Influence of Change of Full-Time Equivalents on Post-prescription Review with Feedback Interventions in an Antimicrobial Stewardship

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Received October 6, 2021, accepted November 23, 2021

Few studies have investigated the influence of more full-time equivalents (FTEs) of infectious disease (ID) pharmacists on the likelihood of a post-prescription review with feedback (PPRF) intervention. This study focused on this in community hospitals before and after the Japanese medical reimbursement system was revised to introduce antimicrobial stewardship (AS) fees. We collected data for two periods: before (April 2017 to March 2018) and after (April 2018 to March 2019) AS fee implementation. The efficacy of the PPRF by the ID pharmacist was assessed based on the usage of broad-spectrum antimicrobials in days of therapy (DOT) per 100 patient-days. Further, we generated the susceptibility rate for antimicrobial-resistant organisms. The number of PPRF drugs was 2336 (2596 cases) before AS fee implementation and 2136 (1912 cases) after implementation. The overall monthly FTE for AS for an ID pharmacist increased from [median (interquartile range; IQR)] 0.34 (0.33–0.36) to 0.63 (0.61–0.63) after AS fee implementation. The DOT of broad-spectrum antibiotics decreased from 10.46 (9.61–12.48) to 8.68 (8.14–9.18). The DOT of carbapenems and quinolones decreased significantly from 4.11 (3.69–4.41) to 3.07 (2.79–3.22) and 0.96 (0.61–1.14) to 0.37 (0.19–0.46), respectively (p < 0.05). Furthermore, the rate of levofloxacin (LVFX)-susceptible Pseudomonas (P.) aeruginosa improved from 71.5 to 84.8% (p < 0.01). We observed that increasing the FTE of ID pharmacists influences the DOTs of broad-spectrum antibiotics; a higher FTE contributes to fewer DOTs. Further, the susceptibility of P. aeruginosa to meropenem and LVFX increased as the FTE increased.

Key words full-time equivalent; pharmacist; infectious disease; antimicrobial resistance

INTRODUCTION

Antimicrobial stewardship (AS) may improve patient outcomes and safety and decrease antimicrobial resistance, costs, and the length of hospital stay.1-2) The core elements of hospital AS programs are hospital leadership, accountability, pharmacy expertise, action, tracking, reporting, and education. The “action” element contains implementation interventions to improve antibiotic use, such as prospective audit and feedback (PAF) or preauthorization.3) Few Japanese hospitals conduct preauthorization, owing to a lack of infectious disease (ID) physicians and pharmacists. However, post-prescription review with feedback (PPRF) is an effective AS method that is comparable with preauthorization.3,4) In Japan, ID pharmacists mainly use PAF or PPRF for broad-spectrum antibiotics,4,5) but are unable to take enough full-time equivalents (FTEs) for AS. For enhancement of AS, the Japanese Society of Chemotherapy recommends FTEs of ID physicians and pharmacists by bed size.5) On the other hand, Maeda et al. reported a large gap between pharmacists’ existing FTEs for AS (0.0 to 0.4 FTE) and the ideal FTE (0.3 to 1.0 FTE).6,9)

In 2018, the Japanese medical reimbursement system was revised to introduce fees for AS. The revised system needs to spend the time for AS (FTE ≥0.5) as physicians, pharmacists, nurses, and medical technologists. In a nationwide survey conducted after the revision of the system, institutes with an AS fee had higher FTEs than those without.9,10) However, few studies have investigated the influence of FTE for ID pharmacists on the likelihood of a PPRF intervention. This study aimed to elucidate these influences in community hospitals.

MATERIALS AND METHODS

Settings This study was approved by the ethics committee of Tosei General Hospital (Approval No. 903). This study was conducted between April 2017 and March 2019 at Tosei General Hospital (a 633-bed hospital). Figure 1 outlines our AS program, beginning with the establishment of an AS team. ID pharmacists started PPRF the weekday after the first administration of broad-spectrum antibiotics using seven checklist items: (1) the target infection organisms, (2) the purpose of use, (3) appropriate culture tests, (4) appropriate use based on the culture test, (5) appropriate dosage, (6) appropriate antibiotic optimization (including de-escalation), and (7) appropriate antibiotic administration period with a comprehensive assessment of the patient’s clinical condition. The broad-spectrum antibiotics comprised carbapenems (e.g., meropenem [MEPM], doripenem, imipenem/cilastatin, and biapenem), tazobactam/piperacillin (TAZ/PIPC), cefozolane/tazobactam, anti-methicillin-resistant Staphylococcus aureus (MRSA) drugs (e.g., injectable vancomycin, teicoplanin, injectable and oral linezolid, and daptomycin), injectable fluoroquinolones, oral vancomycin (for Clostridioides difficile infection), and colistin. If the ID pharmacist identified any intervention points related to the checklist items, they then were addressed to the attending
physician directly or via a conference with ID physicians. Before the period fees were charged for AS (April 2017 to March 2018), the items could only be checked in the afternoon; however, in the period after that (April 2018 to March 2019), the items could be checked in the morning and in the afternoon.

Follow-up of the intervention cases was performed immediately after the intervention to until two weekdays after antibacterial therapy discontinuation, as necessary.

Data Collection We collected data on the chance of a PPRF intervention, the FTE of the ID pharmacist performing the AS, antimicrobial usage, patient-related outcomes, and inpatient antimicrobial resistance for two periods: before and after the AS fee was implemented. During both periods, there was no change in AS activity. The efficacy of the PPRF by the ID pharmacist was assessed based on the broad antimicrobial usage (expressed as days of therapy (DOT) per 100 patient-days), monthly average length of stay (LOS), and 30-d in-hospital mortality rate of patients administered broad-spectrum antibiotics. Further, we generated the susceptibility rate following the guidelines of the clinical and laboratory standards institute (M100 S-22) for antimicrobial-resistant organisms, including Escherichia coli, Enterobacter cloacae, Pseudomonas aeruginosa, and Staphylococcus aureus. The aggregation method was based on the antibiogram guidelines of the Infectious Disease Education Consortium, Japan. To confirm the need to use an alternative broad-spectrum antibiotic, we assessed the usage rate of ceftazidime (CAZ) and cefepime (CFPM) (expressed in DOT) and the susceptibility rate for Pseudomonas aeruginosa of those drugs. We also compared the PPRF intervention and antibiotic dose optimization, changed drugs (e.g., de-escalation, escalation, or other spectrum antibiotics), stopped antibiotics, requested additional examinations (e.g., blood and culture tests and imaging examinations), and added antibiotics before and after the AS fee implementation.

Statistical Analyses Qualitative and stratified continuous variables were compared using Fisher’s exact test or Pearson’s $\chi^2$ test. Continuous variables were compared using the Mann–Whitney U test. The predictive values are presented as odds ratios (ORs) with respective 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$. All analyses were performed using IBM SPSS Statistics version 25 (IBM, Armonk, NY, U.S.A.).
RESULTS

The number of PPRF drugs was 2596 (2336 cases) before the AS fee implementation and 2136 (1912 cases) after the implementation. Before the implementation, the PPRF drug types were TAZ/PIPC (922, 35.6%), carbapenems (942, 36.3%), quinolones (346, 13.3%), anti-MRSA drugs (331, 12.7%), and others (55, 2.1%). After the implementation, they were TAZ/PIPC (897, 42.0%), carbapenems (662, 31.0%), quinolones (232, 10.9%), anti-MRSA drugs (298, 14.0%), and others (47, 2.2%).

Figure 2 shows the overall FTEs of the ID pharmacists for the broad-spectrum AS and DOT. The overall monthly FTEs [median (interquartile range)] increased after AS fee implementation from 0.34 (0.33–0.37) to 0.63 (0.61–0.63). The DOT of the broad-spectrum antibiotics decreased from 10.46 (9.61–12.48) to 8.68 (8.14–9.18).

Figure 3 presents the DOT of the broad-spectrum antibiotics before and after AS fee implementation. The DOT [median (IQR)] of carbapenems and quinolones decreased significantly from 4.11 (3.69–4.41) to 3.07 (2.79–3.22) and 0.96 (0.61–1.14) to 0.37 (0.19–0.46), respectively (p < 0.05). On the other hand, the DOT of TAZ/PIPC [from 4.51 (3.81–4.96) to 4.14 (3.78–4.61)], anti-MRSA drugs [1.44 (1.24–1.49) to 1.19 (0.97–1.38)], CAZ [0.12 (0.07–0.17) to 0.19 (0.10–0.27), and CFPM [1.84 (1.67–1.95) to 2.02 (1.73–2.35)] did not decrease significantly.

Table 1 shows the PPRF suggestions regarding antibiotic therapy. The rates of all suggestions and acceptable suggestions significantly increased from 8.4 to 22.1% and 7.6 to 19.6%, respectively (p < 0.01). The number of acceptable suggestions regarding antibiotic optimization and discontinuation increased from 52/3196 (1.6%) to 190/2136 (8.9%) and 36/3196 (1.1%) to 109/2136 (5.1%), respectively (p < 0.01).

Table 2 shows the differences in the LOS and 30-d in-hospital mortality rate of patients administered broad-spectrum antibiotics and the susceptibility rate of the “before” and “after” periods. The LOS and 30-d in-hospital mortality rate did not decrease after the AS fee implementation. The susceptibility rate demonstrated that the rate of MEPM-susceptible P. aeruginosa improved from 79.3 to 89.8% (p < 0.01). Furthermore, the rate of levofloxacin (LVFX)-susceptible P. aeruginosa improved from 71.5 to 84.8% (p < 0.01). In contrast, the rate of LVFX-susceptible E. coli decreased from 72.0 to 67.5% (p < 0.05).

DISCUSSION

The broad-spectrum antibiotic DOTs targeted by PPRF significantly decreased, and the susceptibility of P. aeruginosa to MEPM and LVFX increased after implementing the AS fee. In Japan, a nationwide survey of AS programs reported a large gap between existing (0–0.4) and required (0.3–1.0) FTEs for pharmacists. However, few reports have investigated the FTEs of pharmacists and outcome measures. In our institute, the FTE of ID pharmacists rose from 0.34 to 0.63 (median), and the DOTs of broad-spectrum antibiotics

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Table 1. Post-prescription Review with Feedback Suggestions for Antibiotic Therapy

| Suggestion                              | Before (n = 2596) | After (n = 2136) | p-Value |
|-----------------------------------------|------------------|-----------------|---------|
| All suggestions, n (%)                  | 239 (9.2)        | 472 (22.1)      | <0.01*  |
| Accepted suggestions, n (%)             | 218 (8.4)        | 418 (19.6)      | <0.01*  |
| Ratio of accepted suggestions           | 91.2%            | 88.6%           | 0.28*   |
| Breakdown of suggestions, accepted/all (%) |
| Dose optimization                       | 131/145 (90.3)   | 80/93 (86.0)    | 0.31*   |
| Change drugs                            | 42/46 (91.3)     | 190/212 (89.6)  | 0.73*   |
| De-escalation                           | 33/35            | 173/195         |         |
| Escalation                              | 2/3              | 3/3             |         |
| Other spectrum antibiotics              | 7/8              | 14/14           |         |
| Antibiotics stopped                     | 29/30 (96.7)     | 109/118 (92.4)  | 0.40*   |
| Add examinations                        | 13/15 (86.7)     | 29/36 (80.6)    | 0.60*   |
| Add antibiotics                         | 3/3 (100.0)      | 10/11 (91.0)    | 1.00**  |

* Pearson’s χ² test. ** Fisher’s exact test.
Our data showed that the LOS and 30-d in-hospital mortality* increased mortality. One report indicated that S. aureus antibiotic use for certain bloodstream infections and interventions.

0.34–0.37) before the AS fee was implemented to suggest AS. As such, in large hospital (period, we intervened more frequently with enough time missed the time to suggest AS, but in the after-intervention tests. Thus, in the before-intervention period, we may have observation of the patient's clinical course and cultivation changes or stop antibiotics must be made after detailed consideration for dose optimization in the “before” period. Suggestions to change or stop antibiotics must be made after detailed observation of the patient’s clinical course and cultivation tests. Thus, in the before-intervention period, we may have missed the time to suggest AS, but in the after-intervention period, we intervened more frequently with enough time to suggest AS. As such, in large hospital (>500 beds) settings, pharmacists did not have enough FTEs (approximately 0.34–0.37) before the AS fee was implemented to suggest interventions.

Regarding the mortality rate, interventions that optimized antibiotic use for certain bloodstream infections and S. aureus bacteremia improved mortality. One report indicated that pharmacist interventions reduced LOS, but interventions that reduced unnecessary prescriptions only slightly reduced LOS. Our data showed that the LOS and 30-d in-hospital mortality decreased, but the difference was statistically insignificant. In particular, a higher FTE for AS led to the de-escalation and stop of antibiotics, explaining why our intervention did not affect LOS or reduce the use of inappropriate broad-spectrum antimicrobials. Another explanation for this result could be that since 2012, we have used AS interventions for all cases of long-term antibiotic use (over 14 d) and since 2016 for all cases of bloodstream infections. Therefore, the FTE did not affect the LOS or 30-d in-hospital mortality.

Our intervention decreased the broad-spectrum antibiotic DOTs, especially for carbapenems and quinolones. The MEPM and LVFX susceptibilities of P. aeruginosa improved. There were no changes in the DOTs of CAZ and CFPM and the susceptibilities of P. aeruginosa. Increasing the FTE may affect the chance of intervening to achieve better outcomes, to reduce inappropriate antimicrobial use, and to increase the susceptibility rate of bacteria.

The development and spread of antibiotic resistance are multi-faceted, with studies assessing the impact of better antibiotic use on resistance rates reporting controversial results. Previous Japanese reports indicated that broad antibiotic consumption was significantly associated with the incidence of P. aeruginosa resistance to MEPM. However, institutes with a good susceptibility rate of P. aeruginosa to carbapenems (>90%) before a PPRF intervention did not observe an improvement after the intervention, despite the reduction of the broad-spectrum antimicrobial consumption. In comparison, our hospital observed a low susceptibility rate of P. aeruginosa to MEPM before PPRF interventions (79.3%) and a reduced DOT of MEPM, which might improve the susceptibility rate of P. aeruginosa to MEPM.

The resistance of P. aeruginosa to fluoroquinolones correlates with the consumption of all antibiotics and LVFX. Furthermore, there is a significant relationship between the percentage of fluoroquinolone-resistant E. coli and LVFX consumption. Our intervention reduced the DOT of LVFX and the incidence of LVFX-resistant P. aeruginosa. However, the incidence of LVFX-resistant E. coli increased after implementing the AS fee. In recent years, some reports have indicated that prescribing fluoroquinolones induces resistance to E. coli. Terahara and Nishiura reported a positive correlation between fluoroquinolone consumption, including inpatient and outpatient settings, and LVFX resistance. Hence, improving the incidence of E. coli resistance to LVFX is difficult using only inpatient AS interventions; outpatient AS interventions are also necessary.

There are some limitations to our study. First, this was a single center, retrospective study conducted at a municipal hospital in Japan. Additional long-term prospective studies in multiple institutions are required. Second, this AS program was implemented as a part of a hospital quality improvement initiative, not for clinical research. Thus, we could not remove various cofactors, such as the quality of infection control and prevention, other clinical research activities, and staff turn-

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### Table 2. Outcome Measures before and after Implementing the AS Fee, Which Increased the Full-Time Equivalent of Pharmacists

| Outcome Measure               | Before                        | After                         | p-Value   |
|-------------------------------|-------------------------------|-------------------------------|-----------|
| **LOS** (d)                   | 26 (13–44)                   | 25 (13–46)                   | 0.80      |
| 30-Day in-hospital mortality* (%) | 8.7 (203/2336)              | 7.9 (152/1912)               | 0.97      |
| **Susceptibility rate (%)**   |                               |                               |           |
| Escherichia coli              | (Ratio of ESBL)              |                               |           |
| MEPM                          | 18.5 (195/1054)              | 22.5 (206/760)               | <0.01     |
| TAZ/PIPC                      | 99.8 (1052/1054)             | 100.0 (760/760)              | 0.51      |
| LVFX                          | 98.8 (1041/1054)             | 99.2 (754/760)               | 0.49      |
| Enterobacter cloacae          | (Ratio of MDR)               |                               |           |
| MEPM                          | 72.0 (759/1054)              | 67.5 (513/760)               | <0.05     |
| TAZ/PIPC                      | 98.8 (162/165)               | 99.2 (123/124)               | 0.64      |
| LVFX                          | 92.7 (153/165)               | 88.7 (110/124)               | 0.30      |
| Pseudomonas aeruginosa        | (Ratio of MRSA)              |                               |           |
| MEPM                          | 79.3 (298/376)               | 89.8 (290/323)               | <0.01     |
| TAZ/PIPC                      | 88.0 (331/376)               | 90.4 (292/323)               | 0.33      |
| CAZ                           | 88.8 (334/376)               | 91.0 (294/323)               | 0.38      |
| CFPM                          | 90.2 (339/376)               | 90.4 (292/323)               | 0.91      |
| LVFX                          | 71.5 (269/376)               | 84.8 (274/323)               | <0.01     |
| Staphylococcus aureus         | (Ratio of MRSA)              |                               | 0.25      |
| MEPM                          | 48.4 (434/897)               | 51.3 (376/733)               |           |

* Patients administered broad-spectrum antibiotics. ESBL, extended-spectrum beta-lactamase; LOS, length of stay; MEPM, meropenem; TAZ/PIPC, tazobactam/piperacillin; LVFX, levofloxacin; CAZ, ceftazidime; CFPM, cefepime; MRSA, methicillin-resistant Staphylococcus aureus.
over. Moreover, ID physicians may influence AS outcomes; we did not investigate the FTEs of ID physicians in our study. Third, we observed a change in the susceptibility rate and antimicrobial consumption after the AS fee was implemented, but a time-series analysis was not performed. However, stewardship beyond six months was associated with changes in the susceptibility rate. As such, we consider that we analyzed this data appropriately over a one-year period.

In conclusion, we identified that increasing the FTE of ID pharmacists influences the DOTs of broad-spectrum antibiotics; a higher FTE contributes to fewer DOTs. Further, the susceptibility of *P. aeruginosa* to MEPM and LVFX increased as the FTE increased. Thus, increasing the chances for ID pharmacists to intervene has good AS outcomes.

**Acknowledgments** We are grateful to all the clinicians at Tosei General Hospital.

**Conflict of Interest** The authors declare no conflict of interest.

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