European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:161–170
https://doi.org/10.1007/s10096-018-3408-2

ORIGINAL ARTICLE

Meropenem antimicrobial stewardship program: clinical, economic, and antibiotic resistance impact

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Received: 30 July 2018 / Accepted: 16 October 2018 / Published online: 26 October 2018

Abstract

There are few prospective studies with sufficient duration in time to evaluate clinical and antibiotic resistance impact of antibiotic stewardship programs (ASP). This is a descriptive study between January 2012 and December 2017, pre-post intervention. A meropenem ASP was initiated in January 2015; in patients who started treatment with meropenem, an infectious disease physician performed treatment recommendations to prescribers. Prospective information was collected to evaluate adequacy of meropenem prescription to local guidelines and to compare results between cases with accepted or rejected intervention. Analysis was performed to verify variables associated with intervention acceptance and with any significant change in meropenem consumption, hospital-acquired multidrug-resistant (MDR) bloodstream infections (BSIs), and 30-day all-cause crude death in MDR BSIs. Adequacy of meropenem prescription and de-escalation from meropenem treatment to narrower-spectrum antibiotic improved progressively over time, after ASP implementation ($p < 0.001$). Interventions on prescription were performed in 330 (38.7%) patients without meropenem justified treatment; in 269, intervention was accepted and in 61 not. Intervention acceptance was associated with shorter duration of treatment, cost, and inpatient days ($p < 0.05$); intervention rejection was not associated with severity of patient. During the period 2015–2017, meropenem consumption decreased compared with 2012–2014 (rate ratio [RR] 0.67; 95% CI 0.58–0.77, $p < 0.001$). Also decreased were hospital-acquired MDR BSI rate (RR 0.63; 95% CI 0.38–1.02, $p = 0{,}048$) and 30-day all-cause crude death in MDR BSIs (RR 0.45; 95% CI 0.14–1.24, $p = 0.096$), coinciding in time with ASP start-up. The decrease and better use of meropenem achieved had a sustained clinical, economic, and ecological impact, reducing costs and mortality of hospital-acquired MDR BSIs.

Keywords Antimicrobial stewardship · Multidrug-resistant · Hospital infections · Bloodstream infections · Carbapenems

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Introduction

Antibiotics are effective drugs in reducing morbidity and mortality of patients, but they have ecological effects such as the appearance and spread of bacterial resistance. Bacterial resistance to antibiotics is a global problem of such magnitude that more than 163 countries committed themselves at the UN General Assembly to put in place measures to deal with it [1]. Among the measures proposed is the implementation of antimicrobial stewardship programs (ASP).

ASP are quality improvement programs that include heterogeneous interventions, such as auditing, restriction of specific antibiotics, restriction of treatment duration, and antibiotic cycling or mixing [2]. The implementation of these measures has shown to significantly reduce use of antibiotics and hospital costs [3, 4], but few studies refer to the impact in clinical outcome [5], antibiotic resistance [6–8], or incidence of *Clostridium difficile* infection [9, 10]. The interventions are

generally more effective in prospective studies, but there are few studies of this type that cover the entire hospital and with a duration long enough in time to evaluate its effect. In addition, the implementation of ASP should be recommended not only on the basis of well-known cost benefits, but also because of the most relevant clinical advantages for patients [11].

The implementation of ASP requires the provision of resources not always available, and it is necessary to prioritize those interventions that may have greater impact. The aim of our study is to evaluate the impact of ASP implementation on the prescription of meropenem in a 350-bed hospital over 3 years.

Methods

Study design This is a descriptive study between January 2012 and December 2017, pre-post intervention. We analyzed the evolution of adequacy of meropenem prescription and clinical impact, antibiotic consumption, and the incidence of bloodstream infections acquired in the hospital.

Setting The study was conducted in a 350-bed teaching hospital from 2015 to 2017. The hospital has one ICU with 10 beds and does not have transplant programs. The infection prevention and control program was the same throughout the study. From 2012, an infectious diseases (ID) physician performed prospective active surveillance of all episodes of bloodstream infections (BSIs) [12].

Intervention A multidisciplinary team of professionals was constituted in the University Hospital of Ferrol for ASP implementation, at the end of 2014. Local guidelines for empiric antibiotic treatment were developed and are accessible on our intranet via an icon on every hospital computer desktop. Between January 2015 and December 2017, a prospective follow-up of meropenem use was performed. It was decided to start monitoring meropenem use because it was the broadest-spectrum carbapenem in our hospital, in a resource-limited setting for ASP implementation. Ertapenem is available with indication for the treatment of infections caused by extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBLs) and we do not have other carbapenems.

Patients who started treatment with meropenem were selected every day using a drug dispensation program (all hospital units, except ICU). Prescribers' counseling measures were performed the first day of prescription, and a course on optimization of antibiotics use, targeted at trainee pharmacists and physicians, as well as at primary care physicians, was carried out each year. An annual ASP update was presented at a hospital general clinical session.

An ID physician was released 6 h a week to perform active surveillance. For each case, the electronic medical record was reviewed by an ID physician and antibiotic treatment recommendations to prescribers were given, on a face-to-face or telephone conversation basis, or through an electronic medical record. Additional differential diagnoses, investigations, and adjunctive therapy (for example, removal of urinary or central venous catheters (CVC), drainage of infected collections) were also recommended. Adherence to or rejection of the recommendations was assessed by an ID physician 24 and 48 h post recommendation as part of the ASP workflow. Prospective and protocolized information was collected for each case: site of infection, place of acquisition, clinical situation of patient, comorbidity (Charlson index), adequacy of treatment to hospital guideline, acceptance of intervention, treatment de-escalation, days of treatment, clinical evolution, collateral damage, inpatient days, treatment cost, and readmission. Patients who received more than one course of meropenem during their hospitalization (29 patients) were only included once in the study. The data was obtained by monitoring the information recorded in the electronic medical record. This study was approved by the Institutional Review Boards and Ethic Committee.

Adequacy of treatment Cases with meropenem prescription during the last 4 months of 2014 were retrospectively reviewed. This sample of the pre-intervention period was used to compare with patients who started treatment with meropenem during the intervention period, to know if the local guideline adequacy of meropenem prescription and antibiotic treatment de-escalation improved since ASP implementation. Appropriate treatment with meropenem was considered when it was prescribed in patients with (1) severe sepsis [13], (2) history of ESBL colonization, or (3) hospital-acquired infection in which a broad-spectrum antibiotic treatment was considered necessary. De-escalation antibiotic treatment was defined as the change from meropenem to narrower-spectrum antibiotic over the longer course of the treatment.

Clinical and economic impact To know the clinical impact of the intervention in cases in whom treatment with meropenem was not justified during 2015–2017, a comparison was made between the cases with accepted intervention (modification of antibiotic treatment) and cases with rejected intervention (they continued with meropenem) in their clinical evolution, days of antibiotic treatment, collateral damage, cost of treatment, inpatient days, and hospital readmission. Death was attributable to an infectious process if it occurred within 7 days after starting treatment with meropenem (or days later if the event was directly related to a persistent infection, e.g., abscesses, endocarditis), and all-cause crude death was defined over the month follow-up. Thirty-day infection-related and all-cause

readmission were defined as readmission occurring within 30 days from discharging of current admission.

The impact on antibiotic treatment cost during the 3-year follow-up was estimated based on the difference of the laboratory price between treatment with meropenem and proposed antimicrobial in the intervention, when it was accepted, and assuming the same duration of treatment. The cost savings per inpatient days were made comparing the inpatient days post intervention between cases with accepted intervention and cases with rejected intervention. The inpatient days potentially avoided in cases with accepted intervention were multiplied by the official cost of 1-day hospital stay (528 €).

During the study period, antibiotic consumption was assessed as defined daily doses (DDD) per 100 occupied bed days (OBDs) [14]. The repercussion on the use of antibiotics was made comparing the DDD/100 OBDs between the years 2012 and 2017.

Impact on resistances In order to assess the impact on antibiotic resistance, we analyzed between January 2012 and December 2017 the evolution of incidence density per 1000 OBDs of hospital-acquired BSIs produced by the most frequently isolated microorganisms (coagulase-negative *Staphylococci* excluded): *Pseudomonas aeruginosa*, *Klebsiella* spp., *E. coli*, *Enterobacter* spp., *Staphylococcus aureus*, and *Candida* spp., between 2012 and 2017.

Hospital-acquired BSIs were defined as those diagnosed from blood cultures obtained ≥ 48 h after hospital admission or in those cases when, even occurring in the first 48 h, the patient had been hospitalized during the previous 2 weeks. Patients with a recurrent isolation of the same microorganisms were considered as a unique episode of BSI unless the sample was obtained 1 month after the last positive blood culture.

The identification of blood isolates and the determination of resistance to antibiotics were performed according to Clinical Laboratory Standard International (CLSI). MDR categorization was applied for extended-spectrum β-lactamases or carbapenemase-producing Enterobacteriaceae, all isolates of methicillin-resistant *S. aureus* and *Candida* spp., and all *Pseudomonas aeruginosa* and *A. baumannii* strains fulfilling the German Society for Hygiene and Microbiology criteria for MDR organisms [15].

Colonization was defined as the isolation of the organism from a nonsterile site in the absence of symptoms of infection, and infection when the patient's doctor prescribed treatment.

Statistical analysis A descriptive and comparative study of the variables was performed. Quantitative variables are reported as means ± standard deviations, and categorical as frequencies (%). Variables were compared between groups using the chi-square test or Fisher's exact test for categorical variables and Student's *t*-test or Mann-Whitney *U* test for continuous variables, as appropriate. Logistic regression was performed to evaluate the predictors of intervention acceptance. Associations between the variables were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Resistance rates per 1000 OBDs of in-hospital acquired BSIs with a 95% CI and rates of mortality were calculated as Poisson event rates, and compared by testing for homogeneity of rates. Statistical analysis was performed using SPSS software version 19. All tests were two-tailed, and a p value < 0.05 was regarded as statistically significant.

Results

Adequacy of treatment During the last 4 months of 2014, 150 patients received treatment with meropenem, and between 2015 and 2017, 852 patients received it. The indication of justified treatment with meropenem progressively improved over time from 47.3% in 2014 to 76.8% in 2017 ($p < 0.001$), without significant changes in the characteristics of the patients (Fig. 1). De-escalation from meropenem treatment to narrower-spectrum antibiotic improved progressively after ASP implementation, from 28% in 2014 to 58.8% in 2017 ($p < 0.05$).

Clinical and economic impact Between 2015 and 2017, 852 patients received treatment with meropenem, of which 565 were male and 287 female, age 68.4 ± 15.9 years (range 1–96 years). The sites of infection were urinary 334, abdominal 219, pulmonary 187, skin and soft tissue 42, febrile neutropenia 20, intravascular catheter 26, and other 24. Place of infection acquisition was as follows: hospital onset 363, healthcare-associated 328, and community-associated 161.

Out of the 852 patients who received treatment with meropenem, in 522 of them the treatment was considered justified because it was adapted to the local empirical treatment guidelines; in 330 (38.7%), the treatment was not considered justified and interventions were performed at the suggestion of appropriate alternative treatment; and in 269 (81.5%) of them, the intervention was accepted and in 61 it was not.

The clinical characteristics of patients were similar between patients with and without acceptance of ASP recommendations, although the degree of intervention acceptance varied according to prescriber (between 29 and 100%) and infection localization (Table 1). The localizations of infection in urine or abdomen accounted for 61% of accepted interventions. By multivariate analysis, pulmonary infection (OR 0.21; 95% CI 0.09–0.45) and abdominal infection (OR 0.25; 95% CI 0.12–0.50) were associated with lower acceptance of the intervention; patient comorbidity (OR 0.98; 95% CI 0.88–1.08) or the presence of severe sepsis (OR 0.45; 95% CI 0.16–1.28) were not associated with the degree of acceptance of the intervention.

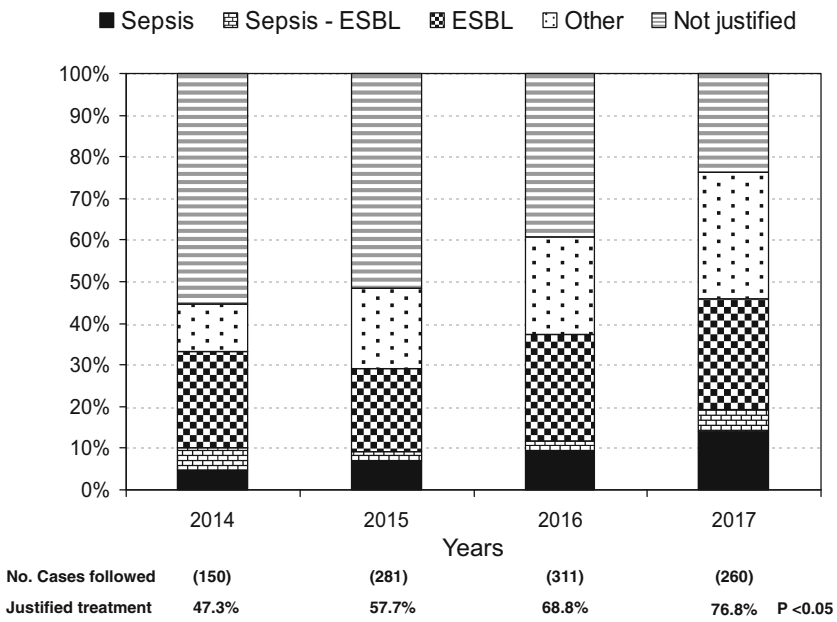

Fig. 1 Evolution of the adequacy of treatment with meropenem years 2014 (last 4 months) and 2015–2017

There were no significant differences between cases with accepted intervention and cases with rejected intervention in clinical evolution or collateral damage (Table 2). The development of colonization or infection with yeast was lower in cases with accepted intervention. The Charlson index was similar throughout the intervention period and was higher in patients who died: 7.2 ± 2.2 vs 5 ± 2.8, $p < 0.001$.

The acceptance of the intervention was associated with shorter duration of antibiotic treatment and inpatient days (Table 3). The duration of antibiotic treatment in the total series did not decrease significantly; in urine infection decerased from, and the decrease was significant in treatment of wound infection in abdominal surgery: 22.8 ± 16.3 days in 2015 to 13.6 ± 8.3 in 2017, $p < 0.05$.

The 269 patients in whom the intervention was accepted presented 5.9 inpatient days post intervention less than cases with rejected intervention, and it was calculated that 1587 days of hospital stay were saved. The estimated cost savings was 866,915.93 € (28,979.93 € in antimicrobials and 837,936 € in 1587 days of hospital stay potentially avoided).

Coinciding in time with the start-up of ASP, there was a 33% decrease in the consumption of meropenem during the intervention period with respect to the years 2012–2014 (RR

Table 1 Baseline demographic and clinical characteristics of patients with and without acceptance of ASP recommendations. Years 2015–2017

Variables	Intervention accepted $n = 269$	Intervention rejected $n = 61$	p
Male gender, *n* (%)	174 (64.7)	40 (65.6)	1
Median age ± SD, years (range)	66.6 ± 15.7 (10–96)	66.2 ± 19 (6–95)	0.87
Charlson s comorbidity score, median ± SD (range)	4.98 ± 3 (0–13.6)	5.06 ± 2.89 (0–12)	0.84
Neutropenia, < 500/mL	5 (1.9)	2 (3.3)	0.62
Severe sepsis	17 (6.3)	6 (9.8)	0.4
Site of infections, *n* (%)			
Pulmonary	44 (16.4)	19 (31.1)	0.01
Abdominal	74 (27.5)	28 (45.9)	0.009
Skin/soft tissue	15 (5.6)	1 (1.6)	0.32
Urinary	90 (33.4)	10 (16.4)	0.009
Other	46 (17.1)	3 (4.9)	0.016
Acquisition place of infection			
Hospital onset	85 (31.6)	24 (39.3)	0.29
Healthcare-associated	93 (34.6)	24 (39.3)	0.55
Community-associated	91 (33.8)	13 (21.3)	0.07

Table 2 Clinical results of patients with and without acceptance of ASP recommendations. Years 2015–2017

Variables	Intervention accepted, $n = 269$	Intervention rejected, $n = 61$	p
Healing	239 (88.8%)	51 (83.6%)	0.28
Death caused by infection	12 (4.5%)	6 (9.8%)	0.11
All-cause crude death	30 (11.2%)	10 (16.40%)	0.28
Readmission in a month	10[#] (3.7%)	3[*] (4.9%)	0.71
Adverse effects	28 (10.4%)	5 (8.2%)	0.81
Phlebitis	44 (16.4%)	8 (13.1%)	0.70
Development of resistance to treatment	6 (2.2%)	0 (0%)	0.60
Diarrhea caused by *C. difficile*	6 (2.2%)	1 (1.6%)	1
Colonization-Infection with *Candida* spp.	30 (11.2%)	9 (14.8%)	0.51

[#] Four relapses of the infection, six due to other causes

*No relapse of infection, due to other causes

0.67; 95% CI 0.58–0.77, $p < 0.001$), with increase in cefepime consumption (1.2 DDD/100 OBDs in 2012–2014 vs 2.1 in 2015–2017) and stabilization of ciprofloxacin and piperacillin-tazobactam consumption (Fig. 2); ceftazidime consumption decreased by 4.7%, and ertapenem decreased by 3.1%.

Impact on resistances The global incidence of bacteremia adjusted by 1000 OBDs increased by 3.5% during the period 2015–2017 vs 2012–2014. The incidence density of candidemia and MDR BSIs acquired in-hospital decreased after ASP start-up in a parallel fashion with the decrease in use of meropenem (Figs. 2 and 3). In 2015–2017, the hospital-acquired MDR BSI rate was 0.084/1000 OBDs vs 0.133 in 2012–2014 (RR 0.63; 95% CI 0.38–1.02, $p = 0.048$). Conversely, the incidence density of in-hospital-acquired BSIs produced by non-MDR strains of the same microorganisms under study increased by 8% during the intervention period (RR 1.08; 95% CI 0.78–1.51) (Table 4).

To assess if there were other changes in hospital activity that could have contributed to the decrease in the incidence density of hospital-acquired MDR BSIs, we monitored some complexity indicators [16] (Table 4). In the period 2015–2017 compared to 2012–2014, the number of blood cultures performed per 1000 OBDs (RR 1.14; 95% CI 1.1–1.17, $p < 0.001$), the prevalence of CVC use (4.56% vs 2.29%, $p = 0.004$), the catheter-associated BSI rate (RR 1.08; 95% CI 0.85–1.38), and the consumption of parenteral nutrition (RR 1.13; 95% CI 1.08–1.18, $p < 0.001$) increased, whereas antifungal consumption decreased by 5% (RR 0.95; 95% CI 0.90–0.99, $p = 0.04$).

The alcohol-based hand-rub consumption increased progressively from 2012 to 2017, by about 9.9% per year, without there being a significant change in this annual increase between the pre- and post-intervention period. The overall antibiotic use in the hospital during the study years increased from 94.7 DDD/100 OBDs in 2012–2014 to 105.8 DDD/100 OBDs in 2015–2017.

Patients with in-hospital-acquired MDR BSIs had higher mortality than patients with non-MDR BSIs: death associated with infection by 16.3% vs 6.9% ($p = 0.008$) and all-cause crude death by 26.3% vs 18.3% ($p = 0.09$). The incidence density of infection-associated mortality for in-hospital-acquired MDR BSIs decreased during the intervention period by 45% (0.012/1000 OBDs vs 0.022 in 2012–2014) (RR 0.52; 95% CI 0.11–1.95), and the incidence density of all-cause crude death decreased by 56.4% (0.017/1000 OBDs vs 0.039 in 2012–2014) (RR 0.45; 95% CI 0.14–1.24, $p = 0.09$) (Fig. 2).

The death rate for hospital-acquired bacteremias produced by non-MDR microorganisms increased over time: infection associated mortality at 0.047/1000 patient-days in 2012–2014

Table 3 Economic results, patients with and without acceptance of ASP recommendations. Years 2015–2017

Variables	Intervention accepted, $n = 269$	Intervention rejected, $n = 61$	p
Days of antibiotic treatment	11 ± 10.1	13.8 ± 9	0.05
Cost of antibiotic treatment	108.3 ± 371.2	202.4 ± 504.8	0.09
Total inpatient days, $X \pm$ SD	17.6 ± 16.8	26.2 ± 23.6	0.001
Inpatient days post intervention, $X \pm$ SD	12.6 ± 14.4	18.55 ± 20.5	0.009

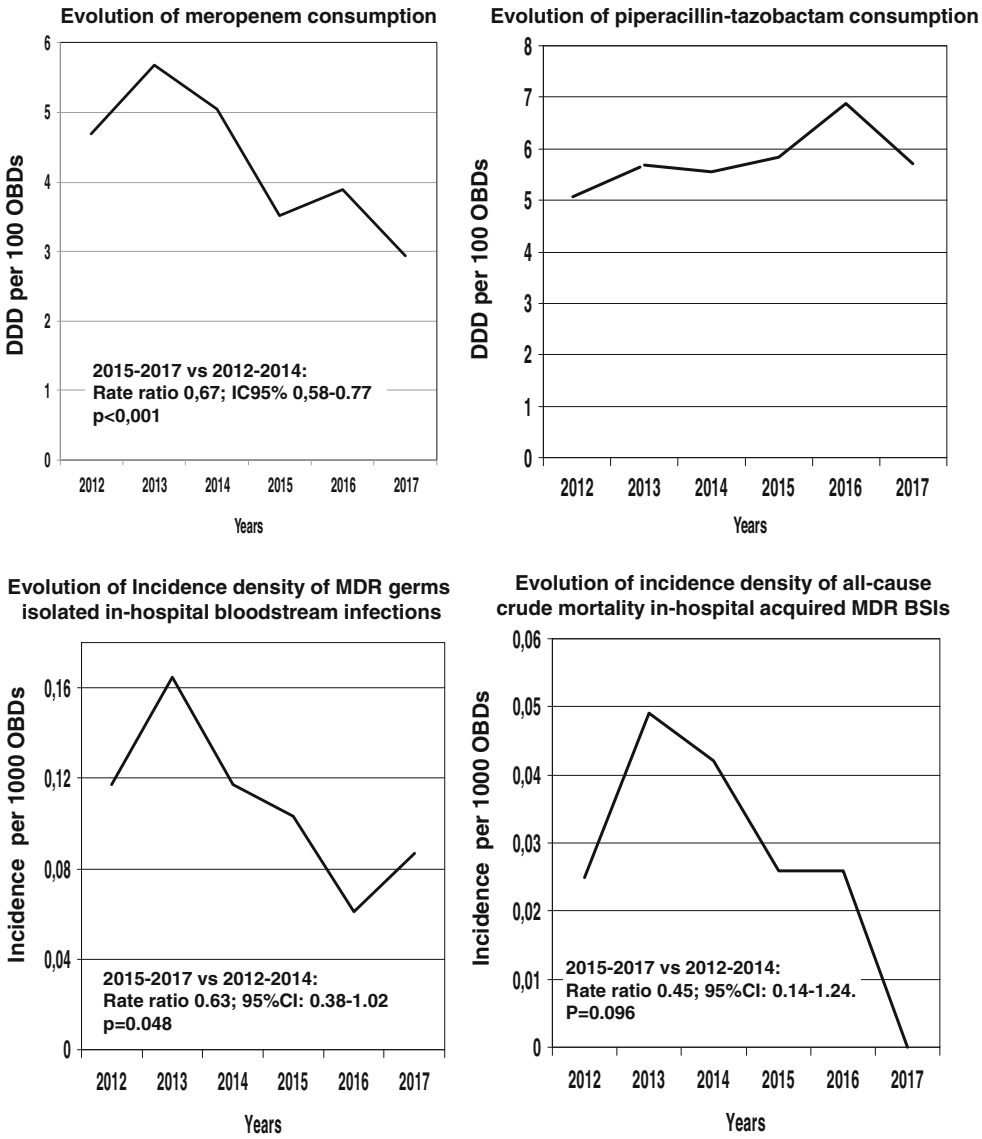

Fig. 2 Evolution of antibiotic consumption, incidence of MDR bloodstream infections and mortality

OBDs: occupied bed days

to 0.058 in 2015–2017 (RR 1.23; 95% CI 0.64–2.34, $p = 0.64$) and all-cause crude mortality at 0.12/1000 patient-days in 2012–2014 to 0.16 in 2015–2017 (RR 1.28; 95% CI 0.86–1.91, $p = 0.26$).

Throughout the study period, we did not have bacteremia due to carbapenemase-producing microorganisms nor vancomycin-resistant *Enterococcus* spp., and the incidence of *Clostridium difficile*-associated diarrhea remained stable at about 0.2/1000 patient-days.

Discussion

The care of patients with suspected infections is complex, and metrics to assess ASP impact are poorly defined [17, 18]. The implementation of our ASP improved the prescription of meropenem and decreased its use, as well as progressively increased the frequency of de-escalation to narrower-spectrum antibiotic. The acceptance of the intervention made by the ID physician decreased the days of treatment, cost, and inpatient days, without a negative impact on patient safety.

Some studies reported shorter length of admission in the intervention group than the control group and lower mortality [19]. Ng et al. [20] reported a significant difference in length of stay between the periods before and after ASP implementation with no difference in mortality, like other studies [21–25]. Tedeschi et al. achieved a decrease in meropenem use with no increases in mortality or length of stay, and with a decrease in antimicrobial resistance patterns in a rehabilitation hospital [26].

Only one study assessed incidence of collateral damage following carbapenem de-escalation in an ESBL endemic

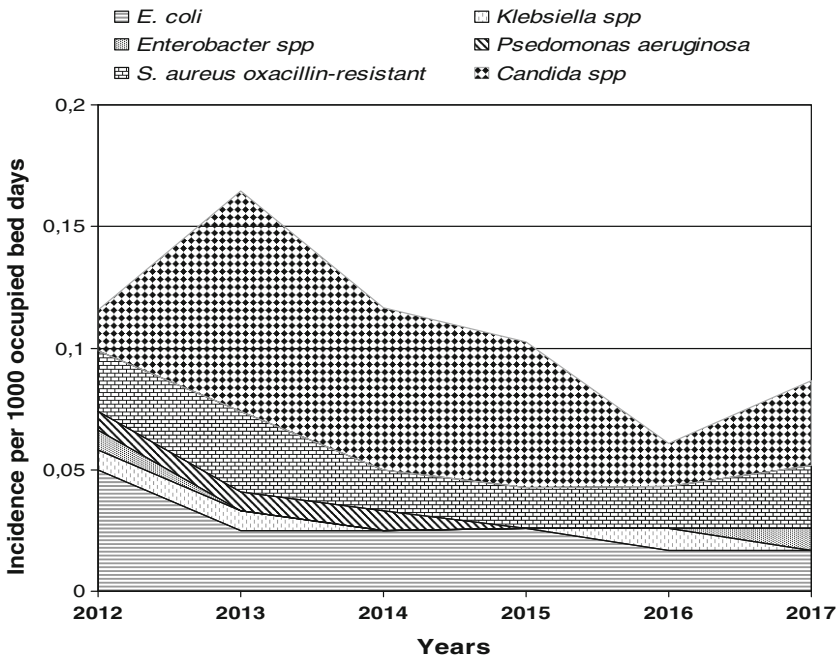

Fig. 3 Evolution of the incidence density of MDR microorganisms isolated most frequently in-hospital bloodstream infections

setting, and reported fewer adverse reactions in the de-escalated group, shorter duration of carbapenem use, and less development of resistances [27]. There are no prospective studies outside the ICUs that analyze the development of infection caused by yeast during antibiotic treatment, and only one prospective study refers to readmissions after discharging, without differences between patients with or without acceptance of ASP recommendation [28]. A study with educational and semi-restrictive measures, carried out in a carbapenem-resistant *Klebsiella pneumoniae* endemic 1200-bed adult care hospital, showed a decrease in antibiotic consumption and incidence of *Klebsiella pneumoniae* bacteremia, without changes in candidemia or consumption of antifungal [29].

In our hospital, the incidence of *Clostridium difficile*-associated diarrhea is low and remained stable and our results show a decrease in the incidence of hospital-acquired candidemia and MDR BSIs; this decrease was parallel to the decrease in meropenem consumption and to a decrease in the duration of antibiotic treatment for wound infection in abdominal surgery [30]. Candidemia is the fourth cause (4.9%) of hospital-associated BSIs in our hospital and is more frequent in the general surgery department (38.5%). The decrease in the duration of antibiotic treatment, the increase in de-escalation from meropenem to narrower-spectrum antibiotics, and the lesser development of colonization caused by yeast in patients in whom the intervention was accepted, all of them have undoubtedly contributed to decrease in candidemia. The decrease in the incidence of yeast infection has occurred despite the increase in the number of surgical interventions, the use of CVC, and parenteral nutrition. This is reflected in the decrease in antifungal drug use during the intervention period [31, 32].

Table 4 Potential changes in healthcare during the study period by year

Healthcare variable	2012	2013	2014	2015	2016	2017
No. of patients admitted	14,721	14,615	14,979	14,867	14,852	15,248
No. of inpatient days	119,885	121,181	119,615	116,588	114,072	114,864
Blood cultures performed (no.)	3242	3340	2985	3003	3419	3074
No. of blood cultures/1000 OBDs	27.04	27.56	24.95	25.76	29.97	26.76
Hospital-acquired no-MDR BSIs/1000 OBDs	0.69	0.76	0.71	0.69	0.76	0.88
Intravascular catheter-associated BSIs/1000 OBDs	0.27	0.39	0.48	0.35	0.42	0.46
Surgical procedures (no.)	8848	9285	8836	9148	9352	9151
Case mix index	1.51	1.54	1.56	1.57	1.58	1.59
Parenteral nutrition units (no./100 OBDs	2.91	3.87	3.95	4.61	4.13	3.40
Consumption of antifungals (DDD/100 OBDs)	2.91	3.84	3.08	3.49	3.31	2.55

MDR multidrug-resistant, *BSIs* bloodstream infections, *OBDs* occupied bed days

We have observed a decrease in MDR BSI-associated mortality incidence after starting up the ASP, as in another study with multifaceted educational intervention [8]. The ASPs are underfunded, and it is necessary to prioritize for undertaking those interventions that may have a greater impact [33, 34]. In a resource-limited setting, we decided to follow the use of carbapenems because they are the antibiotics with the broadest antibacterial spectrum and with a rapid induction of beta-lactamases, and with our intervention we have decreased the incidence of hospital-acquired MDR BSIs and associated mortality despite having increased the total incidence of bacteremia and global consumption of antibiotics.

The results obtained in our study are undoubtedly due to the good acceptance of the interventions by the prescribers, higher than the median change in antibiotic prescribing (42.3%) for the persuasive interventions described in the literature [35, 36]. This should certainly be due to the fact that interventions were performed in a medium-sized hospital and with good interpersonal communication among professionals who also work in infection prevention and control [37, 38]. The intervention rejection level was not associated with the severity or comorbidity of the patient, and it seemed to be more in relation with clinicians' attitudes in different hospitalization units [39]. It is also possible that sensitization measures on resistance to antibiotics conveyed through the media and training courses could have played some role over the general population and physicians [40], but it does not seem that other variables influenced the results of the study.

Our achieved cost savings are much higher than ASP cost (an ID physician was released 6 h a week) warranting the financing of ASPs with more resources to expand the program in the hospital to other antibiotics [26, 35, 36], towards primary care [7, 41] and long-term care settings [42].

The strength of our study is the large number of variables analyzed and prospective data collection over 3 years to evaluate the impact of ASP, and our results prove that ASP is cost-effective. We assessed compliance with local guidelines as the standard for appropriate therapy to reduce the more subjective method of expert opinion-based definitions [18].

Our study has several limitations. The study was restricted to those wards with electronic medication dispensing system (all the hospitals except ICU unit), but patients transferred from the ICU to other hospitalization units and who were receiving treatment with meropenem were also followed. The MDR BSIs acquired in ICU between 2012 and 2017 accounted for 7.8% of hospital bacteremia, without significant differences between the pre- and post-intervention periods, and we believe that the activity of this service has not influenced our results.

The sample size does not allow a regression or time series analysis to provide good stability to the results obtained, but they reflect the changes in consumption of meropenem and in the incidence of in-hospital MDR BSIs and mortality, after starting the ASP; these changes in trend seem to be due to our intervention and not to changes in healthcare during the study period. The single-center design limits the possibility of generalizing our results to other hospitals, and including preferred methods such as control groups or randomization was impractical.

In conclusion, the results of this study show that the decrease and better use of meropenem achieved by our ASP program had a sustained clinical, economic, and ecological impact, reducing costs and mortality of hospital-acquired MDR BSIs.

Acknowledgments The authors acknowledge the Clinical Epidemiology and Biostatistics Unit of the Complejo Hospitalario Universitario A Coruña and the Spanish Platform for Clinical Research and Clinical Trials, SCReN (Spanish Clinical Research Network), for their assistance in methodological design and statistical analysis.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

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