-infective restriction policy for the past 20 years. In September 2016, the hospital adopted an ASP based on the "handshake" strategy of prospective audit and immediate feedback to prescribers with the aim of decreasing high-end antibiotic use, namely antipseudomonal carbapenems, colistin, and tigecycline. In this study, we primarily showed the effect of this ASP on broad-spectrum antibiotic use, total antibiotic expenditure, and nosocomial bacteremia incidence rate caused by antibiotic-resistant pathogens. As secondary endpoints, we checked whether this program had an effect on all-cause in-hospital mortality, intensive care unit (ICU) mortality, length of hospital stay (LOS), and 7-day readmission rate.

Methods

Setting and study design

This study is a retrospective study and was conducted at MGH, which is a 186-bed academic teaching hospital and tertiary-care referral center. The monthly occupancy rate ranges between 70% and 80%, with 17 beds in adult critical care, 18 beds in adult hematology/oncology and bone marrow transplantation, 21 beds in adult surgery, and 71 beds in internal medicine departments. The hospital also includes a regular pediatric ward, pediatric and neonatal critical care units, and a pediatric hematology/oncology ward. However, this study considered data from the adult wards only. The study was extended over two periods: the pre-ASP period from October 2013 to September 2015 (period 1, P1) and the ASP implementation period from October 2016 to September 2018 (period 2, P2). The time interval between October 2015 and September 2016 was a washout period and was excluded from the analysis. The hospital's Institutional Review Board committee approved this study.

Description of the antibiotic dispensing policy before ASP initiation

Before September 2016 and for almost 20 years, antimicrobial dispensing was controlled using an institutional antimicrobial restriction policy established by the hospital's pharmacy and therapeutics committee. This policy included a list of antimicrobials that are defined as "restricted agents" either because of their broad-spectrum of activity or expensive price. It stated that only infectious disease (ID) specialists, intensivists, and chest physicians were allowed to prescribe these agents. The hospital pharmacists did not dispense any "restricted antimicrobial" after the first 24 hours of prescription without a written consent from the formerly mentioned specialists. Antimicrobial utilization strategies and institutional guidelines were unavailable at that time, and prescription was individualized and left to the judgment of each specialist.

Description of the ASP and "handshake" approach

In September 2016, an ID specialist–led ASP was launched at our facility. This program fulfilled the requirements of the Centre of Disease Control and Prevention (CDC) regarding the availability of the essential components of ASPs. During the ASP period, institutional antimicrobial treatment guidelines were created for the most common IDs that were treated. The local antibiotic susceptibility patterns of community- and hospital-acquired bacteria were determined via the continuous surveillance of all positive cultures from any type of clinical specimens. Institutional guidelines were tailored according to the national epidemiology of AMR for community-acquired infections[14–16] and according to the local AMR epidemiology for nosocomial infections.[17–19] Local treatment pathways were validated from international guidelines for community-acquired infections that were not included in the available national guidelines. Institutional protocols for the use of antibiotics such as carbapenems, tigeycline, and colistin were also established. All guidelines and protocols were accessible via the hospital intranet. It is worth noting that antibiotics such as ceftolozane/tazobactam and ceftazidime/avibactam were not available in the country during the study period.

The stewardship team included an ID physician and an ID clinical pharmacist. The "handshake" approach included the following components:

1. Prospective audit of all prescribed antimicrobials and immediate feedback during daily ward rounds
2. Education and dissemination of the local guidelines and treatment pathways of the common infectious syndromes encountered in the hospital

During the ward rounds, the stewards reviewed the medical files and performed bedside evaluation when needed for all patients who were prescribed antimicrobials. The stewards discussed with the treating team the diagnosis, need for antimicrobial therapy, choice of agent(s), dosing, route of administration, and duration of therapy on the basis of the institutional treatment guidelines. In follow-up rounds, the modification of antibiotic therapy was performed on the basis of the patient's clinical response and the availability of microbiology results. Patient stratification according to the risk of acquisition of bacteria resistant to third-generation cephalosporins and carbapenems was a pivotal point in deciding empiric antibiotic therapy. De-escalation was performed according to the patient's clinical status and the availability of culture results and antibiograms, with a continuous attempt to sparingly use broad-spectrum antibiotics. Furthermore, shifting from an intravenous route to an oral route of administration or shortening the duration was also discussed with the treating physicians.

Decisions regarding antimicrobial therapy were taken after discussions with the medical team and after obtaining the consent of the primary treating physician, as part of the "handshake" approach. All suggestions of the stewards were mandated in-person to healthcare providers during the clinical rounds. Furthermore, the stewards detected the need for additional educational activities about AMR epidemiology or antimicrobial treatment guidelines. Thus, oral presentations and discussions that target house staff and attending physicians were undertaken.

Study endpoints and outcome data metrics

Drug use density

Antibiotic use data were obtained from the hospital pharmacy and were expressed as WHO-ATC defined daily doses (DDDs). A DDD corresponds to the daily dose of a specific drug for its main indication in adults.[20] Antibiotic use density was measured as the number of DDDs/1000 patient days (PDs). The number of PDs was calculated by counting the number of patients present in any given location (e.g., hospital or ward) at the same time each day.[21] We studied the monthly variation of antibiotic use density before and after ASP initiation.

Consumption of the following antibiotics and antibiotic combinations was taken into consideration:

- Piperacillin/tazobactam
- Carbapenems (imipenem, meropenem, and ertapenem)
- Antipseudomonal carbapenems (imipenem and meropenem)
- Third- and fourth-generation cephalosporins (3GC/4GC) (ceftriaxone, ceftazidime, cefotaxime, and cefepime)
- Colistimethate sodium
- Tigecycline

- Glycopeptides (vancomycin and teicoplanin)
- High-end antibiotics defined as antipseudomonal carbapenems, tigecycline, and colistin all together

Antibiotic expenditure

Data on actual antibiotic expenditures were also retrieved from the pharmacy database. We studied the monthly variation of the overall cost of antibiotics before and after ASP initiation, and this endpoint was expressed as US dollars/PD.

Incidence of nosocomial bacteremia caused by Antibiotic-Resistant organisms

We retrospectively reviewed microorganisms isolated from positive blood cultures withdrawn from adult patients, along with their corresponding antibiograms from the WHONET database program of the hospital microbiology laboratory department during the study period.

As per hospital policy or the differential diagnosis of the treating clinician, one set of blood cultures (two bottles, 10 cc each) was generally performed on patients who were suspected to have a bacterial infection on the basis of a fever or evidence of sepsis. The two blood samples were withdrawn simultaneously from the patient from either two peripheral sites or from a central venous line (if present) and one peripheral site. The samples were then sent to the Department of Microbiology. All blood samples were processed for aerobic cultures by using the BD BACTEC™ blood culture system (Becton Dickinson Diagnostic Instrument Systems, Sparks, Maryland, USA). Anaerobic cultures were not available in our facility. All microbiological methods were consistent with the guidelines of the Clinical and Laboratory Standards Institute (CLSI), and antimicrobial susceptibility was determined using the CLSI breakpoints of the corresponding year.[22]

Bacteremia was defined as the isolation of at least one clinically relevant pathogen from one blood culture drawn from a patient with an indicative clinical syndrome. Organisms of the same species with the same antimicrobial susceptibility profile isolated from the same patient (matching hospital case number) were considered duplicate isolates and were removed from the analysis. Coagulase-negative staphylococci and other microorganisms that are generally considered contaminants, such as *Corynebacterium* spp., *Bacillus* spp., *Micrococcus* spp., and *Propionibacterium* spp., were also excluded from the analysis.[23] The electronic medical records of patients with positive blood cultures were reviewed to assess whether the bacteremia was nosocomial. Nosocomial bacteremia was defined as the isolation of pathogenic bacteria from blood cultures taken 2 days and more after admission.[23] We reviewed the monthly variation of the incidence rate of nosocomial bacteremia per 1000 PD before and after ASP. We specifically studied the monthly variation of the incidence rate of bacteremia caused by carbapenem-resistant Gram-negative bacteria (CRGNB), CRAB, and CRPA.

Patient outcome and quality of care indicators including mortality, LOS, and 7-Day readmission rate

Data on the all-cause in-hospital mortality, ICU mortality, LOS, and 7-day readmissions of all adult patients admitted to our facility during both periods were obtained from the administration, and the monthly variation of these endpoints was studied using the following metrics:

- Overall mortality: number of deaths/1000 PD
- ICU mortality: number of deaths inside the ICU/1000 patient days in ICU
- LOS: average value in days
- Seven-day readmission rate: percent (number of hospital readmissions within 7 days of discharge/total number of discharges during the same period * 100)

Statistical analysis

The descriptive statistical analysis of the studied endpoints was performed by using the Statistical Package for Social Sciences (IBM Corp., Released 2016; IBM SPSS Statistics for Windows, Version 24.0; Armonk, NY: IBM Corp.). For each endpoint, we defined "percent change in level" (ΔL) as the difference between the mean during P1 (L1) and that of P2 (L2) divided by L1 and multiplied by 100. Paired two-tailed *t*-test was used to compare the endpoints in questions during both periods. The effect of ASP initiation on all endpoints was evaluated via the segmented regression analysis of an interrupted time series. We defined "change in trend" (ΔT) as the difference between the change rates between P1 and P2. We applied linear regressions with Newey–West standard errors with a maximum lag of three to be considered in the autocorrelation structure in STATA version 15 (StataCorp LLC., College Station, TX). Statistical significance was defined as $P < 0.05$.

In addition to the actual change in level between the two periods, we assumed the presence of a hypothetical change in level ($\Delta L'$). For the studied endpoints, we drew a linear trend line for the graph representing the data during P1 and extrapolated it to P2. We assumed that no ASP was initiated and that the endpoints in question followed the baseline trend line, which became the hypothetical trend line in the second period (dotted line in violet color in Figures 1–4). Hypothetical data points were determined from this hypothetical trend line. For each month of P2 (N = 24), we retrieved the corresponding value on the Y-axis. From the 24 hypothetical values, a hypothetical mean was determined (L2'). ΔL' was calculated as follows: ((L2 - L2')/L2') *100.

Results

Effect of the ASP with "handshake" strategy on antibiotic use

Following the initiation of the "handshake" ASP, the overall high-end antibiotic density in adult units decreased by 16.81% ($P = 0.02$), with a mean value of 282.47 during P1 versus 235.0 DDD/1000 PD during P2 (Table 1). The interrupted time series model equally showed a reduction in the rate of consumption, but it was statistically insignificant (ΔT = −47.47 DDD/1000 PD/month, $P = 0.06$) (Table 1, Figure 1(A)).

Marked changes were observed in the consumption of the defined antibiotics, including carbapenems, tigecycline and colistin (Table 1; Figure 1(B–E)). The mean use density levels for antipseudomonal carbapenems (imipenem + meropenem) significantly decreased from 180.97 to 156.14 DDD/1000 PD (ΔL = −13.72%, $P = 0.017$). Regarding time series analysis, there was a nearly significant reduction in antipseudomonal carbapenem prescription from an increasing rate to a decreasing rate of use (ΔT = −24.83 DDD/1,000 PD/month; $P = 0.02$) (Figure 1(C)). For the mean level of consumption of tigecycline, the decrease was from 37.05 DDD/1000 PD before ASP to 11.42 DDD/1000 PD after ASP (ΔL = −69.19%, $P < 0.0001$), and a reduction by 8.71% was also noted in the use of colistin (63.33 to 57.82 DDD/1000 PD, $P = 0.56$) (Figure 1(D,E)). In parallel, the trend analysis showed a marked change from an increasing rate to a decreasing rate of tigecycline use (ΔT = −25.63 DDD/1,000 PD/month; $P < 0.0001$) and colistin use (ΔT = −5.51 DDD/1,000 PD/month; $P = 0.67$). Conversely, the prescription of ertapenem significantly increased by 7.5 folds ($P < 0.0001$) after ASP initiation (Figure 1(F)). Similarly, piperacillin/tazobactam consumption increased by 22.6% (from 85.51 to 104.84 DDD/1000 PD, $P = 0.08$) and that of third- and fourth-generation cephalosporins increased by 29.15% (from 102.78 to 132.74 DDD/1000PD, $P = 0.001$) (Figure 1(G,H)). The interrupted time series model confirmed the increasing rates of piperacillin/tazobactam and broad-spectrum cephalosporins use after ASP (ΔT = 19.33 DDD/1000 PD/quarter, $P = 0.03$ and ΔT = 29.96 DDD/1000 PD/quarter, $P = 0.02$, respectively) (Table 1).

Regarding anti-gram-positive agents, mean glycopeptide consumption levels increased by 4.05% (from 65.0 to 67.63 DDD/1000PD, $P = 0.6$) (Table 1, Figure 1(I)). The trend analysis also indicated an increasing rate of utilization but without statistical significance (ΔT = 2.63 DDD/1000 PD/month, $P = 0.65$) (Table 1).

Effect of ASP with "handshake" strategy on antibiotic cost

The average monthly antibiotic expenditure was 49.55 USD/PD during P1 and decreased to 37.35 USD/PD during P2 (ΔL = −24.6%, $P < 0.0001$) (Table 1, Figure 2). Interrupted time series analysis confirmed the significant variation in expenditure with a distinct change from an increasing rate to a decreasing rate (ΔT = −12.19 USD/PD/month; $P < 0.0001$) (Table 1).

Effect of the ASP "handshake" strategy on the incidence rates of nosocomial bacteremia

The mean monthly incidence of nosocomial bacteremia during P1 was 1.95 cases/1,000 PD regardless of the causative agent and remained stable during P2 (1.65 cases/1,000 PD) (ΔL = −0.68%, $P = 0.97$, ΔT = −0.01 cases/1,000 PD/month, $P = 0.97$) (Table 1, Figure 3(A)). The incidence of nosocomial CRGNB causing bacteremia decreased in level from 0.65 to 0.43 cases/1000 PD (ΔL = −34.84%, $P = 0.09$), and a negative change in trend was documented (ΔT = −0.23 cases/1,000 PD/month, $P = 0.08$) (Figure 3(B)). For specific resistant gram-negative organisms causing nosocomial bacteremia, CRAB incidence prominently decreased from 0.45 to 0.20 cases/1000 PD (ΔL = −54.34%, $P = 0.01$), along with a significant decrease in trend (ΔT = −0.24 cases/1000 PD/month, $P = 0.01$) (Figure 3(C)). A noticeable change in the incidence of CRPA bacteremia was equally seen when there was a decrease in the level (ΔL = −54.5%, $P = 0.15$), yet we could not evaluate the change in the trend of occurrence due to insufficient data points (Table 1, Figure 3(D)).

Effect of the ASP with "handshake" strategy on mortality, LOS, 7-Day readmission rate

The mean monthly all-cause mortality rate per 1,000 PD was 8.2 during P1 and 7.91 during P2 (Table 1, Figure 4(A)). There was a decrease in the level, along with a negative change in trend for in-hospital deaths; however, these were statistically insignificant (ΔL = −3.55%, $P = 0.53$; ΔT = −0.29 deaths/1000 PD/month, $P = 0.6$). Regarding ICU

Table 1 Changing levels and trends of antibiotic use, antibiotic expenditure, patient outcome, quality of care indicators and incidence of nosocomial bacteremia after the implementation of the "handshake" stewardship program.

Endpoint		L1	L2	ΔL (%)	SE	95% CI	*P*	ΔT	SE	95% CI	*P*
Antibiotic consumption (number of DDD/1000 PD)	*TZP*	85.51	104.84	22.60	6.36	6.16, 32.49	0.006	19.33	8.75	1.70, 36.95	0.03
	3GC & 4GC	102.78	132.74	29.15	6.46	16.59, 43.32	<0.0001	29.96	12.34	5.12, 54.80	0.02
	IPM & MEM	180.97	156.14	−13.72	9.67	−44.84, −4.82	0.017	−24.83	10.48	−45.93, −3.73	0.02
	*ETP**	1.13	9.63	754.61	1.08	6.27, 10.73	<0.0001	–	–	–	–
	CAR	182.09	165.77	−8.97	9.67	−36.33, 3.69	0.11	−16.32	10.86	−38.19, 5.54	0.14
	TGC	37.05	11.42	−69.19	4.39	−34.71, −16.55	<0.0001	−25.63	5.52	−36.73, −14.53	<0.0001
	CST	63.33	57.82	−8.71	9.29	−24.74, 13.71	0.56	−5.51	12.68	−31.03, 20.01	0.67
	GLY	65.0	67.63	4.05	5.0	−7.71, 12.97	0.6	2.63	5.70	−8.85, 14.11	0.65
	High-end ABX	282.47	235.0	−16.81	19.43	−87.66, −7.28	0.02	−47.47	24.85	−97.48, 2.54	0.06
Total antibiotic cost (USD/PD)		49.55	37.36	−24.60	1.99	−16.32, −8.06	<0.0001	−12.19	2.76	−17.74, −6.64	<0.0001
Patient Outcome and Patient-care Quality Indicators	*All-cause in-hospital mortality (N. of deaths/ 1000 PD)*	8.20	7.91	−3.55	0.53	−1.39, 0.81	0.59	−0.29	0.54	−1.37, 0.78	0.60
	ICU mortality (N. of deaths in ICU/1000 ICU days)	52.49	49.77	−5.18	8.77	−20.87, 15.43	0.76	−2.72	5.87	−14.54, 9.10	0.65
	LOS (days)	3.57	3.58	0.33	0.05	−0.10, 0.15	0.83	0.01	0.11	−0.20, 0.23	0.91
	7-day readmission rate (%)	0.495	0.491	−0.87	0.08	−0.18, 0.17	0.96	−0.004	0.12	−0.25, 0.25	0.97
	Number of PD	3050	3066	0.54	87.9	−165.29, 198.38	0.85	16.54	121.80	−228.63, 261.71	0.89
	Number of PD in ICU	111	105	−4.96	3.06	−11.83, 0.83	0.09	−5.5	3.41	−12.37, 1.37	0.11
Nosocomial bacteremia incidence rate (N. of cases /1000 PD)	*Total*	1.95	1.94	−0.68	0.31	−0.65, 0.62	0.97	−0.01	0.37	−0.76, 0.74	0.97
	CRGNB	0.65	0.43	−34.84	0.13	−0.49, 0.04	0.09	−0.23	0.13	−0.48, 0.03	0.08
	CRAB	0.45	0.20	−54.34	0.09	−0.43, −0.05	0.01	−0.24	0.09	−0.42, −0.06	0.01
	*CRPA**	0.16	0.07	−54.48	0.06	−0.20, 0.03	0.15	–	–	–	–

KEY= **ABX**: Antibiotics, **CAR**: Carbapenems, **CI**: Confidence interval**, CRAB**: Carbapenem-Resistant *Acinetobacter baumannii*, **CRGNB**: Carbapenem-Resistant Gram-negative Bacteria, **CRPA**: Carbapenem-Resistant *Pseudomonas aeruginosa*, **CST**: Colistimethate sodium, **DDD**: Defined Daily Dose, **ETP**: Ertapenem, **GLY**: Glycopeptides, **ICU**: Intensive Care Unit, **IPM**: Imipenem, **L1**: Monthly average value before intervention, **L2**: Monthly Average value after intervention, **LOS**: Length of Stay, **MEM**: Meropenem, **N**: Number, **PD:** Patient Days, **SE**: Standard Error, **TGC**: Tigecycline, **TZP**: Piperacillin/Tazobactam, **3GC**: third-generation cepahlosporins, **4GC**: fourth-generation cepahlosporins, **ΔL**: Change in Level, **ΔT**: Change in Trend.

N.B.

-The change in level is expressed in percent.

-The change in trend is expressed based on each endpoint's unit per month.

*The change in trend could not be evaluated due to limited occurrence in either of the phases; we only calculated the change in level.

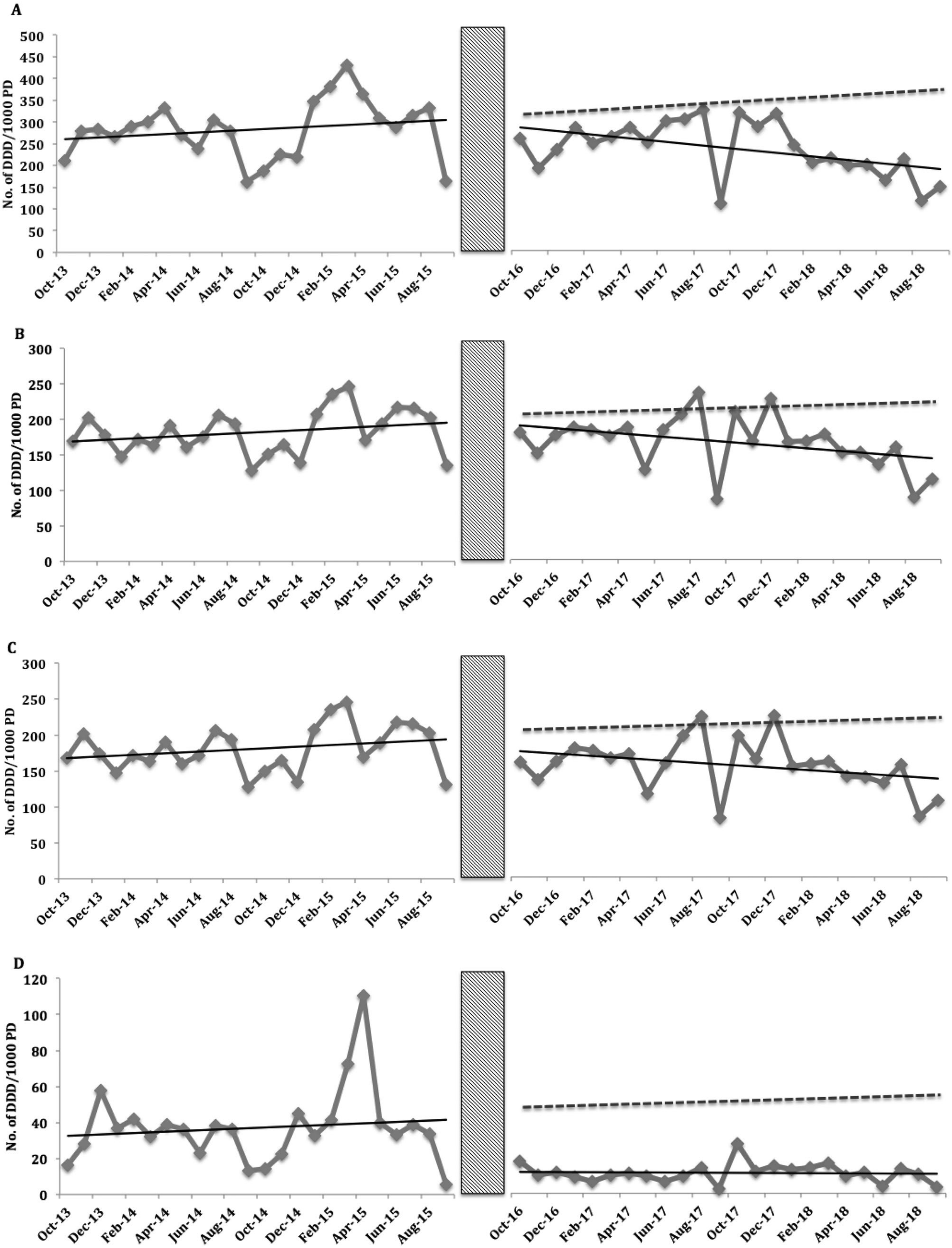

Figure 1. Monthly variation of antibiotic consumption (number of DDD/1000 PD) among adult inpatients before and after the “handshake” stewardship program implementation. (A) High end antibiotics including carbapenems, tigecycline and colistin, (B) All carbapenems, (C) Anti-pseudomonal carbapenems including imipenem and meropenem, (D) Tigecycline, (E) Colistin, (F) Ertapenem, (G) Piperacillin/Tazobatam, (H) Third and fourth generation cephalosporins, (I) Glycopeptides.

KEY: DDD: Defined daily dose, **PD**: Patient day.

N.B.

-Period before the stewardship program initiation: October 2013-September 2015

-Period after and the program initiation: October 2016-September 2018

-Washout period: October 2015-September 2016 (shaded area)

-The dotted trend line represented the hypothetical trend line, which is the extension of the baseline trend line (October 2013- September 2015) where we assumed that there was no ASP from October 2016-September 2018.

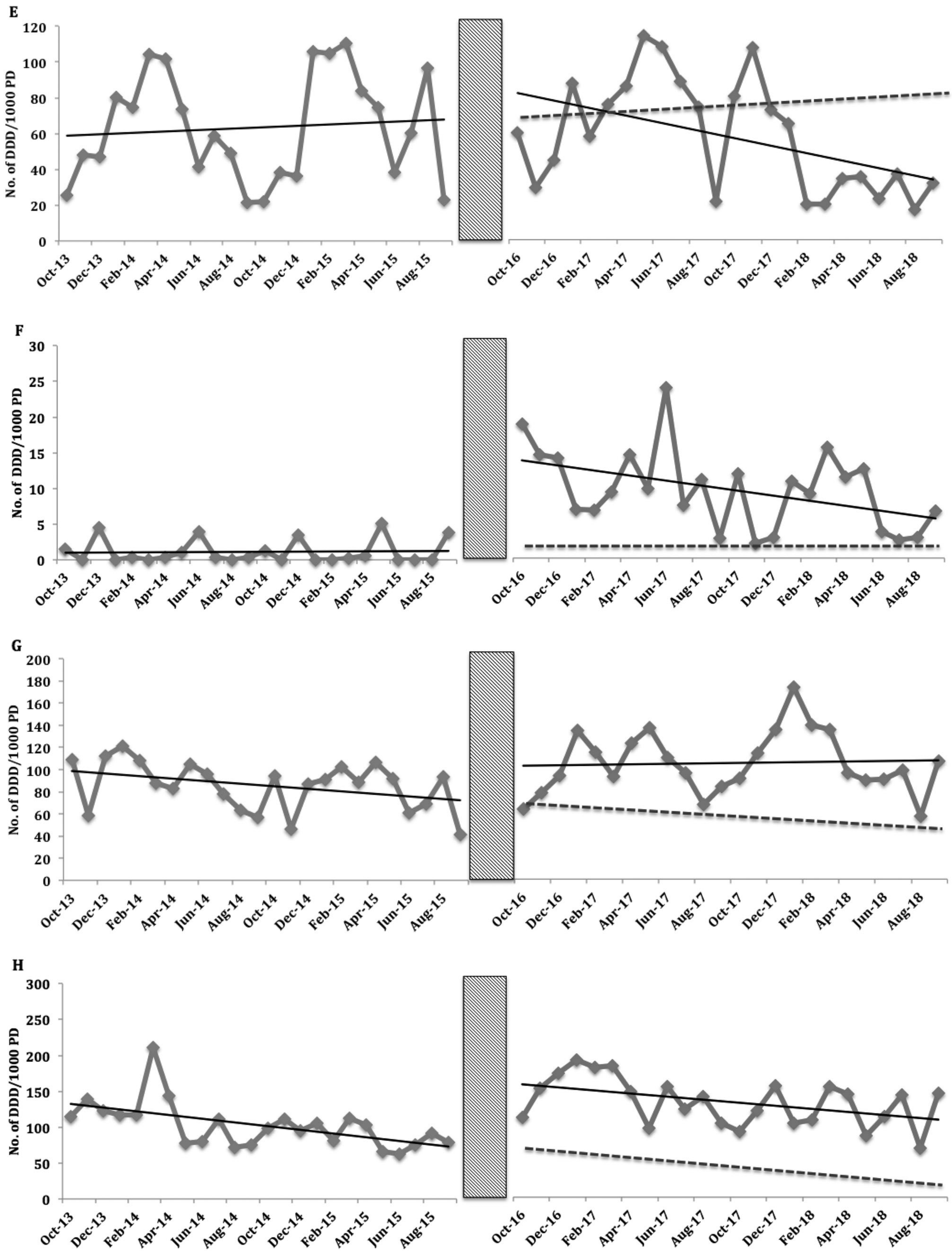

Figure 1. (Continued).

mortality, we similarly noted a 5.18% decrease in level ($P = 0.76$) coupled with a negative change in slope ($\Delta T = -2.72$ deaths/1000 ICU days/month; $P = 0.65$) between the two periods; however, these were statistically insignificant (Table 1, Figure 4(B)). The average LOS for adult patients admitted to our facility remained stable during P1 and P2 (3.57 versus 3.58 days, respectively)

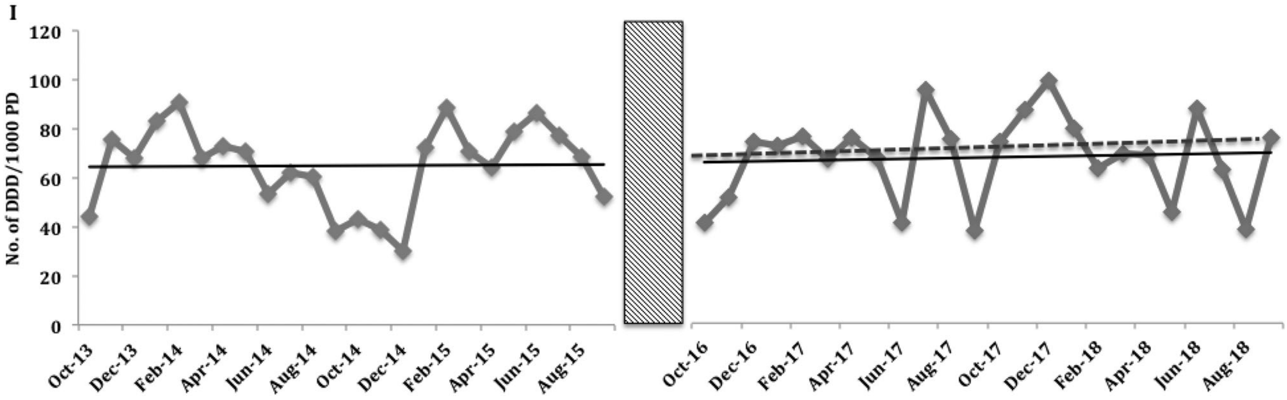

Figure 1. (Continued).

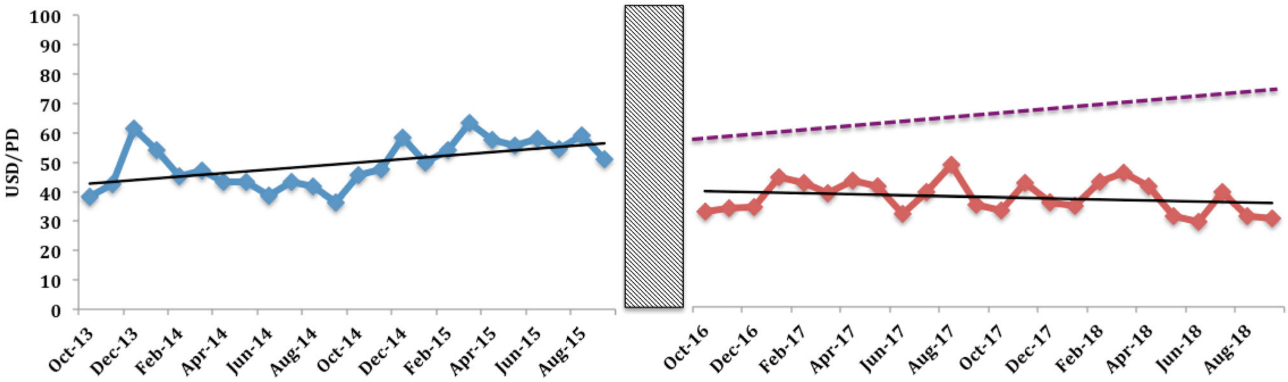

Figure 2. Monthly variation of total antibiotic cost (USD/PD) in adult wards before and after the "handshake" stewardship program implementation.

KEY: USD: United States Dollar, **PD**: Patient day.

N.B.

-Period before the stewardship program initiation: October 2013-September 2015

-Period after and the program initiation: October 2016-September 2018

-Washout period: October 2015-September 2016 (shaded area)

-The dotted trend line represented the hypothetical trend line, which is the extension of the baseline trend line (October 2013- September 2015) where we assumed that there was no ASP from October 2016-September 2018.

(ΔL = 0.28%, $P = 0.9$; ΔT = 0.01 days/month, $P = 0.91$) (Table 1, Figure 3(C)). Similarly, the 7-day readmission rate did not change when comparing both periods despite the slight negative change in level (ΔL = −0.87%, $P = 0.96$) and trend (ΔT = −0.004%/month, $P = 0.97$) (Table 1, Figure 3(D)).

Description of the hypothetical change in level of the studied endpoints

The hypothetical change in level calculated for the studied endpoints accentuated the effect of the ASP, and a negative change was prominent for most of them (Table 2). For example, the consumption of high-end antibiotics collectively decreased (ΔL' = −33.25%, $P < 0.0001$), as well as the consumption of individual agents including carbapenems (ΔL' = −25.82%, $P < 0.0001$), tigecycline (ΔL' = −77.65%, $P < 0.0001$) and colistin (ΔL' = −25.37%, $P = 0.007$). In parallel, the expenditure decreased by 47.37% ($P < 0.0001$). The incidence rate of nosocomial bacteremia significantly decreased by 31.05% ($P = 0.002$), and the incidence rate of nosocomial bacteremia caused by CRGNB decreased by 67.48% ($P < 0.0001$). A noticeable reduction in the incidence rate of CRAB and CRPA causing bacteremia was documented (ΔL' = −74.72%, $P < 0.0001$ and ΔL' = −82.43%, $P < 0.0001$, respectively). For patient outcome, the overall in-hospital mortality and average LOS prominently dropped compared with the hypothetical baseline level (ΔL' = −13.3%, $P = 0.003$ and ΔL' = −4.49%, $P = 0.003$, respectively) (Table 2).

Discussion

In this study, we reported the effect of a "handshake" stewardship program on antibiotic consumption, expenditure, nosocomial bacteremia incidence rates, and patient outcome over a period of 2 years compared with that in a preceding period when an antibiotic restriction policy was only applied in our facility. The difference in controlling antibiotic prescription between the two periods relied on two important points. First, the applied strategy before ASP initiation was preauthorization

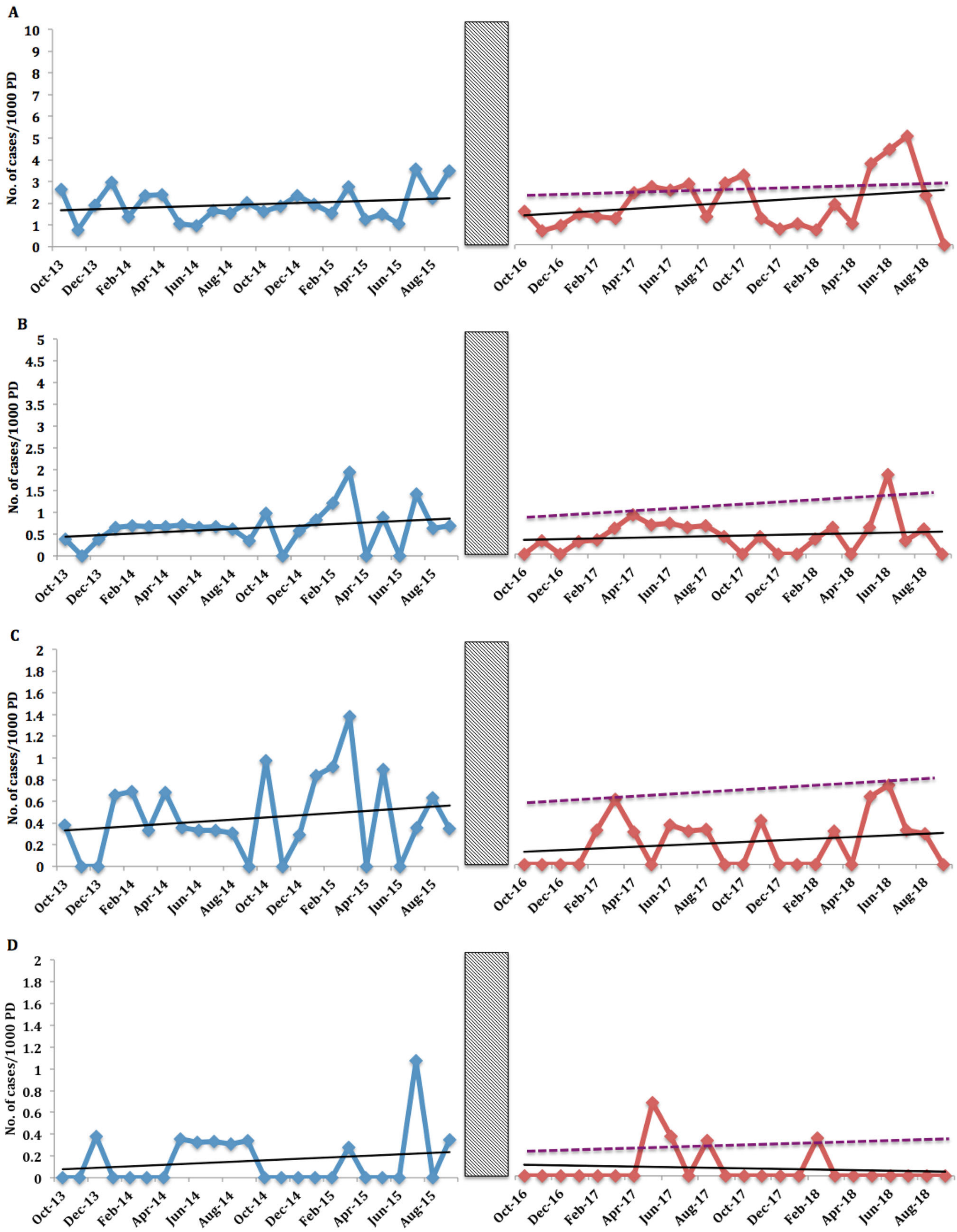

Figure 3. Monthly variation of the incidence rate of nosocomial bacteremia (number of cases/1000 PD) in adult wards before and after the "handshake" stewardship program implementation. (A) Total rate caused by any nosocomial pathogen, (B) Carbapenem-resistant Gram-negative bacteria causing nosocomial bacteremia (C) Carbepenem-resistant A. baumannii nosocomial bacteremia, (D) Carbepenem-resistant P. aeruginosa nosocomial bacteremia.

KEY: PD: Patient day.

N.B.

-Period before the stewardship program initiation: October 2013-September 2015

-Period after and the program initiation: October 2016-September 2018

-Washout period: October 2015-September 2016 (shaded area)

-The dotted trend line represented the hypothetical trend line, which is the extension of the baseline trend line (October 2013- September 2015) where we assumed that there was no ASP from October 2016-September 2018.

Table 2 Hypothetical change in levels of antibiotic use, antibiotic expenditure, patient outcome and incidence of nosocomial bacteremia after the implementation of the "handshake" stewardship program.

Endpoint		L2'	L2	ΔL' (%)	SE	95% CI	P
Antibiotic consumption (number of DDD/1000 PD)	*TZP*	44.24	104.84	137.0	6.0	48.19, 73.01	<0.0001
	3GC & 4GC	13.56	132.74	878.95	5.90	106.89, 131.47	<0.0001
	IPM & MEM	221.96	156.14	−29.66	8.09	−82.56, −49.09	<0.0001
	ETP	1.52	9.63	535.63	1.15	5.74, 10.49	<0.0001
	CAR	223.48	165.77	−25.82	8.44	−75.17,-40.24	<0.0001
	TGC	51.08	11.42	−77.65	1.25	−42.25, −37.08	<0.0001
	CST	77.48	57.82	−25.37	6.65	−33.43, −5.89	0.007
	GLY	66.47	67.63	1.76	3.56	−6.19, 8.52	0.75
	High-end ABX	352.05	235.0	−33.25	14.21	−146.44, −87.65	<0.0001
Total antibiotic cost (USD/PD)		70.99	37.36	−47.37	1.56	−36.86, −30.41	<0.0001
Patient Outcome and Patient-care Quality Indicators	*All-cause in-hospital mortality (N. of deaths/ 1000 PD)*	9.12	7.91	−13.30	0.28	−1.79, −0.64	0.003
	ICU mortality (N. of deaths in ICU/1000 ICU days)	46.55	49.77	6.93	6.29	−9.79, 16.24	0.61
	LOS (days)	3.75	3.58	−4.49	0.05	−0.27, −0.66	0.003
	7-day readmission rate (%)	0.46	0.49	7.60	0.06	−0.08, 0.16	0.56
Nosocomial bacteremia incidence rate (N. of cases /1000 PD)	*Total*	2.81	1.94	−31.05	0.25	−1.39, −0.35	0.002
	CRGNB	1.31	0.43	−67.48	0.08	−1.78, −0.64	<0.0001
	CRAB	0.81	0.20	−74.72	0.05	−0.69, −0.51	<0.0001
	CRPA	0.40	0.07	−82.43	0.04	−0.69, −0.51	<0.0001

KEY= **ABX**: Antibiotics, **CAR**: Carbapenems, **CI**: Confidence interval, **CRAB**: Carbapenem-Resistant *Acinetobacter baumannii*, **CRGNB**: Carbapenem-Resistant Gram-negative Bacteria, **CRPA**: Carbapenem-Resistant *Pseudomonas aeruginosa*, **CST**: Colistimethate sodium, **DDD**: Defined Daily Dose, **ETP**: Ertapenem, **GLY**: Glycopeptides, **ICU**: Intensive Care Unit, **IPM**: Imipenem, **L2**: Actual monthly average value after intervention, **L2'**: Hypothetical monthly average value assuming that there was no intervention, **LOS**: Length of Stay, **MEM**: Meropenem, **N**: Number, **PD:** Patient Days, **SE**: Standard Error, **TGC**: Tigecycline, **TZP**: Piperacillin/Tazobactam, **3GC**: third-generation cepahlosporins, **4GC**: fourth-generation cepahlosporins, **ΔL'**: Hypothetical change in Level.

N.B. - Hypothetical change in level is expressed in percent.

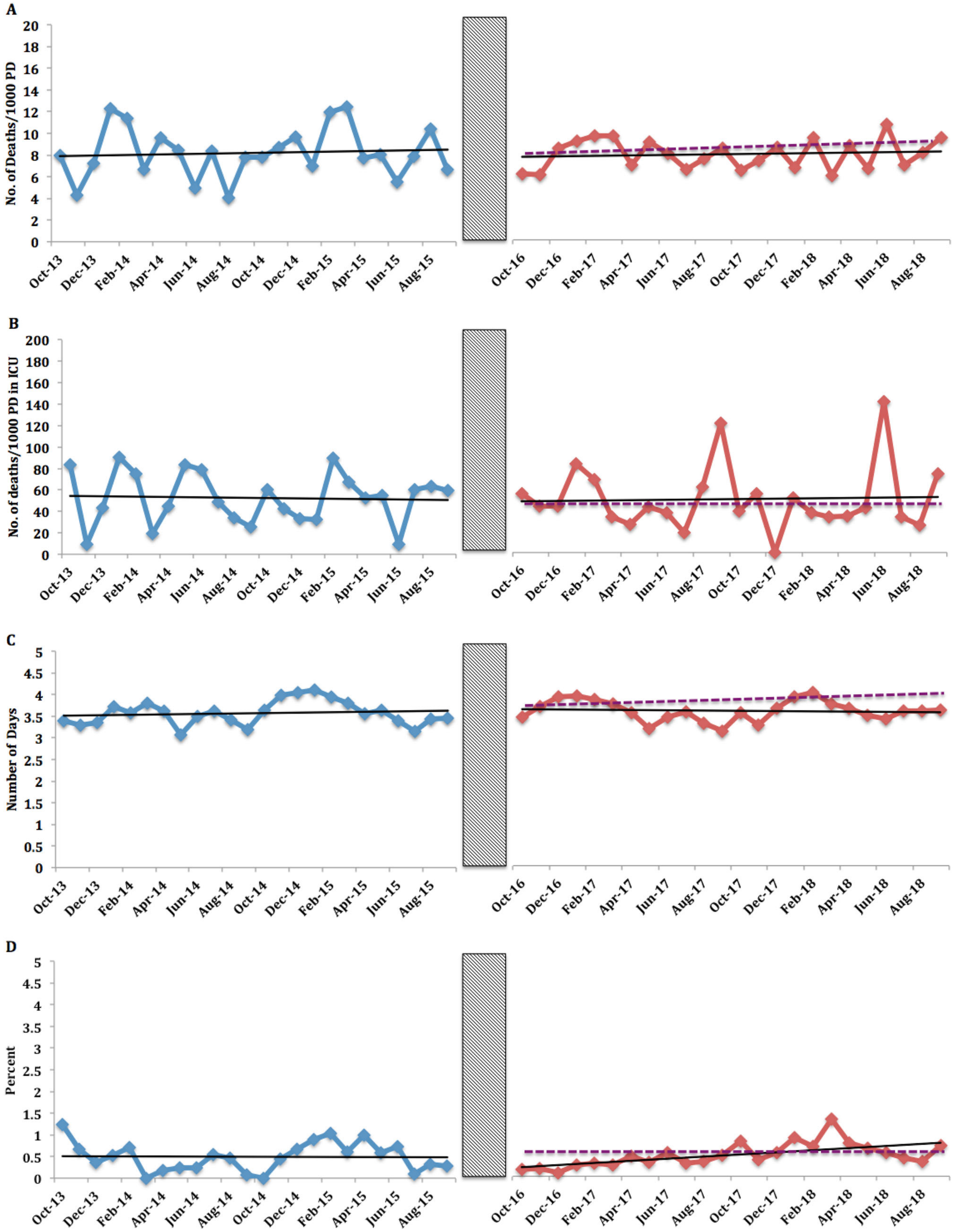

Figure 4. Monthly variation of different parameters describing patient outcome in adult wards before and after the “handshake” stewardship program implementation. (A) All-cause in-hospital mortality expressed as number of deaths/1000 PD, (B) ICU mortality expressed as number of deaths/1000 ICU days, (C) Length of hospital stay expressed in days, (D) 7-day readmission rate expressed as percent.

KEY: ICU: Intensive Care Unit, **PD**: Patient day.

N.B.

-Period before the stewardship program initiation: October 2013-September 2015

-Period after and the program initiation: October 2016-September 2018

-Washout period: October 2015-September 2016 (shaded area)

-The dotted trend line represented the hypothetical trend line, which is the extension of the baseline trend line (October 2013- September 2015) where we assumed that there was no ASP from October 2016-September 2018.

and that after ASP initiation was prospective audit/feedback. Second, the antibiotic restriction policy during the first period was an independent standing alone policy; however in the second period, the handshake intervention was part of a multidisciplinary full-fledged ASP with all core components. As recommended by the CDC, the core components present were leadership commitment, drug expertise, availability of treatment guidelines, educating practitioners about antimicrobial use, tracking, and accountability of the program leaders toward the administration.[24] The prospective audit and feedback or "handshake" approach is best performed by an ID physician who can evaluate a patient with a clinical condition that is usually too complex to be solved by an automatic response. Furthermore, educating prescribers about the guidelines and about the evolving AMR epidemiology, coupled with the "handshake" intervention, would ensure the sustainability of the program results for several years after implementation.[25]

The implementation of the "handshake" ASP led to an important reduction in the level and rate of prescribing "high-end" antibiotics among inpatients in our facility. The use of antipseudomonal carbapenems decreased, whereas the use of ertapenem increased when necessary to spare the use of the former agents. On the other hand, the consumption of both tigecycline and colistin decreased prominently. For example, tigecycline was used in FDA-approved indications only and was not prescribed to septic patients. Owing to the high prevalence of resistance to third-generation cephalosporins in the country, carbapenems are first-line treatment options in community-acquired and nosocomial infections in septic patients.[3,4] In this ASP, a key intervention consisted of modifying the concept of empiric antibiotic therapy. Patients were stratified according to their risk of infection and/or acquisition of 3GCR gram-negative organisms, which have risk factors that are well described in the literature.[16,26,27] Patient stratification based on the risk of contracting antibiotic-resistant organisms is crucial and is increasingly being used in evidence-based medicine to properly choose the empiric therapy options. This is due to the wide and rapid spread of multidrug-resistant bacteria, which resulted in a vicious circle of indiscriminate prescription of broad-spectrum antibiotics and further resistance selection over the past 10 years.[16,28] Carbapenem therapy was preserved for severely ill patients, those at high risk of acquiring 3GCR bacteria, and those who had documented infections or were colonized with these organisms. 3GCs and piperacillin/tazobactam were prescribed to patients with severe infections who were not at risk of 3GCR organism acquisition. Furthermore, piperacillin/tazobactam cautiously replaced carbapenems in patients with mild infections at risk of 3GCR organism acquisition, such as urinary tract infections or respiratory tract infections without bacteremia. This intervention necessitated a close clinical follow-up and could not have been achieved by a nonclinical-based antibiotic restriction policy. The escalation of antibiotic therapy was immediately implemented at any sign of clinical deterioration or lack of response.

Piperacillin/tazobactam has been effective in treating infections caused by 3GCR organisms, according to several observational studies.[29] However, in the MERINO trial, which was published in 2018, piperacillin/tazobactam did not result in noninferior 30-day mortality in patients with bloodstream infections caused by 3GCR Enterobacteriaceae compared with meropenem.[30] Despite this conclusion, uncertainties about the validity and applicability of the study findings arose because of important gaps in the trial design and analysis of its outcomes.[31,32] Further studies are necessary before piperacillin–tazobactam is abandoned as a carbapenem sparing option for the treatment of infections caused by cephalosporin-resistant Enterobacteriaceae.[31,32] On the other hand, ceftolozane/tazobactam and ceftazidime avibactam, which have shown activity against 3GCR bacteria causing urinary tract and intra-abdominal infections, were not readily available in our facility during the study period.[33]

The role of ASP in curbing down AMR is reported by several studies in the literature.[34] However, the methods evaluating this reduction are heterogeneous, and standardized metrics are not well established.[34] In a recently published study from a Korean university hospital examining the effect of ASP on AMR, investigators selected nosocomial bacteria retrieved from blood, urine, and sputum specimens to assess this change.[35] AMR rate was defined as the proportion of resistant bacterial isolates among total isolates.[35] In the current study, we reported the variation in incidence rate of carbapenem-resistant organisms causing nosocomial bacteremia per 1000 PD. Generating an antibiogram is the most common method of reporting AMR and is considered useful for clinicians when assessing resistance patterns and in guiding antibiotic prescription in a specific population.[34,36,37] However, this proportion-based analysis may yield biased estimates where an increase in the frequency of resistant organisms may not necessarily reflect an increase in the burden of resistance.[34,36,37] Instead, calculating a rate such as the number of resistant pathogens per number of PDs might better describe the changes in AMR before and after an intervention.[34,36,37] In our experience, the organisms under study were recently recognized by the WHO to be important for the discovery, research, and development of new antibiotics.[38] Our results showed that the landscape of nosocomial bacteremia after ASP changed with a decreasing incidence of resistant organisms of critical priority including CRAB and CRPA. An important confounding factor in this context is the presence of infection control practices coupled with ASP interventions to prevent the cross-transmission of resistant bacteria.[34] In our case, we did not have a solid infection control program to work in harmony with the ASP. Therefore, AMR reduction could have been attributed to the ASP interventions only, that aimed to decrease the antibiotic selective pressure through rational prescribing.

The implementation of the ASP resulted in a significant decrease in the total targeted antimicrobial costs in our facility by 25%. Interrupted time series analysis additionally showed a distinct change from an increasing rate to a decreasing rate of expenditure. Despite this remarkable change, it is only a partial estimation of cost savings.[12,13] The other operational costs associated with the duration of hospitalization, use of diagnostics, etc., are expected to decrease proportionally. However, these issues were not included in our analysis. Cost reduction without regard to the achievement of the outcomes leads to false savings and could potentially limit effective patient care.[12,13] Hurst et al.,[39] who first termed their antimicrobial stewardship approach as "handshake" stewardship, primarily succeeded in significantly decreasing antimicrobial use and cost among pediatric patients. In parallel, their study showed that clinical outcomes such as length of stay, infection-related mortality, and readmission rates did not change, thus suggesting that there was no harm to pediatric patients secondary to decreased antimicrobial utilization.[39] Similarly, in our study, using high-end antibiotics sparingly did not compromise patient outcome or cause collateral damage and did not increase total-in-hospital mortality or ICU mortality. Furthermore, it did not result in longer hospital stays or a significant increase in the 7-day readmission rate compared to the pre-ASP phase. These measures can be influenced by factors beyond antibiotic use, including comorbidities and disease severity. Similar findings from recent systematic reviews reassure that ASPs do not affect adversely the provided level of care depriving antimicrobials from patients who really need them.[12,13] Our data and those of Hurst et al.[39] emphasize the importance of a dedicated ASP team, including an ID physician and a clinical pharmacist. In-person rounding on a daily basis increases the visibility of the stewards and fosters a collaborative relationship between them and the treating teams. Furthermore, our ASP did not adversely affect the provided level of care compared with depriving antibiotics from patients who really need them. The Joint Commission International recently recognized "handshake" stewardship as a successful rising trend in prospective audit and feedback, thus stressing the value of the active engagement of lead prescribers of antimicrobials.[40,41]

Strengths and limitations

An important limitation is the relatively short duration of the study. A longer assessment period with an adequate and stable implementation of the ASP is needed to reveal the sustainability and improvement of the program outcomes regarding mortality, LOS, and readmission rates. Another limitation that merits mention in this context was the absence of data on infection-related mortality, which is important for understanding the effect of the intervention. Despite the absence of increasing mortality in the hospital in general and among ICU patients, the overall quality of this evidence is limited. It is difficult to establish a clear causal association between ASP interventions and mortality, since it can be confounded by deaths due to non-infectious reasons that are independent of the effect of the ASP. Moreover, the effect of the ASP on AMR rates lags behind the times because the overall microbial ecology in the hospital does not change concomitantly with the change in antibiotic prescription behavior. Another limitation is related to the hypothetical change in level because we speculated that the relationship between the different endpoints and time is linear, as in cases of antibiotic resistance, LOS, and mortality. In the case of antibiotic consumption and expenditure, the relationship might be considered linear in the absence of a program that limits the excessive and unnecessary use of antibiotics. Nevertheless certain external factors such as drug shortages or the emergence of an economic crisis might skew this linear trend. On the other hand, this study describes one of the first experiences of implementing a multidisciplinary "handshake" stewardship program in Lebanon where most hospitals still apply formulary restriction policies alone. This issue highlights the importance of having a full-fledged program led by a team of an ID physician and a drug expert. Another important strength is that we expanded the analysis to include patient outcome and the possibility of causing collateral damage, which is not systematically reported in all antimicrobial stewardship studies.[42]

Conclusion

The rational use of antimicrobials represents an integral part of good clinical practice and is the key to stem the spread of AMR. Our results proved that the implemented "handshake" stewardship program succeeded in significantly controlling the prescription rates of antibiotics and curbing down AMR without compromising patient outcome or causing collateral damage. Furthermore, it had an economic effect in decreasing antibiotic expenditure compared with the previous institutional restriction policy on antimicrobial dispensing. An ASP with all its core elements is needed to achieve the optimal control on antibiotic dispensing. Further research focusing on long-term AMR outcomes is needed to reveal the most effective interventions in turning the tide in AMR and optimizing patient care.

Disclosure statement

The authors declare no conflict of interest.

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