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Proceeding Paper

Effectiveness of Pharmacist-Led Appropriate Antimicrobial Therapy through the Implementation of Daily Prospective Audit and Feedback and Educational Intervention †

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Abstract: In our hospital, a full-time pharmacist specializing in antimicrobial therapy joined the newly launched antimicrobial stewardship team in May 2018, and started daily monitoring to optimize the use of broad-spectrum antimicrobials. For the medical staff to better understand antimicrobial therapy, the educational lectures were conducted four times after intervention. This study aimed to evaluate the impact of a full-time pharmacist's intervention on antimicrobial stewardship. The effects before (May–December 2017) and after the intervention period (May–December 2018) on antibiotic therapy and clinical outcomes were compared. The rate of blood culture collections before starting broad-spectrum antibiotics significantly increased after intervention (71% vs. 82%, $p < 0.001$), and initially prescribed broad-spectrum antibiotics were significantly de-escalated (55% vs. 78%, $p = 0.004$). A significant reduction in the monthly use of antipseudomonal antibiotics was observed (50.5 vs. 41.8 defined daily doses per 1000 patient-days, $p = 0.01$). The incidence of hospital-acquired *Clostridioides difficile* infection (HA-CDI) significantly decreased after intervention (1.12 vs. 0.54 cases per 10,000 patient-days, $p = 0.033$). The 30-day mortality rate did not change between the two periods (19.4% vs. 17.7%, $p = 0.61$). Our intervention ensured appropriate antimicrobial therapy and reduced the incidence of HA-CDI without worsening the clinical outcomes.

Keywords: antimicrobial stewardship; prospective audit and feedback; blood culture collection; de-escalation therapy

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1. Introduction

Infectious diseases caused by pathogens that have a high level of antimicrobial resistance (AMR), are growing global health threats and lead to prolonged illness and high mortality [1]. Antimicrobial stewardship programs (ASPs) foster appropriate antibiotic use, reduce the prevalence of AMR infections, and improve patient outcomes [2–4]. The Infectious Diseases Society of America (IDSA) guidelines recommend the implementation of ASPs in healthcare facilities [2]. Since 2010, we have conducted a multidisciplinary prospective audit and feedback, referred to as the "Big Gun project" in our hospital [3,5]. Our previous report demonstrated that this project was highly effective in reducing the use of antipseudomonal antibiotics and decreasing the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) [3]. However, even under this project, there had been few changes in the use of antipseudomonal antibiotics and clinical outcomes since 2014 [3].

In April 2018, additional reimbursement for antimicrobial stewardship was introduced as a new medical fee in Japan; therefore, a new antimicrobial stewardship team was established to foster ASPs in our hospital. A full-time pharmacist specializing in antimicrobial therapy joined the team and started daily monitoring to optimize the use of broad-spectrum antimicrobials. The aim of the present study was to evaluate the effects of pharmacist-led interventions on antibiotic use, prevalence of resistant pathogens, and clinical outcomes.

2. Methods

2.1. Study Setting

This study was performed at a 934-bed tertiary care university hospital in Japan. We implemented the daily intervention in May 2018 and started an educational intervention in June 2018 at Kobe University Hospital in Japan. Data on antimicrobial therapy and clinical outcomes were compared before (May–December 2017) and after the intervention period (May–December 2018). We referred to and reanalyzed relevant findings of our previous study [6].

2.2. Daily Intervention to Optimize Antimicrobial Therapy

In this study, we defined broad-spectrum antibiotics as antipseudomonal antibiotics and anti-MRSA agents. The broad-spectrum antibiotics available at our hospital are listed in Table 1. A clinical pharmacist monitored the prescription of broad-spectrum antibiotics on a daily basis and contacted prescribing physicians directly to optimize antibiotic use when at least one inappropriate prescription was found. Antimicrobial prescriptions that did not conform to clinical guidelines [7–10] were deemed inappropriate, e.g., those in which the dosage was not adjusted by considering the renal function, those that did not select antimicrobial agents based on microbiological data, those prescribed even though the duration of antimicrobial therapy was inadequate (with respect to recommendations), those that prescribed broad-spectrum antibiotics for suspected infection without any blood culture collection, and those that were provided despite non-performance of therapeutic drug monitoring for targeted antibiotics.

Table 1. Classification of broad-spectrum antibiotics available at Kobe University Hospital.

Classes	Antibiotics (ATC Codes)
Antipseudomonal agents	
Antipseudomonal penicillins	Piperacillin (J01CA12) and piperacillin/tazobactam (J01CR05)
Antipseudomonal third generation cephalosporins	Ceftazidime (J01DD02)
Antipseudomonal fourth generation cephalosporins	Cefepime (J01DE01) and cefozopran (J01DE03)
Monobactams	Aztreonam (J01DF01)
Carbapenems	Meropenem (J01DH02) and doripenem (J01DH04)
Fluoroquinolones	Ciprofloxacin (J01MA02), levofloxacin (J01MA12), and pazufloxacin (J01MA18)
Aminoglycosides	Amikacin (J01GB06), tobramycin (J01GB01), and gentamicin (J01GB03)
Polymyxins	Colistin (J01XB01)
Anti-MRSA agents	Vancomycin (J01XA01), teicoplanin (J01XA02), daptomycin (J01XX09), and linezolid (J01XX08)

2.3. Educational Intervention for Promoting ASPs

The contents of educational lectures included problems of correlation between antibiotic consumption and AMR bacteria, importance of collecting blood cultures, role of antimicrobial stewardship team, and rational antimicrobial strategies such as appropriate choice of empirical and de-escalated antibiotics. The educational lectures were held for all hospital staff in June 2018, for the representative physicians from each medical department in July 2018, and for the medical staff, including physicians, nurses, and pharmacists, in October and November 2018. In medical departments where blood cultures were not often obtained, we held educational meetings with physicians in September 2018. Finally, we started to share the data on monthly blood culture rates from each department at the monthly conferences attended by representative physicians since September 2018.

2.4. Outcomes

We defined antibiotic de-escalation therapy as the discontinuation of at least one antibiotic of empirical therapy or replacing empirical broad-spectrum antibiotics with narrower-spectrum antibiotics based on positive blood bacterial results. The rates of blood culture collections and de-escalation therapy were calculated based on the number of patients who received broad-spectrum antibiotics, except for those who were administered antibiotics prophylactically or who consulted infectious disease physicians. Hospital antibiotic consumption was expressed as the defined daily dose (DDD) divided by 1000 patient-days on monthly electronic records. The DDD was calculated using the Anatomical Therapeutic Chemical/DDD Index 2020 of the WHO Center and recorded as the median of each period. Hospital-acquired *Clostridioides difficile* infection (HA-CDI) was diagnosed in patients with *C. difficile* toxin production with diarrhea after 72 h of hospitalization. Patients confirmed multiple times were counted once. The incidence of HA-CDI is summarized as cases per 10,000 patient-days. The 30-day mortality among patients with bacteremia was defined as death within 30 days after the onset of bacteremia. In patients with a history of two or more episodes of bacteremia within 14 days, only the first episode was included in the analysis. The following bacterial species were defined as concomitants: *Bacillus* spp., *Corynebacterium* spp., *Propionibacterium* spp., *Micrococcus* spp., Viridans group streptococci, and coagulase-negative staphylococci. If concomitant bacterial species were isolated from at least two different sets of blood drawn on the same day, these cases were defined as positive bacterial results and true bacteremia.

2.5. Statistical Analysis

Non-parametric and categorical variables were analyzed using the Mann–Whitney U-test and chi-squared test, respectively. Statistical significance was set at $p < 0.05$. All parameters were analyzed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

3. Results and Discussion

We intervened and advised physicians to collect blood cultures when there was no culture collection before antibiotic administration; therefore, the rate of blood culture collection before starting broad-spectrum antibiotics significantly increased after the intervention (71% vs. 82%, $p < 0.001$) (Table 2). Blood culture collection is the gold standard to detect bacteremia and, if the results are positive, it becomes one of the reasons for the change to narrower-spectrum antibiotics. Broad-spectrum antibiotics are likely to disrupt normal gut microbiota. In addition, if the resistance develops, no antimicrobials will be available and the risk of infection will increase. Moreover, they are expensive compared to narrower-spectrum antibiotics. De-escalation is a rational therapy to change broad-spectrum antibiotics to narrower-spectrum antibiotics and is commonly used in many hospitals. In our study, initially prescribed broad-spectrum antibiotics were significantly de-escalated after the intervention (55% vs. 78%, $p = 0.004$) (Table 2).

The monthly use of antipseudomonal antibiotics was significantly decreased (50.5 vs. 41.8 defined daily doses per 1000 patient-days, $p = 0.01$) (Table 3). This may be attributed to the fact that empirical broad-spectrum antibiotics were changed to narrower-spectrum antibiotics based on positive blood culture results.

Table 2. Rate of blood culture collections before initial antibiotic treatment and de-escalation therapy.

	Before Intervention	After Intervention	*p*
Blood culture collections before each antibiotic, *n* (%)			
Broad-spectrum antibiotics (Antipseudomonal agents and anti-MRSA agents)	562/792 (71)	578/707 (82)	<0.001
Antipseudomonal agents	539/758 (71)	563/681 (83)	<0.001
Anti-MRSA agents	76/95 (80)	66/83 (80)	1
Antimicrobial de-escalation therapy, *n* (%)			
Broad-spectrum antibiotics (Antipseudomonal agents and anti-MRSA agents)	36/66 (55)	67/86 (78)	0.004
Antipseudomonal agents	33/61 (54)	62/81 (77)	0.008
Anti-MRSA agents	7/12 (58)	16/16 (100)	0.019

Table 3. Defined Daily Dose (DDD) of antibiotics per 1000 patient-days, median (IQR).

	Before Intervention	After Intervention	*p*
Broad-spectrum antibiotics (Antipseudomonal agents and anti-MRSA agents)	68.9 (65.7–77.7)	65.2 (54.2–66.1)	0.11
Antipseudomonal agents	50.5 (47.5–55.4)	41.8 (37.0–45.8)	0.01
Anti-MRSA agents	19.4 (17.3–21.5)	20.3 (17.7–22.4)	0.88

C. difficile is a leading pathogen that causes life-threatening infectious diarrhea in hospitals. Restriction of the use of antipseudomonal agents, associated with a high risk of CDI, leads to a reduction in CDI in hospitalized patients [11,12]. The IDSA guidelines recommend implementing interventions designed to reduce the prescription of antibiotics [2]. A recent systematic literature review reported that the prevalence of CDI in Japan was 0.8–4.7 cases/10,000 patient-days [13], which was lower than that reported in Europe or the United States [14–16]. The incidence of HA-CDI in our hospital before intervention was low compared to these previous reports, and we found a further reduction after the implementation of our intervention (1.12% vs. 0.54 cases per 10,000 patient-days, $p = 0.033$) (Figure 1a).

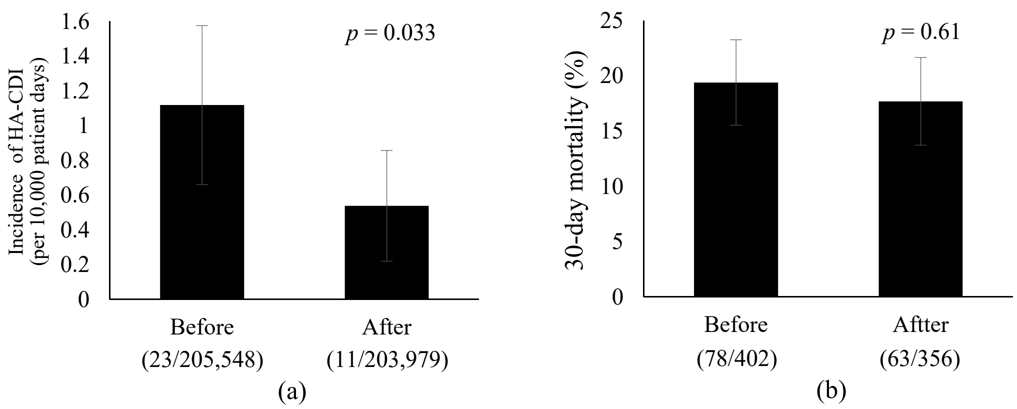

Figure 1. Clinical outcomes before and after the interventions. Error bars represent 95% confidence intervals. (**a**) The incidence of HA-CDI per 10,000 patient-days. HA-CDI, hospital-acquired *Clostridioides difficile* infection. (**b**) 30-day mortality due to bacteremia.

The 30-day mortality showed no significant changes before and after the intervention (19.4% vs. 17.7%, $p = 0.61$) (Figure 1b). This may suggest that our intervention did not have any detrimental effects on clinical outcomes.

Educational lectures on antimicrobial stewardship promote optimized antibiotic use or reduce the prevalence of AMR pathogens as a complement to ASPs [2,17]. In this study, the educational lectures consisted of clinical practices, such as rationalizing blood culture collections and antibiotic choices. In our hospital, nurses obtain blood cultures specifically under the direction of doctors, and pharmacists advise doctors regarding antimicrobial treatment. Therefore, we held educational lectures not only for doctors but also for other medical staff. Physicians need to collaborate with various professionals to practice the best clinical management of patients with infectious diseases.

4. Conclusions

Our findings show that daily and educational interventions to perform accurate diagnosis and clinical management are effective in optimizing antibiotic usage and reducing the incidence of HA-CDI without worsening clinical outcomes.

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