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Original Article

The intervention by an antimicrobial stewardship team can improve clinical and microbiological outcomes of resistant gram-negative bacteria☆

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ABSTRACT

Antibiotic stewardship (AS) improves patient outcomes and rates of antibiotic susceptibilities. However, the long-term effect of AS programs (ASPs) on mortality is unclear. This study aimed to assess the impact of bedside interventions by an AS team (AST) on clinical and microbiological outcomes. This retrospective study enrolled patients with bloodstream infections (BSI) and long-term use of broad-spectrum antibiotics (more than 7 days). The main outcomes were 30-day and in-hospital mortality of patients with BSI. The secondary outcomes were the day of therapy (DOT) and susceptibility of antipseudomonal agents. Cases were classified into two groups: the pre-ASP group comprised cases between 2011 and 2013 and the post-ASP group, between 2014 and 2016. The outcomes were then compared between the two groups. Among the patients with all BSI (n = 1187), no significant differences in 30-day mortality were observed between those in the pre-ASP and post-ASP groups. However, in-hospital mortality was significantly lower in the post-ASP group than that in the pre-ASP group (24.8% vs. 18.0%; P = 0.004). Furthermore, the 30-day and in-hospital mortality of resistant gram-negative bacteraemia was significantly lower (20.4% vs.10.5%; P = 0.04 and 28.0% vs.16.1%; P = 0.03). The DOT of broad-spectrum antibiotics decreased except that of tazobactam/piperacillin. The susceptibilities of tazobactam/piperacillin, ceftazidime, cefepime, sulbactam/cefoperazone, gentamicin, ciprofloxacin levofloxacin, imipenem and meropenem were significantly better. Interventions by the AST can improve the clinical and microbiological outcomes, especially resistant gram-negative bacteria. Furthermore, this effect of our ASP can continue for a long term.

1. Introduction

Antimicrobial resistance (AMR), defined as microbes developing resistance to drugs that generally limit their growth or cause death, has become a serious health concern worldwide [1,2]. Infections caused by AMR lead to increased mortality and healthcare costs [3,4]. AMR is primarily caused by inappropriate antibiotic use, which

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leads to the prevalence of resistant bacteria [5]. The World Health Organization (WHO) has developed the "Global action plan on antimicrobial resistance" and recommended to optimize the use of antimicrobial medicines [6]. Furthermore, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America have encouraged the implementation of antimicrobial stewardship programs (ASPs) [7]. The benefits of antibiotic stewardship include improved patient outcomes, reduced adverse events, improvement in rates of antibiotic susceptibilities, and optimized resource utilization [7]. Some systematic reviews have proven its effectivity in reducing antibiotic consumption, improving the quality of prescriptions, and decreasing antimicrobial resistance [8–10]. However, the long-term effect of ASPs in clinical outcome, such as reduction in mortality, is unclear. Furthermore, studies showing improvement of both clinical outcome and antibiotic susceptibilities from ASP are limited.

In January 2014, we organized an interdisciplinary AS team (AST) at Osaka City University Hospital consisting of infectious disease physicians, pharmacists, a microbiological technologist, and nurses. This study aimed to assess the long-term effect of bedside interventions by AST on clinical outcomes of bacteraemia, rates of antibiotic susceptibilities, and antibiotic use.

2. Materials and methods

2.1. Antimicrobial stewardship programs (ASPs)

The ASPs were commenced in January 2014 at the Osaka City University Hospital, which is a 972-bed tertiary-care teaching hospital. The core strategy of ASPs in our institution was prospective audit and feedback that mainly consisted of interventions for cases of BSI and long-term use of broad-spectrum antibiotics (i.e., more than 7 days). AST members began each weekday morning with a meeting to discuss information on new patients with positive blood cultures by microbiological technologists. The responsibilities of the infectious disease physicians included (1) guiding the attending physician on the appropriate antimicrobials and dosage as needed for patients with positive blood cultures; (2) suggesting de-escalation when the pathogen and susceptibility were clear; and (3) observing the clinical course of the cases until the treatments are completed (more than 2 weeks). Patients prescribed with antimicrobials were put on a list the day after prescription (the next business day when this date fell on a holiday) by pharmacists, and their medical charts were immediately reviewed by the infectious disease physicians. If the appropriate antibiotics had not been selected, an appropriate dosage had not been set, or if the appropriate blood culture and other tests had not been performed, the infectious disease physicians recommended sampling cultures and appropriate therapies to the attending physician. Pharmacists monitored the use of anti-MRSA agents and prepared a list of long-term use of broad-spectrum antibiotics (more than 7 days). Hospital rounds focused on patients with positive blood cultures (until the previous 2 weeks) and those with long-term and antimicrobial prescriptions were conducted. With regards to the target group, history of present illness, culture results, blood test results, and treatment details were confirmed by infectious diseases physicians. The AST conducted a meeting once weekly every Tuesday to decide the necessary interventions for each case. Infectious disease physicians advised and discussed treatment policies with attending physicians in the ward. The ASPs that we carried out are shown in Table 1.

2.2. Study design and target group

This was a single-centre, retrospective, and observational study that included patients with bloodstream infections (BSI), those administered broad-spectrum antibiotics, and identified to be susceptible to *Pseudomonas aeruginosa*. The exclusion criterion was the isolation of skin microflora, including coagulase-negative staphylococci, Bacillus spp., Corynebacterium spp., and Propionibacterium spp [11–13]. The patients were classified into two groups as follows: those admitted between January 2011 and December 2013 and between January 2014 and December 2016 were placed in the pre-ASP group and the post-ASP group, respectively. Cases with the same microorganism isolated multiple times within 14 days were defined as the same episode [14]. The broad-spectrum antibiotics that were investigated in this study were antipseudomonal agents. In our hospital, they consisted of third- and fourth-generation cephalosporins, tazobactam/piperacillin (TAZ/PIPC), carbapenems, and fluoroquinolones. The days of therapy (DOTs)/1000 patient-days was calculated by multiplying the number of antimicrobials therapy days divided by the number of patients who were hospitalized by 1000. The data on susceptibility of *P. aeruginosa* (n = 2254; pre-ASP n = 1227, post-ASP = 1027) were obtained from microbiological laboratory records. The first isolate from each patient was included in the analysis. The susceptibility tests were performed via MicroScan WalkAway systems (Siemens, Munich, Germany). Susceptibility was evaluated based on the breakpoint of CLSI M100-S22. The primary outcomes were 30-day and in-hospital mortality of patients with BSI. The secondary outcomes were the DOT and the susceptibilities of antipseudomonal agents. We also analysed the interventions for cases with long-term antimicrobial prescriptions (more than 7 days). The rate of accepted interventions was determined according to the number of interventions accepted within 3 days after recommendation. This study was approved by the ethics committee of Osaka City University (Approval number: 3724).

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS® Statistics 22.0 (IBM Japan, Tokyo). The nominal variables of the two groups were compared using the Chi-square test or the Fisher's exact test, and the continuous variables were compared using the Student's t-test. A P-value <0.05 was considered statistically significant.

3. Results

A total of 1187 who had BSI were included in the study. The pre-ASP and post-ASP group comprised 492 and 695 patients, respectively. The characteristics of patients enrolled in this study were described in Table 2. The age was higher in post-ASP group (P = 0.01). On the other hand, the cardiovascular patients were more frequent in the pre-ASP group (P < 0.01). The prognosis of all patients with bacteraemia is shown in Fig. 1. Among the patients with BSI, no significant differences in 30-day mortality were observed between the two groups (16.9% [83/492] vs. 13.1% [91/695]; P = 0.07). Meanwhile, in-hospital mortality was significantly lower in the post-ASP group than that in the pre-ASP group (24.8% [122/492] vs. 18.0% [125/695]; P = 0.004). Furthermore, the 30-day and in-hospital mortality of resistant gram-negative bacteraemia (*Serratia* spp.[Pre-ASP : 6, Post-ASP:16], *P. aeruginosa* [Pre-ASP : 36, Post-ASP:35], *Acinetobacter* spp. [Pre-ASP : 11, Post-ASP:12], *Citrobacter* spp. [Pre-ASP : 6, Post-ASP:12], *Enterobacter* spp. [Pre-ASP : 34, Post-ASP:49] [SPACE]) was significantly lower in the post-ASP group (20.4% [19/93] vs. 10.5% [13/124]; P = 0.04 and 28.0% [26/93] vs. 16.1% [20/124]; P = 0.03). In particular, compared with the other bacterial species, the prognosis of *P. aeruginosa* (30-day mortality: 22.2% [8/36] vs. 5.7% [2/35]; P = 0.09) and *Acinetobacter* spp. (30-day mortality: 36.3% [4/11] vs. 0% [0/12]; P = 0.04 tended to be better in the post-ASP

Table 1
Prospective audit and feedback in our antimicrobial stewardship programs.

Prospective audit and feedback
① Interventions for bloodstream infections (BSI)
· Infectious disease physicians suggest empiric therapies if not appropriate.
· They also suggest de-escalation when the pathogen and susceptibility are clear.
· They observe clinical course of the cases until the treatments are completed (more than 2 weeks).
② **Interventions for patients prescribed antibiotics**
· Infectious disease physicians check all broad spectrum antibiotics prescribed on previous day.
· Pharmacists are recommended to perform therapeutic drug monitoring of anti-MRSA agents.
· Pharmacists list the long-term use of broad-spectrum antibiotics (more than 7 days).
· The antimicrobial stewardship team identifies the cases for which interventions are necessary.

Table 2
Characteristics of patients enrolled in this study.

	Pre-ASP group (n = 492)	Post-ASP group (n = 695)	p-value
Sex (male/female)	302/190	423/272	0.86
Age≧70	168 (34.1%)	288 (41.4%)	0.01
Department			
Emergency	80 (16.3%)	113 (16.3%)	1.00
Hematology	82 (16.7%)	108 (15.5%)	0.60
Gastrointestinal surgery	47 (9.6%)	88 (12.7%)	0.10
Gastroenterology	34 (6.9%)	49 (7.1%)	0.93
Urology	23 (4.8%)	42 (6.1%)	0.31
Gynecology	24 (4.9%)	34 (4.9%)	0.99
Hepatobiliary and pancreatic surgery	24 (4.9%)	33 (4.7%)	0.92
Cardiology	35 (7.1%)	21 (3.0%)	< 0.01
Cardiovascular surgery	22 (4.5%)	28 (4.0%)	0.71
Hepatobiliary and pancreatic internal medicine	11 (2.2%)	28 (4.0%)	0.09
Respirology	17 (3.5%)	21 (3.0%)	0.68
Others	93 (18.9%)	130 (18.7%)	0.93
Pathogen			
Methicillin susceptible Staphylococcus aureus	53 (10.8%)	89 (12.8%)	0.29
Methicillin resistant Staphylococcus aureus	48 (9.8%)	54 (7.8%)	0.23
Escherichia coli	47 (9.6%)	90 (12.9%)	0.07
ESBL-Escherichia coli	15 (3.0%)	29 (4.2%)	0.31
Enterococcus faecalis	30 (6.1%)	28 (4.0%)	0.10
Enterococcus faecium	26 (5.3%)	40 (5.8%)	0.72
Enterobacter spp.	34 (6.9%)	49 (7.1%)	0.93
Klebsiella pneumoniae	25 (5.1%)	51 (7.3%)	0.12
Pseudomonas aeruginosa	36 (7.3%)	35 (5.0%)	0.10
Candida spp.	24 (4.9%)	31 (4.5%)	0.74
Others	154 (31.3%)	199 (28.6%)	0.32

group. The DOTs of third- and fourth-generation anti-pseudomonal cephalosporins and carbapenems significantly decreased in the post-ASP period (P < 0.01). Particularly, that of carbapenems decreased from 33.2 ± 5.7 to 25.5 ± 4.6. Meanwhile,

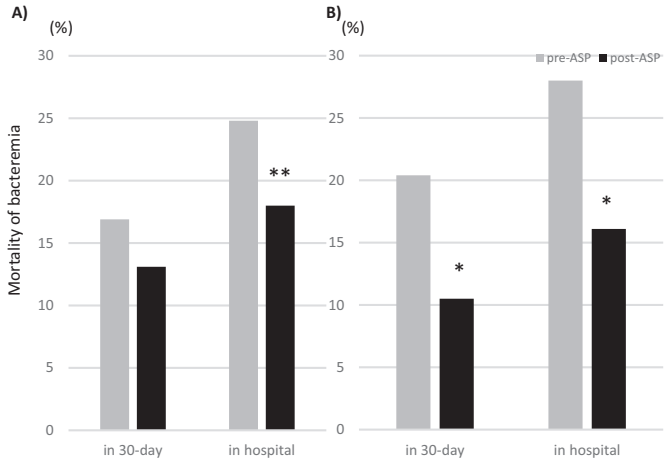

Fig. 1. In-hospital and 30-day mortality rate of bacteremia. A) All bacteremia, B) SPACE bacteremia. SPACE: *Serratia* spp., *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Citrobacter* spp. and *Enterobacter* spp. *P < 0.05,**P < 0.01 compared with pre-ASP.

the DOT of TAZ/PIPC significantly increased from 18 ± 4.8 to 23.3 ± 2.7 (P < 0.01) (Fig. 2). The susceptibilities of TAZ/PIPC(90.6 → 93.9%), ceftazidime (91.4 → 94.1%), cefepime (87.9 → 93.5%), sulbactam/cefoperazone (87.2 → 89.9%), gentamicin (83.3 → 88.9%), ciprofloxacin (85.7 → 89.1%), levofloxacin (84.7 → 89.1%), imipenem (78.7 → 82.0%) and meropenem (84.7 → 89.6%) were significantly better in the post-ASP period. No antibiotics had worse susceptibilities in the post-ASP period (Fig. 3). The interventions for long-term use of broad-spectrum antibiotics are detailed in Table 3. Discontinuation was accepted in 140 of the 155 cases in which it was recommended (90.3%), while de-escalation was accepted in 133 of the 145 cases it was recommended (91.7%). The rate of acceptance for other recommendations was more than 80%.

4. Discussion

This study showed that AST could reduce the 30-day and in-hospital mortality of resistant gram-negative bacteraemia and the in-hospital mortality of all BSI. Moreover, the DOT of some broad-spectrum antibiotics significantly decreased, and the susceptibilities of antipseudomonal agents were significantly recovered. Furthermore, the accepted rates of interventions to cases with long-term antimicrobial prescriptions were very high.

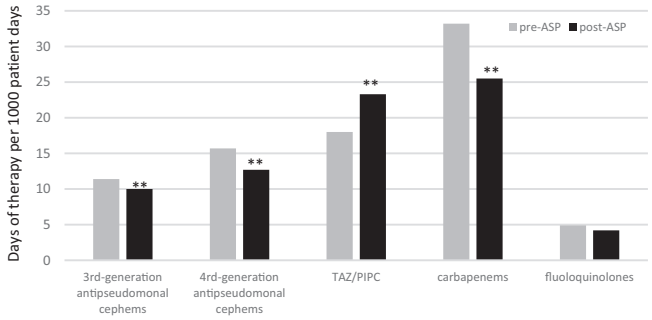

Fig. 2. Days of therapy with antipseudomonal agents. Note: Third-generation antipseudomonal cephems consist of ceftazidime and sulbactam/cefoperazone. Fourth-generation antipseudomonal cephems consist of cefepime and cefozopran. Carbapenems consist of imipenem, meropenem, doripenem, and biapenem. Fluoroquinolone consists of ciprofloxacin and levofloxacin. -Day of therapy per 1000 patient days are expressed as monthly mean. TAZ/PIPC: tazobactam/piperacillin. **P < 0.01 compared with Pre-ASP.

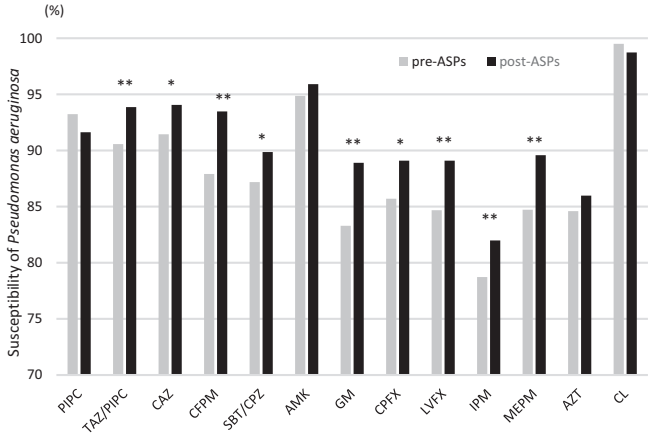

Fig. 3. Susceptibility of *Pseudomonas aeruginosa* to antipseudomonal agents. PIPC: piperacillin, TAZ/PIPC: tazobactam/piperacillin, CAZ: ceftazidime. CFPM: cefepime, SBT/CPZ: sulbactam/cefoperazone, AMK: amikacin, GM: gentamycin, CPFX: ciprofloxacin, LVFX: levofloxacin, IPM: imipenem, MEPM: meropenem, AZT: aztreonam, CL: colistin. *P < 0.05, **P < 0.01 compared with pre-ASP.

Table 3
Interventions for long-term use of broad-spectrum antibiotics.

Recommendation	Cases, n (%)	Accepted rate (%)
· Discontinuation	155 (37.5)	90.3
· De-escalation	145 (35.1)	91.7
· Switch to oral agents	59 (14.3)	84.7
· Alternate agents	28 (6.8)	89.3
· Dose optimization	16 (3.9)	93.8
· Others	11 (2.7)	100

Note: n = 413. One case was recommended for two interventions.

In the present study, the in-hospital mortality was significantly lower in the post-ASP period. The 30-day and in-hospital mortality of SPACE were also significantly lower. Several systematic reviews have reported no increase in mortality after implementation of ASPs [8,15,16]. Furthermore, two meta-analyses that included studies conducted in the Asia Pacific region have reported that ASP reduces mortality rates [9,10]. Although these meta-analyses obtained similar results, some points were different. Honda et al. demonstrated improved mortality in 2-group comparative studies but not in before-after trials [9]. Meanwhile, Lee et al. reported that mortality rates were significantly improved by ASP using drug monitoring or formulary restriction or intravenous-to-oral conversion. However, most studies that reported improved clinical outcomes were only short-term studies [17,18]. Our study was a before-after trial in which all-cause mortality rates were significantly improved for 3 years without formulary restriction.

In general, resistant gram-negative bacteraemia has poor prognosis. Recently, Thaden et al. have demonstrated that *P. aeruginosa* BSI is associated with increased mortality relative to *S. aureus* or other gram-negative BSI [19]. Other studies also have demonstrated increased crude mortality in *P. aeruginosa* BSI compared with other bacterial infections [20,21]. A Japanese multicentre study showed that the crude mortality of patients with *P. aeruginosa* bacteraemia was 20.3% [13], which is similar to that of our pre-ASP. The worse prognosis of *P. aeruginosa* bacteraemia can be attributed to the following factors. First, *P. aeruginosa* commonly infects those that are chronically ill or immunosuppressed, and this pathogen is often associated with high antibiotic resistance. The associated delay in appropriate therapy can increase mortality [20]. Furthermore, there is no bundle approach (for example *S. aureus* bacteraemia) that can improve the prognosis of SPACE infections *S. aureus*[22,23]. Thus, the management of *P. aeruginosa* bacteraemia is difficult. However, the prognosis of *Pseudomonas* bacteraemia BSI was improved during the post-ASP period in our study. It is possible that this result correlated with the recovery of susceptibilities in *P. aeruginosa.* Several studies demonstrated that resistant *P. aeruginosa* infections resulting in higher mortality rates are most likely related to the severity of these infections and less frequent early provision of appropriate antimicrobial therapy [24,25]. The better prognosis of *P. aeruginosa* bacteraemia in our study may be due to the improvement of the efficacy of appropriate antimicrobial therapy associated with the recovery of susceptibility. Furthermore, we believe that the strict observations of each case could contribute to the better clinical outcomes of resistant gram-negative bacteraemia and all BSI.

The DOTs of third- and fourth-generation antipseudomonal cephalosporins and carbapenems significantly decreased in our study. DOTs have several advantages over the defined daily dose (DDDs). DOTs are not influenced by dose adjustments and can be used independent of age [7]. Furthermore, the evaluation of antimicrobial consumption using DDD can be inaccurate because the approved maintenance dosages of some antimicrobials in Japan have been lower than the DDD defined by the WHO [26]. Previous meta-analyses have evaluated the monitoring of antibiotic use by DDD or cost have proven the efficacy of ASPs [8,9]. Kimura et al. reported that ASPs effectively decreased the DOT of antipseudomonal agents, and this efficacy was maintained during the 7-year study period [14]. The findings of our study are consistent with those of these previous reports. Meanwhile, the DOT of TAZ/PIPC significantly increased in post-ASP period, which may be because TAZ/PIPC was used as an alternative to carbapenems for severe infections and those with long-term antibiotic use. Some studies reported that TAZ/PIPC was not associated with increased 30-day mortality and may result in fewer multi-drug resistant and fungal infections compared with carbapenem [27,28]. In our study, the increase of TAZ/PIPC consumption did not affect the susceptibility of this agent to *P. aeruginosa*. However, the resistance of other pathogens to TAZ/PIPC should be investigated in the future.

In this study, the susceptibilities of antipseudomonal agents were significantly recovered. This may be primarily due to the high accepted rates of the recommendations, such as de-escalation and discontinuation, in all cases of BSI and broad-spectrum antibiotics. Some studies have shown that implementing ASPs resulted in reduced use of broad-spectrum antibiotics and improved susceptibility of Gram-negative bacilli including *P. aeruginosa* [29–31]. Our result was somewhat similar to those of these reports.

P. aeruginosa P. aeruginosa Our study showed that the DOTs of 3rd and 4th cephems and carbapenems significantly decreased and the susceptibilities of these agents were recovered. The DOT reduction by AST activity may have contributed to the recovery of these drug susceptibility rates. However, there was no correlation between the DOTs of TAZ/PIPC and fluoroquinolones and the susceptibilities of these agents. The susceptibility to *P. aeruginosa* is largely influenced by the nosocomial transmission and the introduction from outside the hospital. Thus, the improvement of susceptibility of anti-pseudomonal agents in this study may be affected by the compliance of infectious control measures such as hand hygiene and contact precautions.

The accepted rates of interventions for cases of long-term antimicrobial prescriptions were very high in our study. Fukuda et al. reported that the accepted rate of recommendations on supplemental elements was 38.9–89.6% [32]. However, the mechanism for this difference cannot be determined, although the result may be due to the good communication with prescribers.

This study had some limitations. First, this was a single-centre, retrospective, and observational study. Patient background, isolation frequency, and susceptibility of bacteria vary among hospitals. Thus, selection bias cannot be eliminated. Second, we did not evaluate the cost of antimicrobials, length of stay and resistance rate of other pathogens in this study. Furthermore, we could not perform the severity assessments and background adjustments. Further study that include these data will be necessary and can be used to promote the use of ASPs. Thirdly, we evaluated the clinical outcomes using the in-hospital mortality. The in-hospital mortality rate may not accurately reflect the effectiveness of AS, because it is related to the length of stay in the hospital and underlying diseases other than BSI. It is also necessary to study infection-related mortality in the future. Lastly, guidelines and knowledge of prescribers probably might be improved during the post-ASP period. These may contribute to better clinical outcomes. High-quality studies using standardized surveillance methodology for antimicrobial consumption and similar metrics for outcome measurement are needed.

In conclusion, this study showed that our ASPs, including the intervention for all cases of bacteraemia and long-term use of broad-spectrum antibiotics, could improve clinical outcomes of BSI and the susceptibility of antipseudomonal agents and reduce the DOT of these agents. Furthermore, this effect of our ASP can continue for a long term. Our findings emphasize the importance of close cooperation between multidisciplinary teams and attending physicians in enhancing ASP.

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Transparency declarations

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