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Title: Long-term efficacy of comprehensive multidisciplinary antibiotic stewardship programs centered on weekly prospective audit and feedback

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Abstract

Objective: To evaluate the long-term effects of comprehensive antibiotic stewardship programs (ASPs) on antibiotic use, antimicrobial-resistant bacteria, and clinical outcomes.

Design: Before-after study.

Setting: National university hospital with 934 beds.

Intervention: Implementation in March 2010 of a comprehensive ASPs including, among other strategies, weekly prospective audit and feedback (PAF) with multidisciplinary collaboration.

Methods: The primary outcome was the use of antipseudomonal antibiotics as measured by the monthly mean days of therapy per 1,000 patient days each year. Secondary outcomes included overall antibiotic use and that of each antibiotic class, susceptibility of *Pseudomonas aeruginosa*, the proportion of patients isolated methicillin-resistant *Staphylococcus aureus* (MRSA) among all patients isolated *S. aureus*, the incidence of MRSA, and the 30-day mortality attributable to bacteremia.

Results: The mean monthly use of antipseudomonal antibiotics significantly decreased in 2011 and after as compared with 2009. Susceptibility to levofloxacin was significantly increased from 2009 to 2016 (P = 0.01 for trend). Its susceptibility to other antibiotics remained over 84% and did not change significantly during the study period. The proportion of patients isolated MRSA and the incidence of MRSA decreased significantly from 2009 to 2016 ($P < 0.001$ and = 0.02 for trend, respectively). There were no significant changes in the 30-day mortality attributable to bacteremia during the study period (P = 0.57 for trend).

Conclusion: The comprehensive ASPs had long-term efficacy for reducing the use of the targeted broad-spectrum antibiotics, maintaining the antibiotic susceptibility of *P. aeruginosa,* and decreasing the prevalence of MRSA, without adversely affecting clinical outcome.

Keywords: Antibiotic stewardship, Prospective audit and feedback, Multidisciplinary collaboration, long-term efficacy

Introduction

The increase in the prevalence of infections caused by antimicrobial-resistant bacteria has become a worldwide public health threat [1-3], resulting in increased mortality and healthcare costs [4-5]. Since inappropriate use of antibiotics leads to selection of resistant bacteria [6-7], health systems around the world are taking steps to promote optimal antibiotic use [8]. In response to the crisis caused by antibiotic resistance and to improve patient care and clinical outcomes, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America have published guidelines for antibiotic stewardship programs (ASPs) [9-10]. Several systematic reviews have shown that ASPs foster appropriate antibiotic use and decrease antibiotic resistance without having a negative impact on clinical outcomes [11-14]. In the guidelines for implementing ASPs, a core strategy is prospective audit and feedback (PAF) [9-10]. Many studies have verified the efficacy of this approach for correcting antibiotic-prescribing patterns, reducing administration of broad-spectrum antibiotics, decreasing *Clostridium*（*Clostridioides*）*difficile* infection (CDI), and suppressing the emergence of resistant bacteria [15-24]. However, PAF is very labor-intensive, so its effectiveness depends on adequate institutional resources [10]. Moreover, few reports have demonstrated its long-term effects [15, 20-23]. While many studies of ASPs have been reported in the Asia Pacific region, high-quality studies using standardized surveillance methodology are needed in this area [25]. Moreover, several studies on the implementation of ASPs have been also reported in Japan [24, 26-27]; however, it was difficult for many hospitals to

implement substantial ASPs, because the number of infectious disease physicians has been insufficient [28]. Establishing effective and sustainable ASPs with positive long-term effects is an urgent need, especially in settings where the numbers of physicians and pharmacists specializing in infectious diseases are limited.

At Kobe University Hospital, an ASPs using PAF was implemented beginning in 2010. The PAF strategy, which we referred to as the "Big Gun Project," involved infectious disease pharmacists performing weekly audits of all cases in which broad-spectrum antibiotics were used in the preceding week. A multidisciplinary team then met each week to discuss the management of problem cases, determining cases in which intervention was indicated. In addition to the Big Gun Project, the hospital's comprehensive ASPs also used various other strategies to encourage appropriate antibiotic prescribing and complement the effect of the PAF.

The objective of this study was to evaluate the long-term effects of our comprehensive ASPs on antibiotic use, the prevalence of resistant bacteria, and clinical outcomes.

Methods

Study Design and Setting

The 934-bed Kobe University Hospital is one of the national university hospitals in Japan. A before-after study was conducted to analyze data generated from January 2009 to December 2016, allowing the comparison of outcomes from before and after the implementation of the ASPs in 2010. The study protocol was approved by the Ethics Committee of Kobe University Hospital.

Intervention: Antibiotic Stewardship Programs consisting of Prospective Audit and Feedback and other strategies

Prospective Audit and Feedback

The Big Gun Project was established in March 2010. The project team was directly under control of the hospital director, and it consisted of two to four infectious disease physicians, two pharmacists, and one to two microbiology technologists, although the number of each medical professional in the team varied from year to year. Either one of the two infectious disease pharmacists conducted each weekly PAF in turns, and the pharmacist audited all patients being treated with the targeted antibiotics and recorded the problem cases once a week. Typical examples of problems included inappropriate selection, dosing, or duration of antibiotics; lack of appropriate de-escalation; and failure to collect necessary specimens for bacterial culture. On the day after the pharmacist identified the problem cases, the project team met to discuss each case. If the team agreed that intervention was required, it was generally provided by an infectious disease physician. At the following week's meeting, the pharmacist reported on the clinical

course of the cases following intervention in the previous week. The agents targeted by the Big Gun Project included parenteral antipseudomonal antibiotics, those used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) agents, antifungals, and oral vancomycin (Table 1).

Other Strategies

Other strategies of our ASPs and their implemented year are shown in Table 2. When physicians used linezolid or daptomycin, preauthorization by infectious disease physicians was mandatory. For patients with bacteremia, infectious disease physicians advised the attending physician on the initial selection of antibiotics, de-escalation after antibiotic sensitivity was determined, and the duration of treatment. The infectious disease specialists also followed the patients' clinical course as indicated. The antibiotics listed in the hospital formulary were evaluated by the Departments of Pharmacy, Infection Control and Prevention, and Infectious Diseases and renewed regularly (at least once a year). When vancomycin, teicoplanin, aminoglycosides, or voriconazole were prescribed, therapeutic drug monitoring was performed, and the pharmacists made dose adjustments based on the measured drug concentrations. The pharmacists also optimized other antibiotic dosing for each patient based on the international standard doses. The hospital antibiogram was available to all physicians and medical staff on the hospital website. Seminars for all physicians and medical staff on appropriate antibiotic use were conducted by infectious disease physicians ten times each year.

Outcomes

The primary outcome was the total use of parenteral antipseudomonal antibiotics during the study period. Secondary outcomes included the use of all parenteral antibiotics and of each class of antibiotic, the antibiotic susceptibility of *Pseudomonas aeruginosa*, the proportion of patients isolated MRSA among all patients isolated *S. aureus*, the incidence of MRSA, the incidence of CDI, the 30-day mortality among patients with bacteremia caused by all microorganisms except contamination, MRSA, and *P.aeruginosa*, and the hospital mortality.

Based on the previous study and the guidelines for implementing ASPs [10, 29], the use of the parenteral antibiotics was evaluated by recording the days of therapy (DOTs) per 1,000 patient days, which were calculated monthly from electronic medical records. DOTs were recorded as monthly averages for each year and compared between 2009 and each year from 2010 to 2016. The data on susceptibility of *P. aeruginosa* was obtained from microbiology laboratory records. The first isolate of each organism from each patient was included in the analysis, but organisms isolated multiple times were also included if the susceptibility profile changed. The proportion of patients isolated MRSA among all patients isolated *S. aureus* and the incidence of MRSA were counted as the number of inpatients isolated them from any culture. The incidence of CDI was determined as the number of inpatients with microbiologically confirmed *C. difficile* toxin production. Patients with multiple confirmations were

counted only once. The 30-day mortality among patients with bacteremia included all patients with blood cultures positive for bacterial, fungal, and Mycobacterial species except contaminant, and was calculated from the day of onset of bacteremia. Additionally, the 30-day mortality among patients with bacteremia isolated MRSA and *P. aeruginosa* was also calculated. Bacterial species defined as contaminant included coagulase-negative staphylococci, *Bacillus* spp., *Corynebacterium* spp., *Propionibacterium* spp., Viridans-group streptococci, and *Micrococcus* spp. [30-31], but cases wherein these bacterial species were isolated from two or more sets of blood cultures on the same day were defined as the true bacteremia and included the study. Cases with the same microorganism isolated multiple times within 14 days were defined as the same episode.

Statistical Analysis

The difference in mean values of the use of parenteral antibiotics was analyzed by one-way analysis of variance, followed by Dunnett's post hoc test. The Cochrane-Armitage test for trend was used for comparison of the proportions of categorical variables between groups (susceptibility of *P. aeruginosa*, proportion of MRSA, the incidence of MRSA, the incidence of CDI, 30-day mortality of bacteremia, and the hospital mortality). P values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed with JMP statistical software version 9.0.0 (SAS Institute Inc., Cary,

NC, USA).

Results

Antibiotic Use

The monthly mean (standard deviation) use of antipseudomonal antibiotics in 2009 was 85.5 (6.1) DOTs per 1,000 patient days. After implementation of the ASPs, those values decreased gradually through 2016, with those from 2011 and the subsequent years significantly lower than the 2009 value (Fig. 1).

The amount of each antibiotic by class is shown in Table 3. The total use of carbapenems decreased significantly in the years after 2010 compared with 2009. Unlike the antipseudomonal antibiotics, the total use of anti-MRSA agents did not significantly change during the study period. The use of penicillins, except for antipseudomonal agents, significantly increased in 2013 and after compared with 2009. The overall antibiotic use, however, was significantly lower in 2015 and 2016 compared with 2009.

Antibiotic Resistance

The susceptibility of *P. aeruginosa* isolates to each antibiotic during the study period is shown in Fig. 2. The susceptibility to meropenem was 91.0% in 2009, was maintained over 90% in each subsequent year from 2010 to 2016, and no significant differences were observed during the study period ($P = 0.57$ for trend). Similarly, the susceptibility to piperacillin, cefepime, and amikacin remained over 84%, and there were no significant difference during the study period ($P = 0.17$, 0.14, and 0.05 for trend, respectively). Susceptibility to levofloxacin was significantly increased from 2009 to 2016 ($P = 0.01$ for trend).

The proportion of patients isolated MRSA among all patients isolated *S. aureus* decreased significantly from 2009 to 2016 ($P < 0.001$ for trend) (Fig. 3). The incidence of MRSA was also decreased significantly from 2009 to 2016 ($P = 0.02$ for trend) (Fig. 4).

Clostridioides difficile infection

Although the incidence of CDI was higher in 2011 than in other years, there was no significant change during the study period ($P = 0.80$ for trend) (Fig. 5).

Clinical Outcomes

The 30-day mortality among all patients with bacteremia did not change significantly during the study

period (P = 0.57 for trend) (Fig. 6-a). The 30-day mortality among patients with MRSA bacteremia significantly decreased from 2009 to 2016 (P = 0.01 for trend) (Fig. 6-b). The 30-day mortality among patients with *P. aeruginosa* bacteremia decreased from 2009 to 2011, but increased from 2014 to 2016, and there was no significant change throughout the study period (P = 0.89 for trend) (Fig. 6-c).

The hospital mortality was significantly decreased from 2009 to 2016 ($P < 0.001$ for trend) (Fig. 7).

Discussion

Our study showed the long-term efficacy of comprehensive ASPs on reducing the use of the targeted antibiotics and suppressing the emergence of resistant bacteria without adversely affecting the clinical outcome. These findings are in line with previously published systematic reviews reporting that implementation of ASPs improved antibiotic use and decreased antibiotic resistance without causing worse clinical outcomes [11-14]. Many studies have specifically demonstrated the efficacy of PAF as a core strategy of ASPs [15-24]. Most of these, however, have only reported short-term results, and, as noted above, high-quality studies were needed particularly in the Asia Pacific region [25]. In Japan, many hospitals do not have enough infectious disease specialists to implement an ASPs [28]. Our study is important in that our ASPs were conducted with multidisciplinary collaboration to reduce the burden on the infectious disease specialists, and we verified its long-term efficacy in a Japanese hospital.

Using DOTs as the measure, the prescribing of antipseudomonal agents was reduced by 37.0% and that of carbapenems by 49.2% nearly 7 years after initial implementation of our ASPs. Although a number of studies have used daily defined doses (DDD) as a measure of an ASPs' effectiveness, the guidelines we followed suggested that DOTs are preferable to DDD for assessing the effect of an ASPs [10]. Moreover, evaluation of the antimicrobial consumption using DDD may not be accurate because the approved maintenance dosages of some antimicrobials in Japan have been lower than the DDD defined by the World Health Organization [32]. Therefore, herein, we used DOTs to measure antibiotics use in this study. Using DDD per 1,000 patient days, a meta-analysis of 26 studies of hospital-based ASPs from around the world reported a 26.6% decrease in the use of restricted antibiotics and an 18.5% drop in use of carbapenems [13]. Those authors found that total antibiotic consumption in the Asian studies included in their analysis was smaller than that in the studies from the United States or Europe. Although there were differences in the outcome measures used, our study in Japan showed a greater degree of reduction in use of the targeted antibiotics compared with the findings of the meta-analysis. Moreover, we showed a gradual decease in antibiotic use over a longer period than the studies included in the meta-analysis, suggesting the long-term efficacy of our ASPs incorporating PAF.

We found that the susceptibility of *P. aeruginosa* to each antibiotic tested remained around 90% from before the start of our ASPs and through the 7-year study period. Because one of the main objectives of our ASPs was to maintain the susceptibility of *P. aeruginosa* as high as prior to implementing ASPs, we selected it as a core measure in this study. Several studies have shown that implementing ASPs resulted in

a reduction in the use of broad-spectrum antibiotics and an improvement in the susceptibility of Gram negative bacilli such as *P. aeruginosa* [16, 21, 23]. In our study, the only agent to which the susceptibility of *P. aeruginosa* improved was levofloxacin, although it was already quite high (86.0%) in 2009 before the intervention began. However, although it cannot be proven, it is quite possible that maintaining such a high level of sensitivity in pseudomonal isolates was due to improved management of the use of the broad-spectrum antibiotics because of the ASPs.

The proportion of patients isolated MRSA among all patients isolated *S. aureus* and the incidence of MRSA were significantly decreased in this study. Several other studies have also reported similar results [23, 24], and it has been reported that removal of key antibiotic selection pressures by a national antibiotic stewardship intervention may have played an important part in the reductions of hospital-associated and community-associated MRSA in Scotland [33]. Meanwhile, the use of anti-MRSA agents did not change during our study period. However, the use of anti-MRSA agents did not change during our study period possibly because of gradual increase in the number of blood cultures taken during the study period (data not shown), whereby the diagnostic process of bacteremia and other infectious diseases improved accordingly, and anti-MRSA agents were selected appropriately when these agents were required, such as catheter-related bloodstream infection [34] as a result of the ASPs. On the other hand, the incidence of CDI did not decreased after implementation of our ASPs. The incidence of MRSA and CDI may be affected by good hand hygiene or contact precautions, besides antibiotics use [10]. To evaluate the association between the change in antibiotic use because of the ASPs and the

incidence of MRSA or CDI, these infection control measures should also be surveyed, which were not evaluated in our study. Evaluating and improving compliance with these infection control measures remains a problem to be solved.

Since an ASPs by its very nature modifies physicians' prescribing behavior, clinical outcomes must be assessed to ensure that the program is not causing harm. Several systematic reviews have reported no increase in mortality after implementation of ASPs [11-14], and the meta-analysis including studies conducted in the Asia Pacific region reported similar results [25]. In our ASPs, infectious disease physicians assessed the all cases with bacteremia and advised the attending physician on appropriate treatment. While patients with bacteremia only were not subjects of our ASP, they were the important target population, so we included their mortality in the results. The 30-day mortality among patients with MRSA bacteremia was significantly decreased in our study. This result may have been a result of consultations regarding bacteremia patients with infectious disease physicians, as previously reported [35]. In contrast, the 30-day mortality among patients with *P. aeruginosa* bacteremia was no significant change, although the rate did fluctuate during the study period. A previous Japanese multicenter study reported that the crude mortality of patients with *P. aeruginosa* bacteremia varied with patients' clinical characteristics; 46.0% in intensive care units, 12.7% in non-intensive care units ward, and 20.3% in total [36]. In our study, the subject cases in each year were small and those clinical characteristics may have affected the fluctuation of those 30-day mortality. In total, we found no increase in the 30-day mortality among all patients with bacteremia during the study period. Moreover, the hospital mortality decreased

significantly in this study. Although these results did not reflect the exact mortality among all subjects of our ASPs, they suggest that our ASPs did not, at least, cause clinical harm.

Since PAF was performed only once a week, we were able to continue it for 7 years, with ongoing effectiveness. Several reports have verified the long-term effect of PAF conducted daily or on every weekday [15, 20-23]. Although those results are impressive, it might be difficult for institutions with limited human resources to maintain that demanding a schedule. For those healthcare settings, our results showing that once-weekly PAF is effective may encourage implementation of a similar program. However, only implementation of PAF did not bring positive results in our study. In our PAF, because the infectious disease pharmacists audited all the targeted cases, the burden imposed on infectious disease physicians was lightened and all cases including those not consulted with infectious disease physicians could be actively checked. In addition to the PAF conducted only once a week, we encouraged the attending physician to consult with infectious disease physicians about the cases requiring continuous intervention as needed. Furthermore, knowledge and awareness of other medical staff for the appropriate antibiotic use can be developed by other elements of the ASPs combined with PAF, such as the education of appropriate antibiotic use, renewal of the antibiotics listed in the hospital formulary, antibiotic dose optimization by the pharmacists, and dissemination of the hospital antibiogram. The number of each specialized team member conducting our PAF was not so small especially in Japan, but PAF was not their full-time work. By combining various strategies as a bundle, our ASPs may have enhanced and sustained its efficacy while reducing the burden on each specialist. For a hospital lacking infectious disease

specialists, to construct comprehensive ASPs which supplement the effecacy of PAF was considered to be essential.

Several limitations of this study should be acknowledged. First, it was an observational study conducted at a single university hospital in Japan. Therefore, our results may not be generalizable to other care settings or countries. Secondly, as mentioned above, our ASPs included a variety of strategies in addition to PAF, but we could only assess the overall results of the entire program. We also cannot determine if more frequent PAF team interventions would have led to even better results. Further study of individual ASPs elements and application of PAF may help sort out the most effective strategies for maintaining the long-term effect of the ASPs. Thirdly, since we first implemented the ASPs in 2010, guidelines have been revised and newly published studies have led to changes in the standard of care, especially with recommendations for shorter courses of antibiotics [37-40]. These changes may also have contributed to our good results, so that our study findings may not be entirely attributable to the ASPs alone. On the other hand, our study reflects long-term, real-life application of ASPs which would naturally be expected to incorporate new recommendations as they are developed. Fourthly, we could not verify the changes made for each patient requiring intervention during the study period. Our outcome measures were surrogates for case-by-case improvement, but at the very least, the fact that the 30-day mortality among all patients with bacteremia was no increase and the hospital mortality was significantly decreased indicates that our patients were not harmed by implementation of the ASPs. Future studies might focus on investigating specific results in terms of antibiotic selection, dose, and duration of

administration on a case-by-case basis.

In conclusion, this study suggests that our comprehensive ASPs, including various strategies built around a core weekly PAF with multidisciplinary collaboration, reduced the use of the targeted antipseudomonal antibiotics while maintaining good susceptibility of *P. aeruginosa* isolates to the antibiotics, decreased the incidence of MRSA, and had no adverse effect on clinical outcome. The ASPs remained effective over the 7-year study period. Even with limited availability of infectious disease specialists, ASPs can have sufficient efficacy by multidisciplinary collaborations and various supplemental strategies in conjunction with PAF. We believe this strategy contributed to maintaining the long-term effectiveness of our ASPs.

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Conflict of interest. All authors reports no conflicts of interest relevant to this article.

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Figure captions

Fig. 1 Days of therapy per 1000 patient days of antipseudomonal antibiotics, calculated monthly. ** $P < 0.01$ compared with 2009

Fig. 2 Susceptibility of *Pseudomonas aeruginosa* to each antibiotic. * $P < 0.05$ for trend. Abbreviations: MEPM, Meropenem; PIPC, Piperacillin; CFPM, Cefepime; AMK, Amikacin; LVFX, Levofloxacin

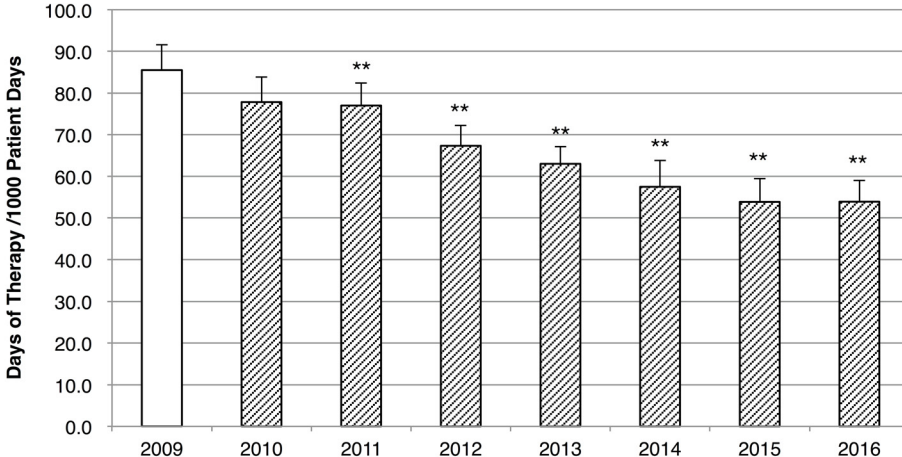
Fig. 3 The proportion of patients isolated MRSA among all patients isolated *S. aureus* ** $P < 0.01$ for trend. Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*

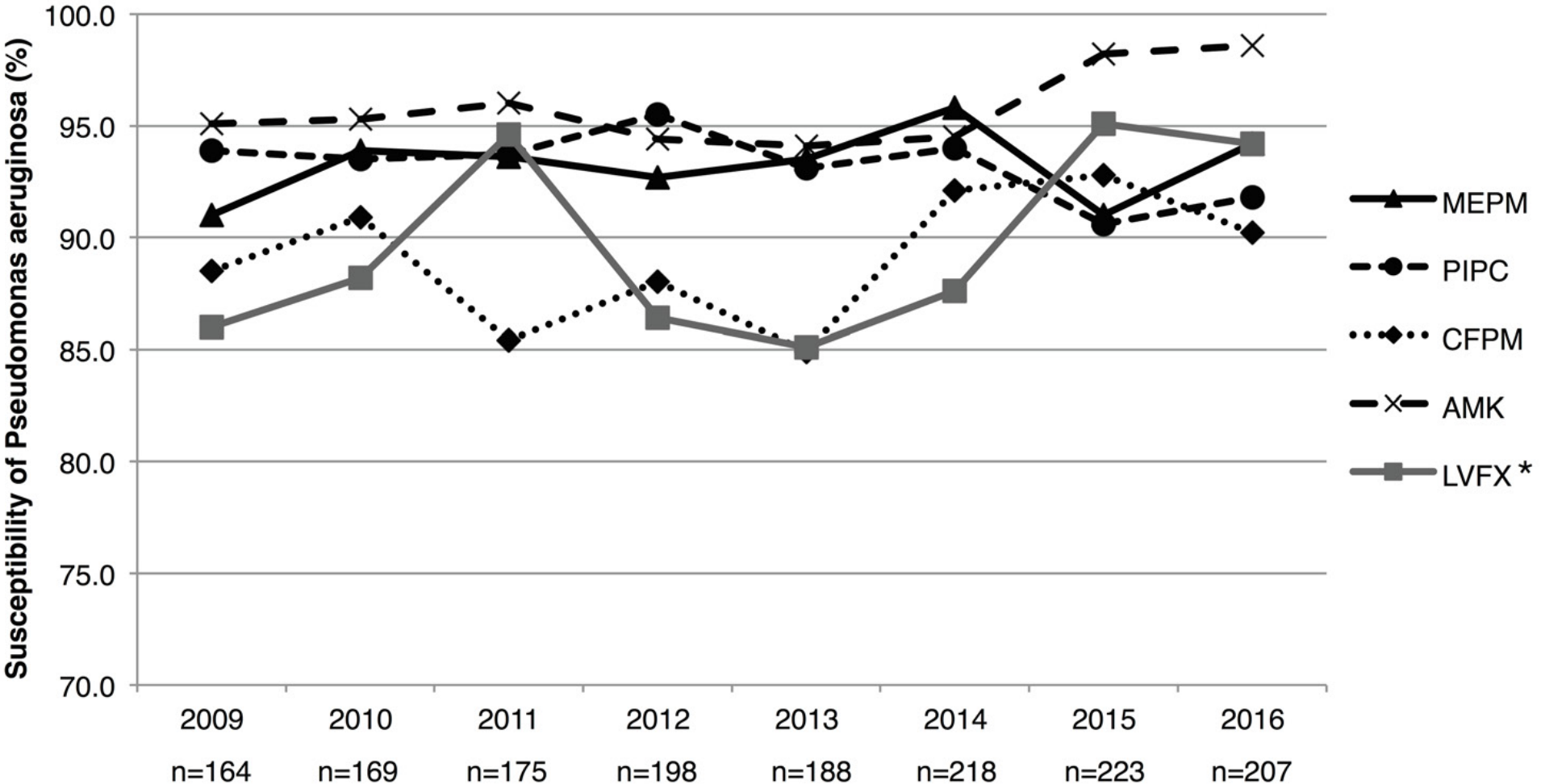
Fig. 4 The incidence of MRSA per 1000 patient days * $P < 0.05$ for trend. Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*

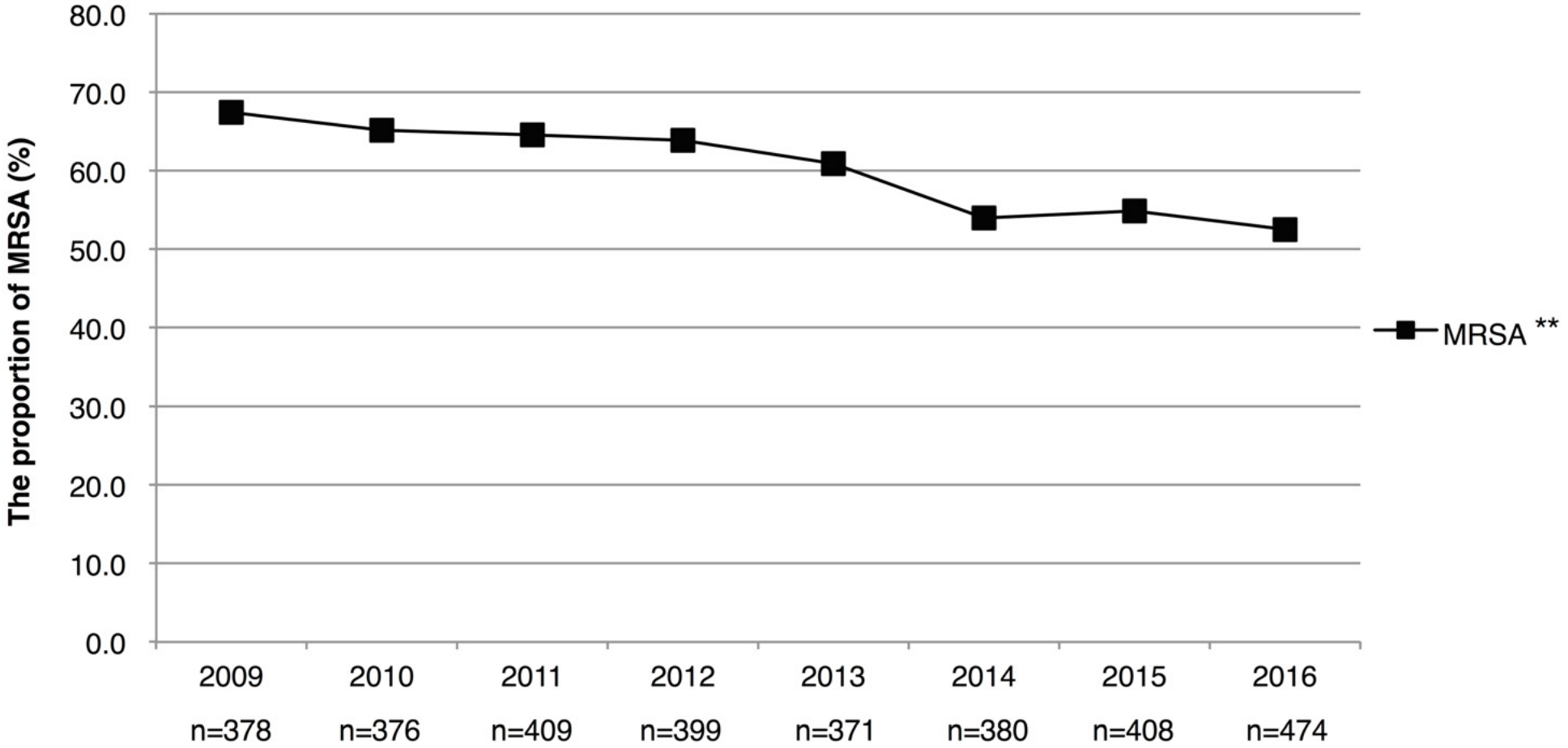
Fig. 5 The incidence of CDI per 1000 patient days Abbreviations: CDI, *Clostridioides difficile* infection

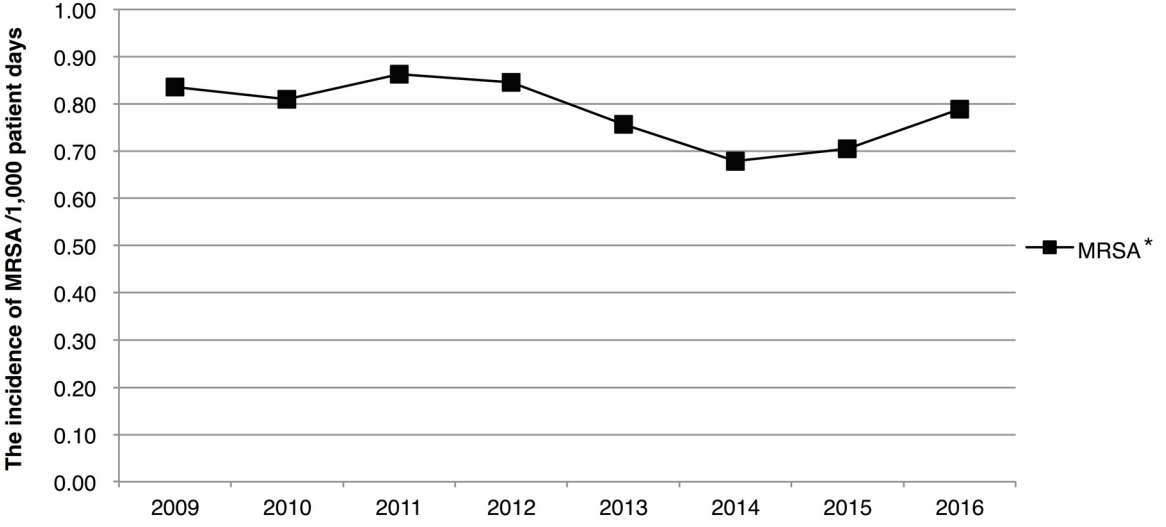
Fig. 6 The 30-day mortality of bacteremia **a)** All patients with bacteremia, **b)** MRSA bacteremia, and **c)** *Pseudomonas aeruginosa* bacteremia. * $P < 0.05$ for trend. Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*; *P. aeruginosa, Pseudomonas aeruginosa*

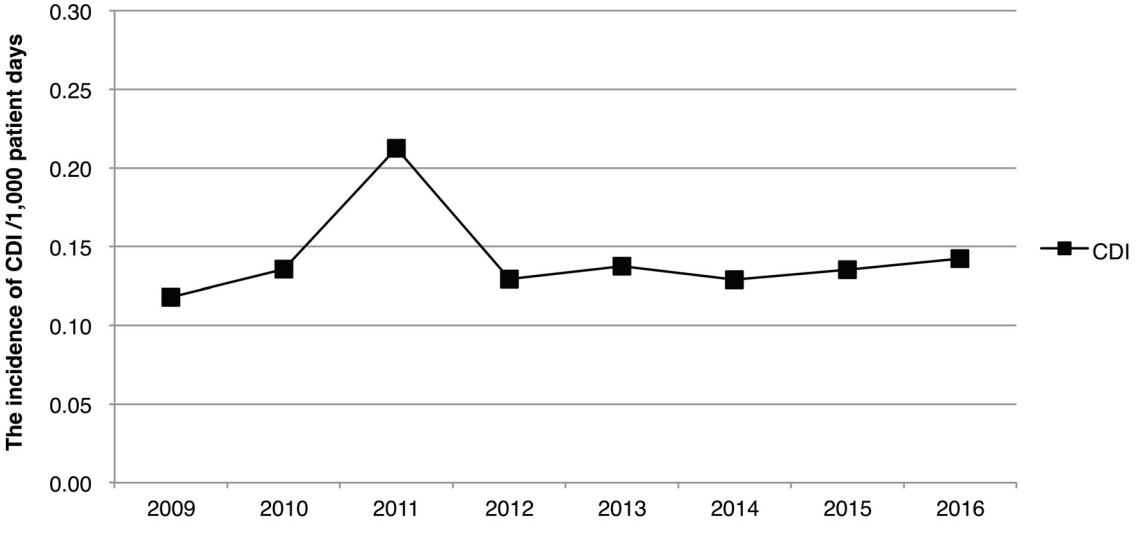
Fig. 7 The hospital mortality * $P < 0.05$ for trend.

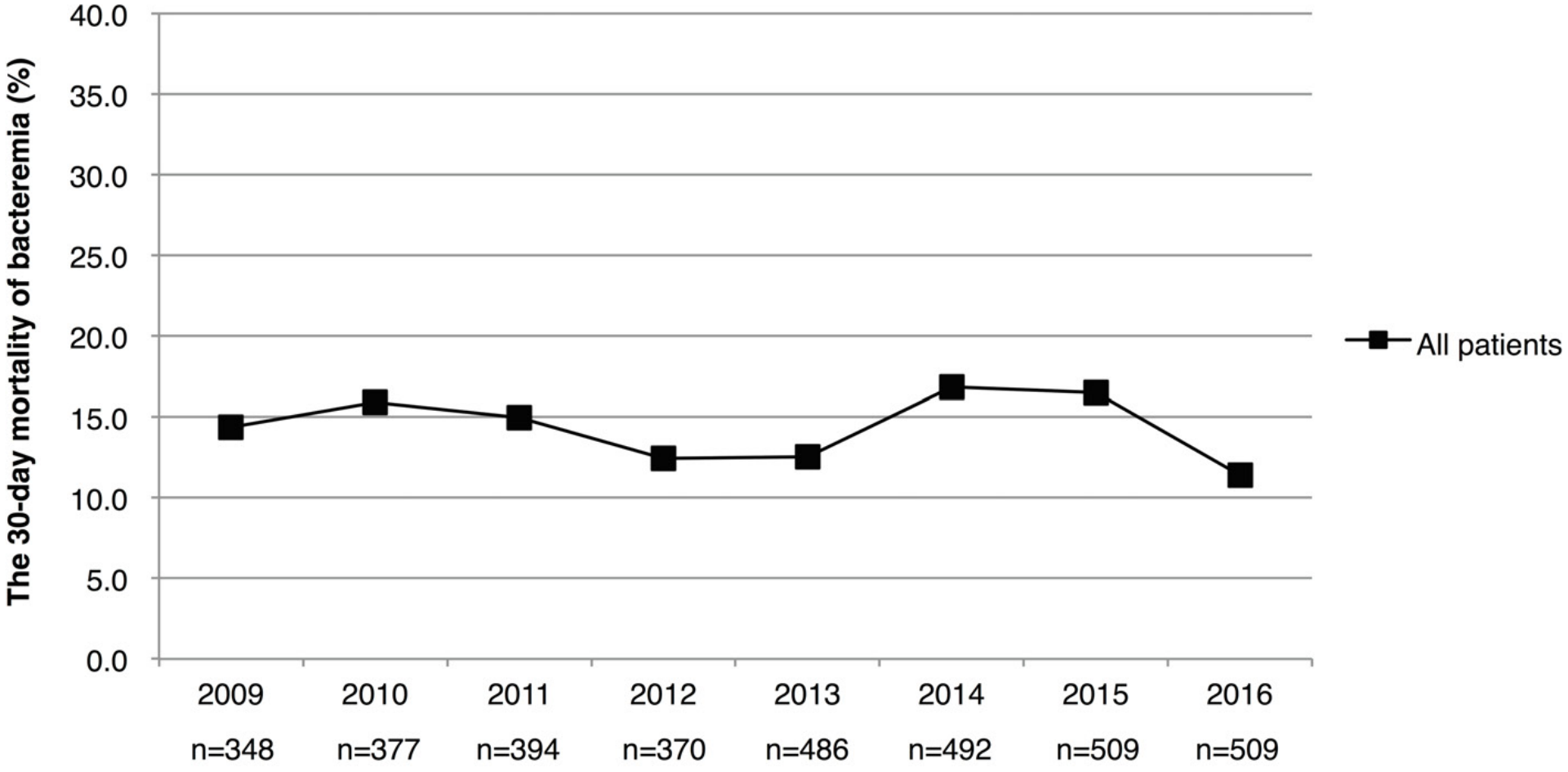

Days of Therapy /1000 Patient Days
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
**
**
**
**
**
**
2009
2010
2011
2012
2013
2014
2015
2016

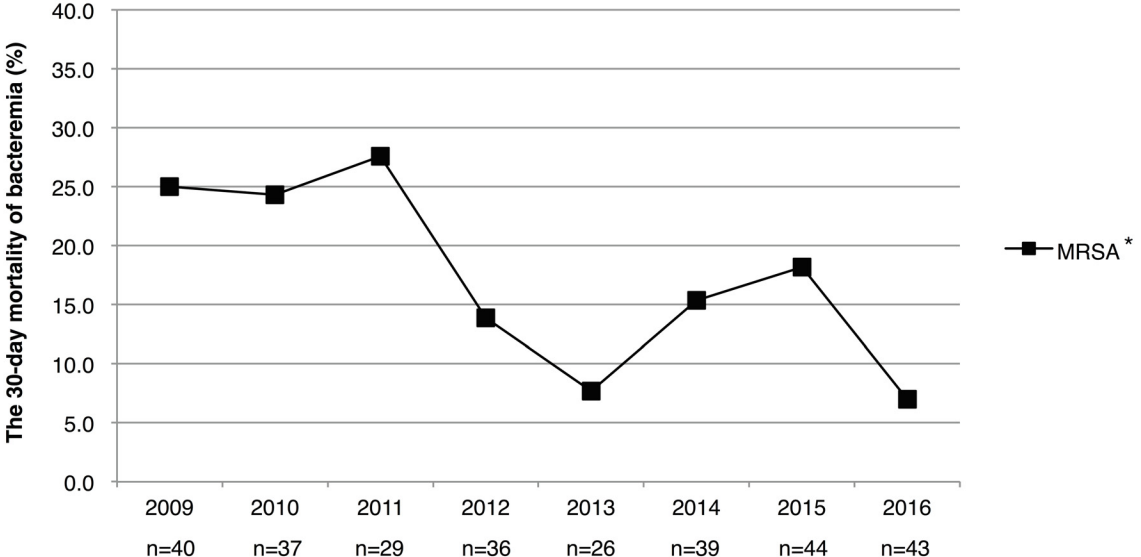

Susceptibility of Pseudomonas aeruginosa (%)
100.0
95.0
90.0
85.0
80.0
75.0
70.0
2009
n=164
2010
n=169
2011
n=175
2012
n=198
2013
n=188
2014
n=218
2015
n=223
2016
n=207
MEPM
PIPC
CFPM
AMK
LVFX *

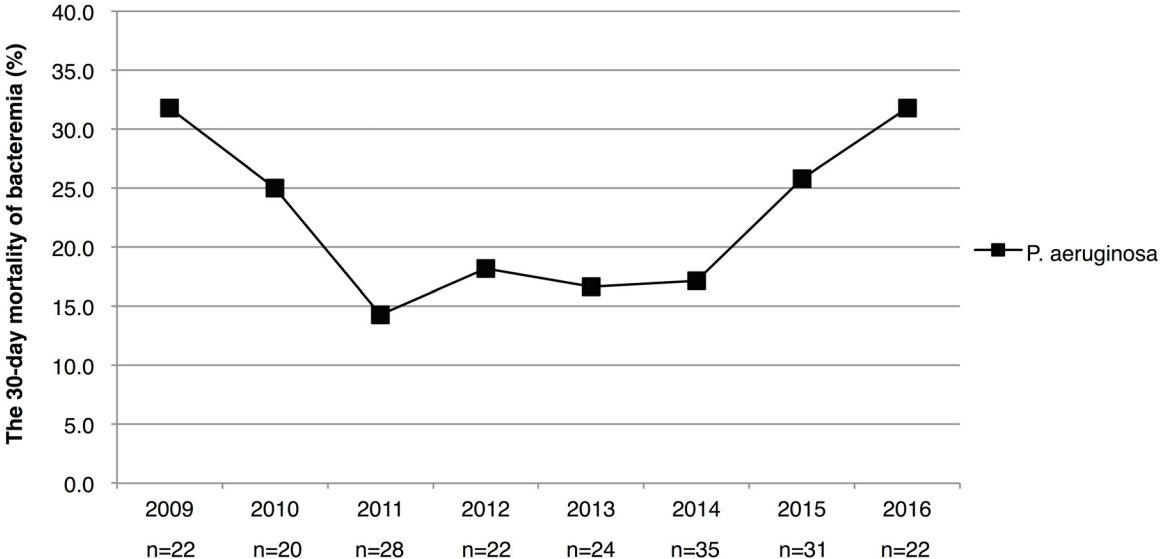

80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
The proportion of MRSA (%)
MRSA **
2009
n=378
2010
n=376
2011
n=409
2012
n=399
2013
n=371
2014
n=380
2015
n=408
2016
n=474


The incidence of MRSA /1,000 patient days
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
2009
2010
2011
2012
2013
2014
2015
2016
MRSA*


The incidence of CDI /1,000 patient days
0.30
0.25
0.20
0.15
0.10
0.05
0.00
2009
2010
2011
2012
2013
2014
2015
2016
CDI


The 30-day mortality of bacteremia (%)
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
2009
2010
2011
2012
2013
2014
2015
2016
n=348
n=377
n=394
n=370
n=486
n=492
n=509
n=509
All patients


The 30-day mortality of bacteremia (%)
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
2009
2010
2011
2012
2013
2014
2015
2016
n=40
n=37
n=29
n=36
n=26
n=39
n=44
n=43
MRSA *


The 30-day mortality of bacteremia (%)
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
2009
n=22
2010
n=20
2011
n=28
2012
n=22
2013
n=24
2014
n=35
2015
n=31
2016
n=22
P. aeruginosa

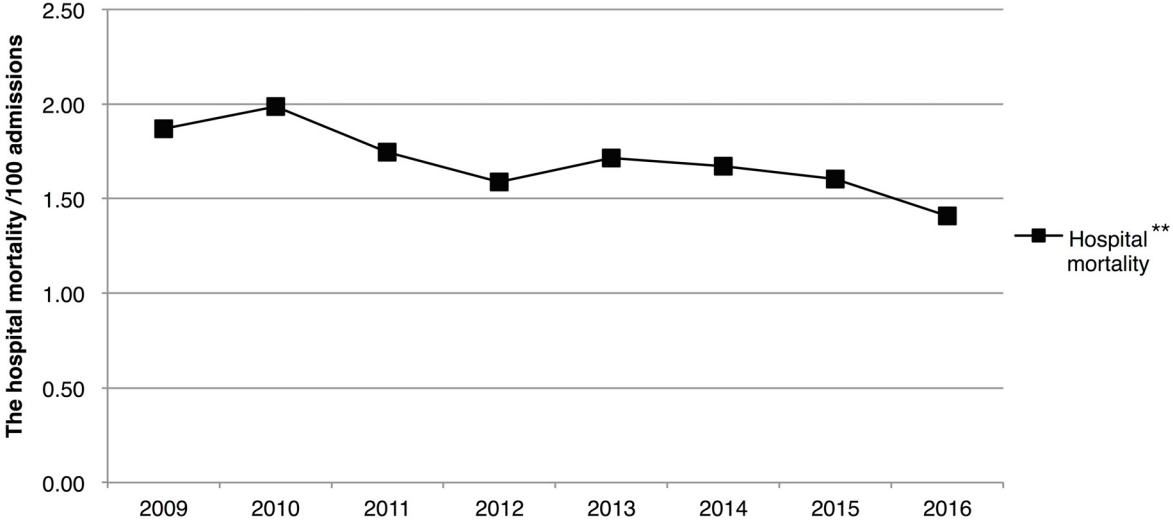

The hospital mortality /100 admissions
2.50
2.00
1.50
1.00
0.50
0.00
2009
2010
2011
2012
2013
2014
2015
2016
Hospital mortality **

Table 1 Targeted antibiotics in the prospective audit and feedback

Classes	Antibiotics
Anti-methicilin-resistant *Staphylococcus aureus* agents	Vancomycin, Teicoplanin, Arbekacin, Linezolid, Daptomycin
Antipseudomonal agents	
Carbapenems	Meropenem, Doripenem, (Imipenem/Cilastatin), (Biapenem), (Panipenem/Betamipron)
Antipseudomonal penicillins	Piperacillin, Piperacillin/Tazobactam
Antipseudomonal cephalosporins	Ceftazidime, Cefepime, Cefozopran, (Cefpirome)
Fluoroquinolones	Levofloxacin, Ciprofloxacin, Pazufloxacin
Aminoglycosides	Gentamicin, Tobramycin, Amikacin, (Isepamicin)
Antifungals	Fosfluconazole, Itraconazole, Voriconazole, Micafungin, (Caspofungin), Liposomal-amphotericin B
Oral agents	Vancomycin

Medications removed from formulary by 2017 are indicated in parentheses.

Table 2 Strategies of the antibiotic stewardship programs and the year of implementation

Year	Strategies
Before 2005	Therapeutic drug monitoring
2006	Mandatory preauthorization when using linezolid
2008	Consultation on bacteremia patients by infectious disease physicians
2009	Dissemination of the hospital antibiogram
2010	Prospective audit and feedback (*The Big Gun Project*)
	Renewal of the antibiotics listed in the hospital formulary
	Dose optimization of antibiotics by the pharmacist
2012	Seminars on appropriate antibiotic use by infectious disease physicians
2013	Mandatory preauthorization when using daptomycin

Table 3 Days of therapy with each antibiotic targeted in the antibiotic stewardship program

Classification	2009 DOTs (SD)	2010 DOTs (SD)	2011 DOTs (SD)	2012 DOTs (SD)	2013 DOTs (SD)	2014 DOTs (SD)	2015 DOTs (SD)	2016 DOTs (SD)
Antipseudomonal agents								
Carbapenems	26.7 (3.4)	21.9 (3.7)*	21.8 (3.6)*	17.5 (1.5)***	15.6 (2.7)***	14.1 (1.9)***	12.3 (2.3)***	13.5 (2.3)***
Antipseudomonal penicillins	14.7 (1.8)	17.2 (2.9)	15.0 (2.0)	14.6 (2,4)	19.6 (3.4)*	21.9 (3.4)***	20.8 (2.5)***	20.1 (1.9)***
Antipseudomonal 3rd generation cephalosporins	17.3 (2.3)	16.0 (1.9)	16.6 (2.7)	15.7 (1.3)	11.3 (2.1)***	9.0 (1.6)***	8.4 (1.5)***	7.6 (1.9)***
Antipseudomonal 4th generation cephalosporins	12.9 (1.6)	12.4 (2.5)	11.8 (2.4)	10.8 (1.9)*	9.5 (1.6)***	7.0 (1.6)***	6.4 (1.4)***	6.9 (1.7)***
Fluoroquinolones	5.4 (1.0)	5.5 (1.4)	6.3 (1.5)	5.4 (2.0)	4.4 (2.2)	3.6 (1.5)*	4.6 (1.9)	4.7 (1.1)
Other antipseudomonal agents	8.5 (2.6)	4.8 (1.1)*	5.5 (1.3)**	3.4 (1.0)***	2.7 (0.8)***	2.0 (0.6)***	1.4 (0.6)***	1.2 (1.1)***
Anti-MRSA agents	17.9 (2.9)	20.1 (2.7)	18.0 (3.0)	21.5 (4.3)	19.6 (2.6)	19.2 (2.7)	18.5 (3.2)	20.4 (2.2)
Antifungals	10.4 (1.5)	11.1 (2.1)	10.1 (2.5)	9.1 (1.9)	7.9 (2.2)*	11.4 (3.2)	7.7 (2.5)	8.1 (2.1)*
Penicillins except for antipseudomonal agents	27.7 (2.3)	29.0 (3.0)	28.0 (2.4)	29.5 (3.0)	35.1 (5.4)**	39.9 (3.2)***	42.1 (3.9)***	44.4 (3.8)***
1st generation cephalosporins	38.5 (2.3)	39.3 (3.9)	41.5 (2.4)*	43.9 (3.6)**	44.0 (3.3)*	41.3 (1.8)*	44.2 (3.2)**	45.0 (2.9)***
2nd generation cephalosporins	21.8 (4.4)	18.8 (2.3)	19.0 (2.4)	21.7 (1.7)	20.7 (2.1)	17.6 (2.2)*	18.2 (1.7)	18.2 (1.2)
3rd generation cephalosporins except for antipseudomonal agents	5.5 (2.0)	7.2 (1.3)	7.3 (2.1)	8.0 (1.2)*	9.7 (2.2)**	7.4 (1.4)	7.5 (2.1)	8.4 (1.4)*
Other antibiotics	8.8 (1.7)	8.4 (1.7)	7.0 (2.0)	5.9 (1.0)**	4.0 (0.9)***	5.7 (1.7)*	6.9 (2.1)	8.0 (1.6)
Total	215.9 (11.4)	211.7 (9.0)	207.9 (10.6)	207.0 (13.0)	204.0 (6.4)	199.0 (12.9)	198.9 (8.0)*	206.4 (7.7)*

Days of therapy per 1,000 patient days expressed as monthly mean (standard deviation). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with 2009.

Abbreviation: DOTs, days of therapy per 1,000 patient days; MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation