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ORIGINAL ARTICLE

Clinical outcome of pharmacist-led prospective audit with intervention and feedback after expansion from patients using specific antibiotics to those using whole injectable antibiotics

Kengo Ohashi[1] · Tomoko Matsuoka[1] · Yasutaka Shinoda[1,2] · Takayuki Mori[1] · Shinya Yoshida[1] · Tomoaki Yoshimura[1,2] · Tadashi Sugiyama[2]

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Abstract

Prospective audit with intervention and feedback (PAF) and preauthorisation of antimicrobials are core strategies for antimicrobial stewardship (AS). PAF participants were expanded from patients using specific antibiotics to those using whole injectable antibiotics to evaluate clinical outcome. From January 2016 to December 2016, PAF was performed in patients using specific antibiotics (period 1) and from January 2017 to December 2017, PAF was performed in patients using whole injectable antibiotics (period 2). PAF was implemented for 5 days every week by pharmacists involved in infectious diseases chemotherapy. In total, 11,571 and 11,103 patients used antibiotic injections during periods 1 and 2, respectively. No significant difference in mortality within 30 days from the initial use of injection antibiotics was observed. The average duration of hospitalisation was significantly shorter during period 2 among patients using antibiotics; however, this was not significantly different from that of patients not receiving antibiotics. The average duration of therapy for intravenous antibiotics was significantly shorter during period 2 than during period 1. The ratio of methicillin-resistant *Staphylococcus aureus* (MRSA) to *S. aureus* was significantly low during period 2. The duration of intravenous antibiotic therapy for *Escherichia coli* bacteraemia during period 2 decreased significantly. De-escalation and appropriate antimicrobial treatment rates at specific doses during period 2 increased significantly. Expansion of patients eligible for PAF from patients using specific antibiotics to patients using whole injectable antibiotics shortened hospital stays, suppressed drug resistance, and promoted the appropriate use of antibiotics.

Keywords Antimicrobial stewardship · Antimicrobial resistance · Prospective audit with intervention and feedback · Pharmacist · Intervention · Japan

Introduction

Antimicrobial resistance (AMR) has become a significant global problem [1]. Unsuitable formulation of antibiotics is closely related to the spread of drug-resistant bacteria [2]; thus, activities encouraging appropriate antibiotic use (antimicrobial stewardship, AS) have been adopted worldwide [3, 4]. The core strategies for AS include prospective audit with intervention and feedback (PAF) and preauthorisation of antimicrobial use [4]. An advantage of PAF is its timely intervention, but it is difficult to secure the time and cost [5]. In Japan, reports on useful evaluations of fragmentary AS that target specific antibiotics used by patients are uncollated [6–9]. Ideally, AS should be conducted for all infectious diseases, and future expansion of patient monitoring is desirable. Currently, there are no studies on the clinical outcome of expanding AS target patients.

In Japan, there is a shortage of infectious disease specialists; however, a few institutions currently practice AS under the initiative of doctors, and pharmacists are expected to lead and practice AS [10]. In January 2012, we initiated PAF (5 days/week) for patients administered carbapenems and anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drugs, leading to appropriate antibiotic usage, reduced mortality rates, and shortened hospital stays

✉ Kengo Ohashi
jamyway.kengo@gmail.com

[1] Department of Pharmacy, Ogaki Municipal Hospital, 4-86 Minaminokawa-cho, Ogaki-city, Gifu 503-8502, Japan

[2] Laboratory of Pharmacy Practice and Social Science, Gifu Pharmaceutical University, Gifu, Japan

[11]. In January 2014, we introduced a personalised infection control support system, which has made the work more efficient and enabled the expansion of number of patients subjected to PAF [12]. To strengthen AS, PAF has been expanded since 2017 by including patients using injections of antibiotics. In the current study, we examined the change in clinical outcome when PAF subjects were expanded from patients using specific antibiotics to those using whole injectable antibiotics to enable further development of AS.

Methods

Study design and setting

A before–after study was conducted at a 903-bed public hospital in Japan (Ogaki Municipal Hospital) to analyse data generated from January 2016 to December 2017. Patient outcomes before and after the expansion of PAF were compared. The periods before expansion (January 2016–December 2016) and after expansion (January 2017–December 2017) were classified as periods 1 and 2, respectively. Pharmacists specialising in infectious diseases implemented the PAF during period 1 including patients using specific antibiotics (anti-MRSA, carbapenem, and broad-spectrum penicillin drugs) and period 2 including those using all-injectable antibiotics (Table 1).

Prospective audit and feedback

Core members of the antimicrobial stewardship team (AST) included doctors, infectious diseases chemotherapy pharmacists, microorganism examination technicians, and nurses certified in infection control. The AST pharmacists conducted PAF among patients who started using injectable antibiotics. This was performed using our infection management support system (BACT Web®) jointly developed with Eiken Chemical Co., Ltd. and customised at our hospital [12]. PAF was started on the first working day following antibiotic injection initiation, was implemented 5 days/week (Monday to Friday), and continued until infection remission or patient discharge from the hospital. The AST pharmacists selected antibiotics based on the pathogenic microorganisms and infected organs and the optimal dose based on renal function; they also considered antibiotic pharmacokinetics/pharmacodynamics (PK/PD), the need for continuing treatment or adding culture testing, and the possibility of de-escalation or switching to oral antibiotics. The pharmacists issued written prescription improvement proposals into the electronic medical record or directly to the doctor or conveyed them by telephone to the doctor. They held bi-weekly discussions, and as a member of the AST, presented cases considered problematic at the AST conference and provided feedback to the attending doctors. Doctors from other hospitals specialising in infectious disease were invited to participate in discussions with our hospital AST.

Outcome

The primary endpoints were 30-day mortality from the initiation of antibiotic injection, duration of hospitalisation, and duration of intravenous antibiotic therapy. Secondary endpoints revealed the rate of drug-resistant bacteria, proportion of long-term cases for intravenous antibiotics, and the proposal number and acceptance rate when transferred from

Table 1 Targeted intravenous antibiotics in the prospective audit and feedback

Class	Antibiotics
Carbapenems*	Meropenem, doripenem, imipenem/cilastatin
Broad-spectrum penicillin*	Piperacillin/tazobactam
Anti-methicillin-resistant *Staphylococcus aureus* agents*	Vancomycin, teicoplanin, arbekacin, linezolid, daptomycin
Penicillins	Benzylpenicillin, ampicillin, piperacillin, sulbactam/ampicillin
First-generation cephems	Cefazolin
Second-generation cephems	Cefotiam, flomoxef, cefmetazole
Third-generation cephems	Cefotaxime, ceftriaxone, ceftazidime, latamoxef, sulbactam/cefoperazone
Fourth-generation cephems	Cefepime, cefozopran
Fluoroquinolones	Levofloxacin, pazufloxacin
Aminoglycosides	Gentamicin, tobramycin, amikacin
Others	Minocycline, azithromycin, clindamycin, fosfomycin, metronidazole, Sulfamethoxazole/trimethoprim

*The only targeted specific antibiotics used during period 1 of the prospective audit and feedback

pharmacists to doctors. Clinical outcomes were compared with those of patients with *Escherichia coli* infection to evaluate appropriate antibiotic use.

The endpoints were retrospectively evaluated using electronic medical records. The hospitalisation period was assessed for all inpatients and patients with and without antibiotics delivered via injection. The therapy duration for intravenous antibiotics began with the administration of antibiotic injections during hospitalisation and was calculated as the days at which antibiotic injections were administered continuously. When treatment resumed more than 3 days post the termination of a treatment, a new treatment period was calculated. The rate of drug-resistant bacteria was calculated based on the performance indicator of the AMR action plan [13] and the ratio of MRSA to total *S. aureus*. Ratio of levofloxacin-resistant *E. coli* to total *E. coli* and that of imipenem-resistant *Pseudomonas aeruginosa* to total *P. aeruginosa* were also calculated. *E. coli* bacteraemia was defined as one or more *E. coli* detected in blood culture. Patient exclusion criteria included non-hospitalisation, multiple bacteraemia, death within 48 h after *E. coli* detection, received palliative care, did not receive antibiotics, and < 18 years of age. For severity and comorbidity evaluations, Pitt bacteraemia score [14] and Charlson comorbidity index [15] were used. To evaluate kidney function, creatinine clearance was calculated using Cockcroft-Gault formula [16]. Based on acquisition modality, infections were classified as community acquired or others (healthcare-related and in-hospital) [17]. The duration of hospitalisation and intravenous antibiotic therapy for patients with *E. coli* bacteraemia were based on the submission date of blood culture specimens. Appropriate antibiotic dosage was evaluated by referring to the JAID/JSC guide for clinical management of infectious diseases 2014 [18].

Statistical analyses

Mann–Whiney *U* test was used to analyse the continuous variables in outcome assessment of patients with *E. coli* bacteraemia. Student's *t* test was used for other continuous variables. Fisher's exact test and log-rank test were used to analyse the category variables and duration of hospitalisation, respectively. In all cases, *P* values < 5% indicated statistical significance. EZR (v 1. 37) software was used for statistical analysis [19].

Results

Patient characteristics before and after expansion of PAF

Patient characteristics before and after PAF subject expansion are shown in Table 2. The mean age was 59.8 ± 24.6 and 61.9 ± 23.9 years during periods 1 and 2, respectively ($P < 0.001$). The number of PAF target patients increased significantly from 973 (8.4%) to 11,103 (100%) from periods 1 to 2 ($P < 0.001$). No significant difference in all-cause mortality was found, including 30-day mortality from the start of antibiotic injection. Based on drug tolerance, the MRSA to total *S. aureus* ratio from periods 1 to 2 decreased significantly from 46.9 to 40.3% ($P = 0.049$).

Inappropriate antibiotic use

The number of prescription improvement proposals (proposal acceptance rate) from pharmacists to doctors was 256 (96%) and 732 cases (90%) during periods 1 and 2, respectively. A breakdown of the proposal contents and acceptance rates is shown in Fig. 1.

Duration of intravenous antibiotic therapy

The mean therapy duration for intravenous antibiotics was 4.74 ± 5.50 and 4.57 ± 5.32 days during periods 1 and 2 ($P = 0.013$), respectively. Injectable antibiotics exceeding 10 days of use were 10.9% and 9.6% during periods 1 and 2, respectively ($P < 0.001$).

Hospital stay duration

Kaplan–Meier plot of hospitalisation is shown in Fig. 2a. The median hospitalisation duration during periods 1 and 2 was 9.0 days (interquartile range 9–9 days), with a significantly shorter period during period 2 ($P < 0.001$). The average hospital stay for patients using injectable antibiotics was significantly shorter ($P < 0.001$) during period 1 (15.4 ± 19.1 days) than that during period 2 (13.9 ± 14.7 days; Fig. 2b). However, no significant difference occurred between periods 1 and 2 in patients not administered antibiotic injections (10.2 ± 11.0 and 10.2 ± 11.4 days, respectively). The duration of stay was significantly shortened from 13.2 ± 16.3 to 12.3 ± 13.5 days ($P < 0.001$) from periods 1 to 2, respectively.

Clinical outcomes in patients with *E. coli* bacteraemia

Among the patients with *E. coli* bacteraemia during the study period ($n = 383$), 55 and 64 cases were excluded during periods 1 and 2, respectively. During period 1, 38 patients were not hospitalised, 9 patients had multiple bacteraemia, 7 died within 48 h after detection of *E. coli* infection, and 1 underwent palliative care. During period 2, 38 patients were not hospitalised, 17 patients had multiple bacteraemia, 5 died within 48 h after detection of *E. coli* infection, and 2 underwent palliative care. During period 2, only 1 patient did not receive antimicrobial drugs and was younger than 18 years. An overview of patients with *E. coli* bacteraemia

Table 2 Overview of injectable antibiotic use in patients before and after the expansion of PAF target patients

	Period 1 ($n = 11,571$)	Period 2 ($n = 11,103$)	P value
Sex (male/female)	6298/5273	6052/5051	0.915
Age, years (SD)	59.8 (24.6)	61.9 (23.9)	< 0.001
PAF target patients	973 (8.4)	11,103 (100)	< 0.001
All-cause mortality	501 (4.3)	481 (4.3)	1.000
30-day mortality from intravenous antibiotics started	395 (3.4)	404 (3.6)	0.368
Detection of resistant bacteria			
Number of MRSA in total *Staphylococcus aureus*	215/458 (46.9)	173/429 (40.3)	0.049
Number of levofloxacin-resistant *E. coli* in total *E. coli*	121/398 (30.4)	147/433 (33.9)	0.298
Number of imipenem-resistant *P. aeruginosa* in total *P. aeruginosa*	13/225 (5.8)	16/209 (7.7)	0.449

Data are expressed as the number of patients (%), unless otherwise indicated

SD standard deviation, *PAF* prospective audit and feedback, *MRSA* methicillin-resistant *Staphylococcus aureus*, *S. aureus Staphylococcus aureus*, *E. coli Escherichia coli*, *P. aeruginosa Pseudomonas aeruginosa*

and their clinical outcomes during periods 1 and 2 is shown in Table 3. The number of patients included in PAF increased significantly from 20 (17%) to 146 (99.3%) from periods 1 to 2 ($P < 0.001$). Prescription improvement proposals from pharmacists to doctors significantly increased from 12 (10.3%) to 36 (24.5%) ($P = 0.004$). The median hospitalisation period from bacteraemia onset in surviving patients decreased from 13 (interquartile range 9–21 days) to 12 (8–18.5) days; however, no significant difference was found ($P = 0.152$). There was no significant difference in all-cause mortality, 30-day mortality, and relapse rates in either group. The total antimicrobial treatment period, including oral antimicrobial drugs, did not differ significantly between the groups; however, the duration of intravenous antibiotic therapy was significantly shortened from 9 (7–12) to 8 (6–10.5) days ($P = 0.036$). The treatment rate at the appropriate antimicrobial dose significantly increased between periods 1 and 2 from 82.9 to 98.0%, respectively ($P < 0.001$). The de-escalation rate increased significantly from 21.4 to 36.1% ($P = 0.010$). The switch rate to oral antimicrobials increased from 33.3 to 44.2%, without a significant difference ($P = 0.077$).

Discussion

The IDSA/SHEA and Japanese guidelines recommend PAF as a core strategy of AS [3, 4]. In our study, the effects of expansion from patients using specific antibiotics to those using whole injectable antibiotics on clinical outcomes of PAF were evaluated.

The number of proposals from pharmacists to doctors increased by 2.9-fold. We previously reported that approximately 75% of proposals were for patients using injectable antibiotics rather than specific antibiotics [20]. Thus, expanding patients requiring monitoring was important. Niwa et al. [21] reported the proposal rate was 3.1% when PAF was conducted once every 2 weeks for patients using whole injectable antibiotics. The proposal rate in the current study was 6.6% during

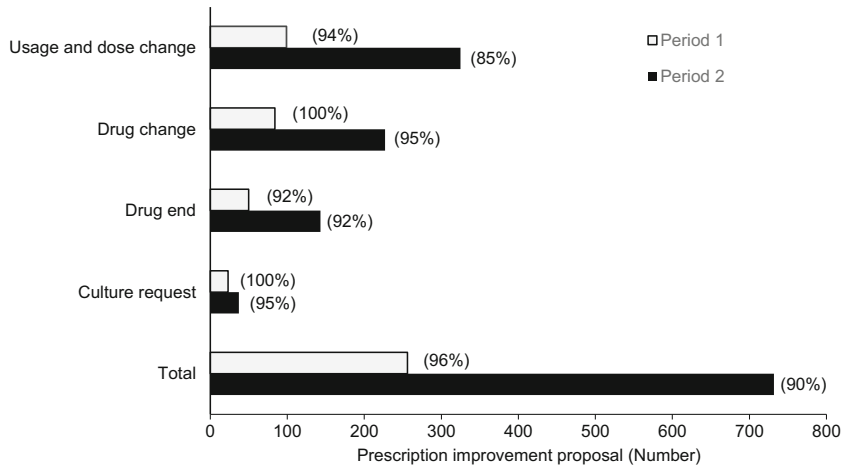

Fig. 1 Contents of the recommendation by pharmacists to prescribers. Percent values indicate the accepted rate by the prescriber

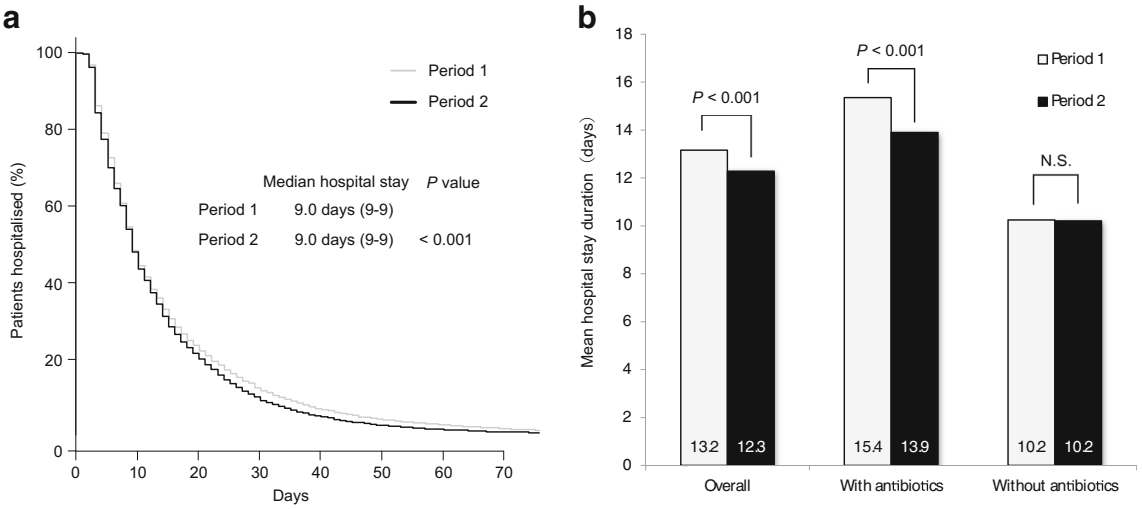

Fig. 2 Kaplan–Meier plot for the duration of hospital stay of patients who received intravenous antibiotics. A Comparison of the duration of hospital stay in patients (**a**) with and without antibiotics and in all patients (**b**) before and after target expansion. The number of patients receiving intravenous antibiotics was 11,571 and 11,103 during periods 1 and 2, respectively, whereas the overall number of patients was 20,293 and 19,711 during periods 1 and 2, respectively. The expansion of PAF target patients significantly shortened the duration of hospital stay (log-rank test). Solid line: the period of expansion of PAF target patients (period 2), grey line: the period targeted only antibiotics with notifications in the PAF (period 1)

period 2, a value higher than that previously reported, corresponding to a more frequent PAF. Therefore, intervening daily at appropriate times is essential. The proposal acceptance rate was almost 90%. In our hospital, the proposal acceptance rate in 2012 when PAF was initiated was 78%; however, the acceptance rate increased with time. This was due to the trusting relationship developed between the doctors and AST pharmacists.

There was no significant difference between all-cause or 30-day mortality rates from the onset of antibiotic injections, because we targeted patients using all-injectable antibiotics, including those with low risk of death. Since the inception of PAF in 2012, we have reported a significant improvement in mortality rate from 28.2% before PAF to 19.9% after inception [11]. We believe that the reduced mortality rate was not detected because the infectious diseases were already controlled in patients at high risk of death.

The duration of intravenous antibiotic therapy was significantly shortened during period 2. Additionally, the proportion of prolonged use of intravenous antibiotics exceeding 10 days significantly decreased because we extended patient monitoring to include pharmacists and proposed switching to oral antimicrobials or discontinuing antimicrobial drugs at appropriate times. We previously reported the median days from antibiotic injections to the proposal of termination as 7 days [20], which is believed to be shorter when treatment exceeds 10 days. A significant shortening in the duration of intravenous antibiotic therapy following a pharmacist-led switch from injectable antibiotics to oral antimicrobial drugs has been reported [22], while only 36% of infectious disease experts recommend short-term antimicrobial treatment [23]. Thus, compared to infectious disease specialists, pharmacists appeared to recommend shorter treatment durations. Therefore, daily PAF by pharmacists may shorten the duration of intravenous antibiotic therapy.

There was no change in the duration of hospital stay for patients without antibiotics, but stays were shortened by 1.5 days in patients using antibiotics. This may be a result of promoting appropriate antibiotic use throughout hospitals, which was achieved by expanding the scope of monitoring to patients using all-injectable antibiotics. Intervention by pharmacists in a randomised control study significantly reduced the hospitalisation period of patients with respiratory infections, from 15.8 to 14.2 days [24]. This subsequently contributed to a significant reduction in medical costs. In addition, a study in a 606-bed university hospital reported that PAF conducted initially and at 2 weeks for patients using all-injectable antibiotics shortened inpatient hospital stays by 1.2 days and reduced medical expenses by 3.9 million dollars [21]. Although our study did not consider medical cost reduction, it may have had a similar effect.

We evaluated drug resistance with reference to the AMR plan. The appropriate use of antibiotics reduces the proportion of MRSA in *S. aureus* infection in the community and hospitals [25]. We found a significant decrease in the proportion of MRSA in *S. aureus* infections. This was considered to be an effect of effective therapeutic intervention based on the bundle of MRSA bacteraemia by our hospital AST [26]. The ASP centred on PAF for 7 years has reduced the proportion of MRSA in *S. aureus* infection with time [8]. The possibility of further decline by continuing ASP is expected in the future. However, to control MRSA, countermeasures against

Table 3 Overview of patients with E. coli bacteraemia before and after expansion of PAF target patients and their clinical outcomes

	Period 1 ($n = 117$)	Period 2 ($n = 147$)	*P* value
Background			
Sex (male/female)	60/57	79/68	0.711
Age, years (IQR)	81 (74–87)	80 (71–86)	0.218
Pitt bacteraemia score (IQR)	2 (1–3)	2 (1–3)	0.700
Charlson comorbidity index (IQR)	2 (1–3)	2 (1–3)	0.491
Haemodialysis	2 (1.7)	6 (4.1)	0.307
Community acquired infection	95 (81.2)	119 (81.0)	1.000
Levofloxacin susceptible	95 (81.2)	121 (82.3)	0.873
Creatinine clearance, mL/min (IQR)	35.2 (19.4–55.3)	38.8 (26.0–59.6)	0.102
Source control	46 (39.3)	58 (39.5)	1.000
Source of bacteraemia			
Unknown origin	5 (4.3)	15 (10.2)	0.100
Respiratory tract	4 (3.4)	1 (0.7)	0.174
Biliary tract	29 (24.8)	40 (27.2)	0.675
Intra-abdominal	6 (5.1)	9 (6.1)	0.795
Kidney and urinary tract	73 (62.4)	81 (55.1)	0.259
Skin and/or soft tissue	0 (0)	1 (0.7)	1.000
Antibiotics (first choice)			
Penicillins	11 (9.4)	13 (8.8)	1.000
First-generation cephalosporins	2 (1.7)	1 (0.7)	0.586
Second-generation cephalosporins	2 (1.7)	9 (6.1)	0.119
Third-generation cephalosporins	80 (68.4)	103 (70.1)	0.789
Fourth-generation cephalosporins	9 (7.7)	7 (4.8)	0.437
Carbapenems	11 (9.4)	13 (8.8)	1.000
Oral quinolones	2 (1.7)	1 (0.7)	0.586
Outcome			
PAF target patients	20 (17)	146 (99.3)	< 0.001
Prescription improvement proposal	12 (10.3)	36 (24.5)	0.004
All-cause mortality	5 (4.3)	9 (6.1)	0.588
30-day mortality from bacteraemia	4 (3.4)	5 (3.4)	1.000
Relapse	2 (1.7)	4 (2.7)	0.696
Length of stay, days,[a] (IQR)	13 (9–21)	12 (8–18.5)	0.152
Total antibiotics treatment duration, days,[a] (IQR)	12 (8–15)	12 (8–15)	0.609
Intravenous antibiotics treatment duration, days,[a] (IQR)	9 (7–12)	8 (6–10.5)	0.036
Appropriate dose adjustment	97 (82.9)	144 (98.0)	< 0.001
De-escalation	25 (21.4)	53 (36.1)	0.010
Switch	39 (33.3)	65 (44.2)	0.077

[a] After bacteraemia, in surviving patients

Data are expressed as the number of patients (%), unless otherwise indicated

E. coli Escherichia coli, *PAF* prospective audit and feedback, *IQR* interquartile range

horizontal infection, such as hand washing, are important. Thus, it is important to promote activities together with the infection control team.

The time taken for PAF per week in our study was 14.5 and 36 h during periods 1 and 2, respectively. The average time spent by a pharmacist per week for AS is 32 h in North America, where AS is advanced [27]. The result of the present study indicated that the time spent on AS was comparable to that of advanced countries. Therefore, implementation of an ideal AS requires an increase in working hours.

In ASP guidelines, de-escalation and switching to oral antibiotics are recommended [4], which require appropriate evaluation of antibiotic use for which there is no fixed method currently. In this study, outcomes in patients with *E. coli*

bacteraemia were evaluated as surrogate endpoints for appropriate use of antibiotics. During period 2, PAF was performed for 99.3% of the patients, except for 1 patient who completed treatment and was treated with oral quinolone. Practicing PAF for almost all cases of bacteraemia could be achieved by using antibiotic injections. The mortality rate remained low at an estimated 4%–6% in both groups. This was probably due to the broad-spectrum antibiotics used in patients with severe diseases, and during period 1, it was possible to support the appropriate infection treatment as a subject of PAF. The median duration of therapy including oral antibiotics was 12 days during both periods 1 and 2. However, the median duration of therapy for intravenous antibiotics was 9 and 8 days during periods 1 and 2, respectively, indicating significant shortening. Although a fixed treatment period does not exist for patients with *E. coli* bacteraemia, Wintenberger et al. [28] recommend a 7-day treatment period for patients with non-complicated *Enterobacteriaceae* bacteraemia. In addition, there is no significant difference in the mortality or relapse rate between short-term (≤ 7 days) and long-term (≥ 8 days) treatment groups for patients with favourable drainage cholangitis and complicated bacteraemia [29]. In contrast, Nelson et al. [30] reported that when short-term treatment (7–10 days) is compared with long-term treatment (> 10 days) for non-complicated gram-negative bacteraemia, the short-term treatment group possessed a significant risk of treatment failure. Antibiotic treatments with good intravenous bioavailability also significantly reduce the risk of failure. In our study, the duration of therapy with intravenous antibiotics was shortened without exacerbating the mortality or relapse rate because AST pharmacists were able to recommend a switch to oral antibiotics at an appropriate time for each patient by PAF. A significant improvement was observed during period 2 in the treatment rate of an appropriate antimicrobial dose. We believe that practicing PAF by pharmacists makes treatment possible at appropriate dosages based on PK/PD. De-escalation of treatment significantly increased during period 2. While there was no significant difference following the switch, an increasing trend was observed. These function as part of the strategy covered in the ASP guidelines and may assure that antimicrobials are properly used. Promoting the appropriate use of antibiotics should improve clinical outcomes, not only in patients with *E. coli* bacteraemia, but also in inpatients as a whole, shortening hospitalisation and treatment durations, and reducing the percent of MRSA infections.

There are some limitations to our study. First, this was a before–after study at a single facility. Therefore, it would be beneficial to collect data from other types of studies such as a randomised control study conducted among multiple facilities. Second, the effect of factors other than PAF contributed to the outcomes observed. In Japan, the momentum to promote appropriate antimicrobial use has recently increased. Our PAF may have also exerted a greater effect than expected.

Conclusions

The expansion of subject samples from patients using specific antibiotics to patients using all-injectable antibacterial drugs for PAF by pharmacists improved clinical outcomes in patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol was approved by the Ethics Committee of Ogaki Municipal Hospital (Approval number: 20180628-2).

Informed consent We disclosed this research and opted out.

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