Improvement of antibiotics susceptibility of *Escherichia coli* in a tertiary hospital in Japan

ABSTRACT

Antimicrobial stewardship team (AST) and Infection Control Team (ICT) have recently been linked Infectious diseases (ID) physicians, and implemented in clinical settings in Japan. The microbiological effects of an AST and ICT, in addition to Diagnostic stewardship team (DST) supported by ID physicians in our tertiary hospital were shown in significant reduction of antibiotic resistance of *Escherichia coli* (*E coli*) including extended spectrum beta-lactamases (ESBL)-producing *E coli*

Key words: Antimicrobial stewardship team (AST), Diagnostic stewardship team (DST), Infection Control Team (ICT), Infectious diseases (ID) physicians, *Escherichia coli*, extended spectrum beta-lactamases (ESBL)

SHORT REPORT

Antimicrobial stewardship (AS) has been defined as an activity that includes appropriate selection, dosing, route, and duration of antimicrobial therapy [1, 2].

The benefits of AS are improved patient outcomes, reduced-frequency adverse events, improved rates of antibiotic susceptibility to targeted antibiotics, and optimization of resource utilization across the continuum of care. The Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS) have strongly suggested that AS program (ASP) are best led by infectious disease physicians with additional stewardship training [1, 2].

In addition to Infection Control Teams (ICT), interdisciplinary AS teams (AST), comprising infectious disease physicians, pharmacists, nurses, and microbiological technicians who recently contributed Diagnostic stewardship (DS), have begun to be organized at university and/or tertiary hospitals in Japan, and the efficacy of the resulting interventions in preventing inappropriate antibiotic use have been reported for Japanese AST and its related staffs [3-6].

In our hospital, a 650-bed tertiary-care university hospital in the city of Sendai in Japan, all adult patients who were (a) hospitalized at our facility from 2015 to 2018, (b) received antibiotic therapy, and (c) for whom an intervention was recommended by our ICT/AST in addition to diagnostic stewardship team (DST) and Infectious diseases (ID) physicians, were eligible for enrollment in this analysis.

The roles of the these infection staffs and clinical microbiological laboratory included a review of antimicrobial orders with respect to the usage, dose, isolated pathogens, and sites of infection for all inpatients receiving parenteral antibiotics, and consultation with physicians before the prescription of antibiotics. Cases receiving carbapenems, anti-pseudomonad penicillins, fluoroquinolones, 4^{th}-generation cefems, and anti-Methicillin resistant *Staphylococcus aureus* (MRSA) agents were specifically reviewed. When an inappropriate use of antibiotics was found, infection members made immediate contact with the prescriber over the telephone, via report papers, and/or via electronic messaging on the computer order system. Usually, total 50-100 patients were monitored, and finally a half of them were intervened in each month by our infection staffs and reported to clinical microbiological laboratory.

As the results, antibiotic susceptibility of *Escherichia coli* were significantly improved, especially, resistant *E coli* for penicillin including ampicillin/sulbactam, cefazolin, and levofloxacin were significantly decreased (Figure 1).Furthermore, the rates of extended spectrum beta-lactamases (ESBL)-producing *E coli* among all isolated *E coli* were also reduced (Figure 2).

The occurrences of drug-resistant strains including ESBL- producing *E coli* and related infectious diseases were big issues in Japan[7]. The nationwide surveillance showed that susceptibility rates of *E. coli* were decreased to 38% for ampicillin/sulbactam, 82% for cefazolin, and 92 % for PIPC/TAZ although they were 96% for cefoxitin, and 100 % for ertapenem. Ampicillin/sulbactam are not acceptable especially for intra-abdominal infection (IAI) and urinary tract infection (UTI) , sometimes in pneumonia and blood stream infections (BSI) treatments, and cefozolin should be used for these infections with caution empirically because we have to consider *E coli* as an one of the important pathogens of these infectious diseases. PIPC/TAZ may have the possible of treatment failure in *E coli* treatment in Japan. Therefore, antimicrobial and diagnostic stewardship interventions should work synergistically to decrease ordering of bacterial cultures without clear indication and prevent excessive antimicrobial administration in patients without clearly defined these

infectious diseases.

To solve these issues, the infection staffs and clinical microbiological laboratory intervention for pneumonia has been recently reported to yield a significant decrease (from a median of 10 to 7 days) in the duration of antibiotic therapy, and also result in more frequently narrowing of antibiotic spectrum or modification on the basis of susceptibility results [8]. Maeda et al. showed that an AST intervention approach decreases the use of inappropriate therapy and may improve clinical outcomes in blood stream infection (BSI) patients, and previous other studies have reported that clinical intervention by infectious disease specialists also reduces mortality, length of stay (LOS), and medical costs [4, 9, 10]. These results indicate that the infection staffs and clinical microbiological laboratory interventions can decrease inappropriate therapy and also potentially improve clinical and economic outcomes in severe infectious disease, including IAI, UTI, pneumonia, and BSI by *E coli*.

Therefore, a multidisciplinary infection staffs, including microbiologists, is very important for successful interventions and improving drug susceptibility of the pathogenic bacteria, including *Pseudomonas aeruginosa* as we previously reported [4, 11, 12]. Our team could decreased significant resistant rates of *P aeruginosa* in our hospital by the synergistically collaborations. Recommendations regarding appropriate

91 therapies require a broad knowledge of infectious diseases. Interdisciplinary teams that
92 are able to facilitate discussion among specialists from various relevant occupational
93 fields may be lead to successful implementation by the infection staffs and the clinical
94 microbiological laboratory.

***COI**: None*

REFERENCES

1. Dellit TH, Owens R., McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP et al, Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis, 2007. 44: 159-77.

2. Barlam TF, Cosgrove S, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al., Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis., 2016. 62: e51-77

3. Niwa T, S.Y., Suzuki A, Ohmori T, Yasuda M, Ohta H, Fukao A, Kitaichi K, Matsuura K, Sugiyama T, Murakami N, Itoh Y., *Outcome measurement of extensive implementation of antimicrobial stewardship in patients receiving intravenous antibiotics in a Japanese university hospital.* Int J Clin Pract. , 2012. **66**: p. 999-1008.

4. Maeda M, Takuma T., Seki H, Ugajin K, Naito Y, Yoshikawa M, et al, Effect of interventions by an antimicrobial stewardship team on clinical course and economic outcome in patients with bloodstream infection. J Infect Chemother., 2016. 22: 90-95

5. Tagashira Y, Horiuchi.M, Tokuda Y, Heist BS, Higuchi M, Honda H., Antimicrobial stewardship for carbapenem use at a Japanese tertiary care center: An interrupted time series analysis on the impact of infectious disease consultation, prospective audit, and feedback. Am J Infect Control. , 2016. 44: 708-710.

6. Patel R, Fang.F., Diagnostic Stewardship: Opportunity for a Laboratory-Infectious Diseases Partnership. Clin Infect Dis. 2018. 67: 799-801.

7. Takesue Y, Kusachi S., Mikamo H, Sato J, Watanabe A, Kiyota H, et al., Antimicrobial susceptibility of common pathogens isolated from postoperative intra-abdominal infections in Japan. J Infect Chemother. , 2018. 24: 330-340.

8. Avdic E, Cushinotto L., Hughes AH, Hansen AR, Efird LE, Bartlett JG, et al, Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. Clin Infect Dis. , 2012. 54: 1581-7.

9. Schmitt S, McQuillen.D., Nahass R, Martinelli L, Rubin M, Schwebke K, et al , Infectious diseases specialty intervention is associated with decreased mortality and lower healthcare costs. Clin Infect Dis. , 2014. 58: 22-28.

10. Huang AM, Newton.D., Kunapuli A, Gandhi TN, Washer LL, Isip J, et al, Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. Clin Infect Dis., 2013. 57: 1237-45.

11. Briceland LL, Nightingale C., Quintiliani R, Cooper BW, Smith KS., Antibiotic streamlining from combination therapy to monotherapy utilizing an interdisciplinary approach. Arch Intern Med., 1988. 148: 2019-22.

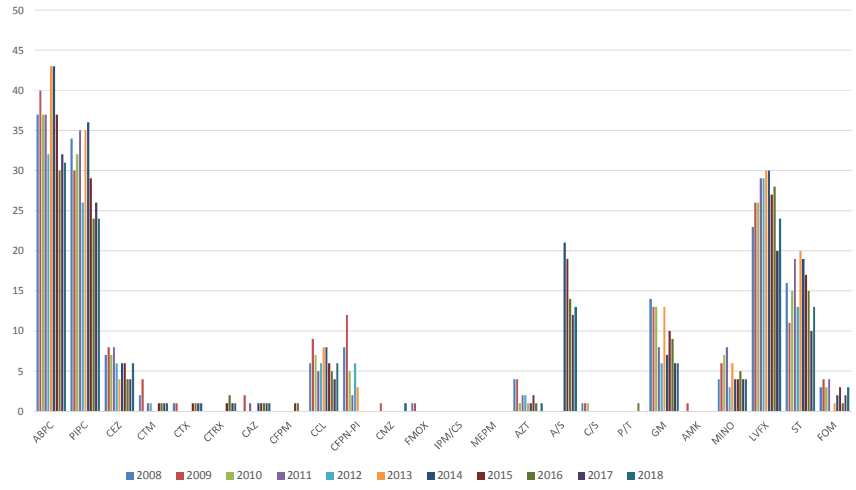
12. Seki M, Watanabe Y, Microbiological improvement by antimicrobial stewardship program and infection control in Japan, J Prev Infect Control 3, 1-2, 2017 DOI: 10.21767/2471-9668.100034

FIGURE LEGENDS

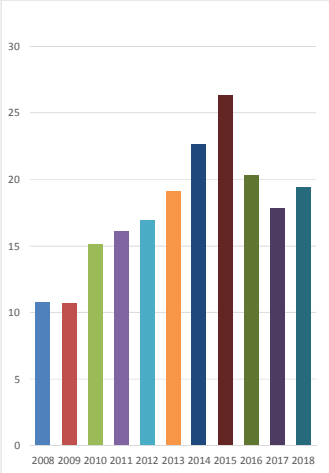
Figure 1: Antibiotics resistant rates of *Escherichia coli* were decreased year by year from 2008-2018.

Figure 2: The rates of extended spectrum beta-lactamases (ESBL)-producing type among all isolated *Escherichia coli* were decreased year by year from 2008-2018.

(Figure 1)



(Figure 2)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