Infect Dis Ther (2015) 4:213–218
DOI 10.1007/s40121-015-0066-x

BRIEF REPORT

Antibiotic Susceptibilities of *Pseudomonas aeruginosa* Isolated from Blood Samples and Antibiotic Utilization in a University Hospital in Japan

Ito Kato · Fumie Fujimoto · Yoshimi Higurashi · Ryo Yamaguchi · Kazuo Takayama · Masashi Suzuki · Shu Okugawa · Mitsuhiro Okazaki · Kyoji Moriya

To view enhanced content go to www.infectiousdiseases-open.com
Received: April 10, 2015 / Published online: May 20, 2015

ABSTRACT

Introduction: *Pseudomonas aeruginosa* is one of the most important causes of nosocomial infection. Several reports indicated a correlation of antimicrobial usages and declined susceptibilities. In this report, we evaluated their relation in a tertiary care teaching hospital in Tokyo, Japan for 4 years.

Methods: We evaluated the susceptibilities of 149 strains of *P. aeruginosa* isolated from blood samples and consumption of anti-pseudomonal antibiotics as antimicrobial use density from 2009 to 2012 in the University of Tokyo Hospital in Tokyo, Japan.

Results: Usages of carbapenems and anti-pseudomonal cephalosporins decreased 44% and 31% from 2009 to 2011, and then increased 30% and 24% in 2012, respectively. Usage of piperacillin–tazobactam increased 87% from 2009 to 2012, which was introduced in the hospital in 2008. Consumption of fluoroquinolones and aminoglycoside remained low in those years. Susceptibilities to cephalosporins, carbapenems (except for panipenem–betamipron), penicillins, and fluoroquinolones declined between 22% and 39% in 2010, increased in the range of 16–31% in 2011, and increased by 1–14% in 2012. Susceptibility of panipenem–betamipron ranged between 25% and 32%. Susceptibility to aminoglycoside was more than 90% during this period. No relationship between antimicrobial usages and susceptibilities of *P. aeruginosa* was observed.

Conclusion: Susceptibilities of *P. aeruginosa* did not correlate with the usage of antibiotics in our hospital. Several infection control measures and other factors might contribute to changing the susceptibilities of bacteria.

Keywords: Antimicrobial usage; *Pseudomonas aeruginosa*; Susceptibility

Electronic supplementary material The online version of this article (doi:10.1007/s40121-015-0066-x) contains supplementary material, which is available to authorized users.

I. Kato · F. Fujimoto · Y. Higurashi · M. Suzuki (✉) · S. Okugawa · M. Okazaki · K. Moriya
Department of Infection Control and Prevention, The University of Tokyo Hospital, Tokyo, Japan
e-mail: suzukima-int@h.u-tokyo.ac.jp

R. Yamaguchi · K. Takayama
Department of Pharmacy, The University of Tokyo Hospital, Tokyo, Japan

INTRODUCTION

Pseudomonas aeruginosa is widely spread in humid environments such as plants, soil and a wide range of aquatic habitats, and could be colonizing in hospital environments [1]. This may include sinks, shower rooms, and bath rooms, thus, it is a common cause of nosocomial infections [1]. *P. aeruginosa* is a common pathogen of blood stream infections in patients with hematologic malignancy and other critical diseases [2, 3]. Blood stream infections could be associated with higher mortality rates depending on the patient's conditions [4].

Pseudomonas aeruginosa has an intrinsic resistance to several antibiotics, because of a low permeability of the outer-membrane, various efflux pumps and production of enzymes, e.g., cephalosporinases [5]. Furthermore, *P. aeruginosa* could acquire several mechanisms of resistance, such as reduced membrane permeability, target modification (DNA gyrase, methylation of 16S rRNA), and production of metallo-beta-lactamases. This is why it is difficult to treat infected patients.

Appropriate use of antibiotics is one of the most important infection control measures [6]. Several reports indicated the correlation of antibiotic usage and resistance [7–9]. On the other hand, one report indicated no relation of antimicrobial usage and resistance of *P. aeruginosa* in the hospitals in United States [10]. In our hospital, susceptibilities of *P. aeruginosa* to several antibiotics declined in 2010, however, subsequently improved in 2011. In this study, we show the consumption of anti-pseudomonal antibiotics and their susceptibility to those agents in a university hospital in Japan.

METHODS

The University of Tokyo Hospital is a 1217-bed tertiary care teaching hospital in Tokyo, Japan. Two hundred and eighty-two strains of *P. aeruginosa* were isolated from blood samples from April 2009 to March 2012. Strains isolated from the same patient within 2 weeks from previous isolations were regarded as duplicate isolates and excluded from the analysis. We included 163 isolates from 151 patients in the analysis. Finally, 149 strains that remained viable in our storage from 137 patients were included in the analysis.

Minimum inhibitory concentrations to anti-pseudomonal intravenous antibiotics used in the hospital, including cefepime (CFPM), ceftazidime (CAZ), piperacillin–tazobactam (PIPC–TAZ), piperacillin (PIPC), meropenem (MEPM), doripenem (DRPM), imipenem–cilastatin (IPM), biapenem (BIPM), panipenem–betamipron (PAPM), ciprofloxacin (CPFX), levofloxacin (LVFX) and amikacin (AMK) were determined by microdilution method. They were performed and interpreted according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) M100-S23 [11]. The breakpoints for carbapenems were applied to BIPM and PAPM.

Antimicrobial utilization was assessed for anti-pseudomonal intravenous antibiotics from the hospital databases. The amount of antibiotics used was expressed by antimicrobial use density, defined daily dose (DDD) per 1000 patient days. DDDs were defined by the World Health Organization [12].

Usual dose regimens for adults with normal kidney function in our hospital were as follows; CFPM: 1 g three times daily (TID), CAZ 1 g TID, PIPC–TAZ: 4.5 g TID, PIPC: 1.0 g twice daily (BID), MEPM 0.5 g TID, DRPM 0.5 g TID, IPM

0.5 g TID, BIPM 0.3 g four times daily (QID), PAPM 0.5 g TID, CPFX 200 mg BID, LVFX 500 mg once daily (QD), AMK 400 mg QD. Usual infusion duration of CPFX and LVFX was 60 min and the other antibiotics was 30 min.

Regression line equations and corresponding correlation coefficients were calculated using JMP Pro 11.0.0 (SAS Institute Japan, Tokyo, Japan) to evaluate the relation between antimicrobial usages and susceptibilities.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Antibiotic Utilizations

Annual consumptions of antibiotics are listed as DDD in Table 1. The most used anti-pseudomonal agents were cephalosporins from 2009 to 2010 and 2012 and penicillins in 2011. Ninety percent of cephalosporins used were cefepime, and almost all penicillins used were piperacillin–tazobactam. Usages of carbapenems and anti-pseudomonal cephalosporins decreased 44% and 31% from 2009 to 2011, and then increased 30% and 24% in 2012, respectively. Usage of piperacillin–tazobactam increased 87% from 2009 to 2012, which was introduced in the hospital in 2008. Consumption of fluoroquinolones and aminoglycoside remained low in those years.

Table 1 Antimicrobial usage by year (DDD/1000 patient days) in the University of Tokyo Hospital from 2009 to 2011

	Antimicrobial usage by year (DDD/1000 patient days)			
	2009	**2010**	**2011**	**2012**
CFPM	26.9	20.9	18.2	24.7
CAZ	3.8	2.5	3.0	1.6
Cephalosporins	**30.7**	**23.4**	**21.2**	**26.3**
PIPC–TAZ	13.3	16.3	21.7	25.3
PIPC	0.3	0.4	0.4	0.1
Penicillins	**13.6**	**16.7**	**22.0**	**25.4**
MEPM	17.1	14.9	9.7	12.0
DRPM	3.1	1.9	2.1	3.3
IPM	1.9	1.1	1.2	1.4
BIPM	0.2	0.0	0.0	0.0
PAPM	1.5	0.9	0.4	0.8
Carbapenems	**23.8**	**18.7**	**13.4**	**17.5**
CPFX	6.4	4.1	2.6	1.3
LVFX	0.0	0.0	1.0	2.3
Fluoroquinolones	**6.4**	**4.1**	**3.6**	**3.6**
AMK	1.1	0.9	0.7	0.7
Total	**75.6**	**63.8**	**61.0**	**73.5**

AMK amikacin, *BIPM* biapenem, *CAZ* ceftazidime, *CFPM* cefepime, *CPFX* ciprofloxacin, *DDD* defined daily dose, *DRPM* doripenem, *IPM* imipenem–cilastatin, *LVFX* levofloxacin, *MEPM* meropenem, *PAPM* panipenem–betamipron, *PIPC* piperacillin, *PIPC–TAZ* piperacillin–tazobactam

Susceptibilities of *P. aeruginosa* to Antibiotics

Susceptibilities of *P. aeruginosa* to antibiotics are listed in Table 2. Susceptibilities to cephalosporins, carbapenems except for PAPM, penicillins, and fluoroquinolones declined between 22% and 39% in 2010 and increased in the range of 16–31% in 2011, and furthermore increased by 1–14% in 2012. Susceptibility to PAPM ranged between 25% and 32%. Susceptibility to aminoglycoside was more than 90% during this period.

Table 2 Susceptibilities (%) of *Pseudomonas aeruginosa* to anti-pseudomonal antibiotics from 2009 to 2012

	Susceptibilities (%)			
	2009 ***n*** **= 43**	**2010** ***n*** **= 31**	**2011** ***n*** **= 47**	**2012** ***n*** **= 28**
CFPM	81.4	58.1	83.0	89.3
CAZ	81.4	58.1	78.7	92.9
PIPC–TAZ	81.4	48.4	76.6	82.1
PIPC	83.7	45.2	76.6	89.3
MEPM	86.0	54.8	72.3	78.6
DRPM	86.0	64.5	80.9	85.7
IPM	72.1	48.4	74.5	75.0
BIPM	81.4	54.8	76.6	89.3
PAPM	30.2	25.8	31.9	25.0
CPFX	93.0	54.8	80.9	85.7
AMK	97.7	93.5	95.7	100.0

AMK amikacin, *BIPM* biapenem, *CAZ* ceftazidime, *CFPM* cefepime, *CPFX* ciprofloxacin, *DRPM* doripenem, *IPM* imipenem–cilastatin, *MEPM* meropenem, *PAPM* panipenem–betamipron, *PIPC* piperacillin, *PIPC–TAZ* piperacillin–tazobactam

Susceptibilities of *P. aeruginosa* and Usages of Antibiotics

Correlation of susceptibilities and antimicrobial usage was not observed in cephalosporins and carbapenems (Fig. 1). Susceptibilities to fluoroquinolones changed simultaneously with other beta lactams, although the consumptions of fluoroquinolones did not change. Susceptibility to piperacillin–tazobactam did not change, despite the significant increase of consumption (Table 1).

DISCUSSION

We investigated susceptibilities of *P. aeruginosa* to anti-pseudomonal agents and utilization of these antibiotics for 4 years. Susceptibilities of *P. aeruginosa* declined in 2010 and increased in the following years. However, corresponding changes in antimicrobial usages were not observed, and correlation between susceptibilities and antimicrobial usages was not seen in our data.

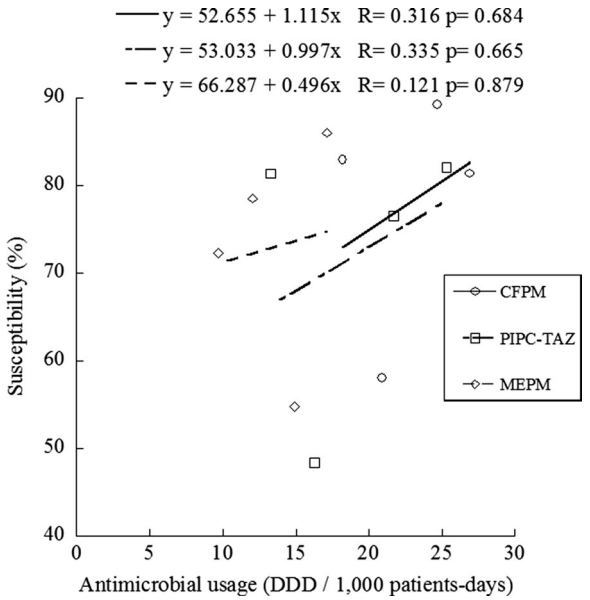

Fig. 1 Relationship between antimicrobial usage and susceptibility. *CFPM* cefepime, *DDD* defined daily dose, *MEPM* meropenem, *PIPC–TAZ* piperacillin–tazobactam

Several reports indicated that increased antimicrobial usage was associated with a decline in susceptibilities or emergence of resistant *P. aeruginosa*. Xu et al. [8] indicated that the resistance rate of *P. aeruginosa* to meropenem increased 1.2% when anti-pseudomonal carbapenems usage increased 1 DDDs/1000 patient days. Nakamura et al. [13] reported the relation of meropenem consumption and emergence of multidrug resistant *P. aeruginosa*. Appropriate use of antibiotics is essential to avoid the emergence of resistant bacteria. However, antimicrobial usage is not the only factor that determines the susceptibilities of bacteria. Other infection control measures, including hand hygiene,

contact precautions, education, environmental cleaning, and antimicrobial stewardship, are also important to avoid the emergence of resistant *P. aeruginosa* [14]. Correlation between antibiotic usage and susceptibility of *P. aeruginosa* was not observed in our data or in a report by Mutnick et al. [10]. Factors other than antimicrobial usage might contribute to these results. Moreover, the usages of anti-pseudomonal antibiotics, except carbapenems, in the report by Xu et al. [8] were three to five times higher than in our hospital. Initial resistance rates of *P. aeruginosa* to aminoglycoside and fluoroquinolones in the report were significantly higher than our data, nevertheless, we used more strict breakpoints according to CLSI M100-S23. We evaluated only blood samples, because we considered causative bacteria of infection more important than those of colonization, while other reports included colonized strains. These factors might affect the result. We compared the total usage of antibiotics in the hospital and susceptibilities of all isolates of *P. aeruginosa* in the hospital, while correlations might be observed in wards with a high consumption of antibiotics, such as the intensive care unit (ICU). Loeffler et al. [15] reported that correlation between antibiotic consumption and resistance in ICU was observed for piperacillin, cephalosporins and aminoglycosides in *P. aeruginosa*. However, Slain et al. [16] reported that statistically significant relationships of antibiotic consumption and resistance were not seen in their ICU despite an antimicrobial stewardship program. Furthermore, Jonas et al. [17] indicated that an increased resistance rate was associated with cross-transmission rather than antimicrobial usage. The declines of susceptibilities in our hospital might have been associated with cross-transmission.

We compared the usage of antibiotics and susceptibilities of bacteria on an annual basis. To clarify the exact relationship between antimicrobial usages and susceptibilities, shorter-period comparisons are desirable. Our isolates were only 30–40 a year. A larger number of isolates are required for short-term comparisons.

CONCLUSION

Susceptibilities of *P. aeruginosa* did not correlate with the usages of antibiotics in our hospital. Several infection control measures and other factors might contribute to the susceptibilities of bacteria. Further studies are needed to clarify the factors that determine susceptibility to antibiotics.

ACKNOWLEDGMENTS

No funding or sponsorship was received for this study or the publication of this article. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Conflict of interest. Masashi Suzuki has received research grants from Taisho Toyama Pharmaceutical Co., Ltd. Kyoji Moriya has received research grants from Bristol-Myers K.K., Pfizer Japan Inc., MSD K.K., Chugai Pharmaceutical Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Daiichi Sankyo Company, Limited and Sumitomo Dainippon Pharma Co., Ltd. Ito Kato, Fumie Fujimoto, Yoshimi Higurashi, Ryo Yamaguchi, Kazuo Takayama, Shu Okugawa, Mitsuhiro Okazaki declare that they have no conflict of interest.

Compliance with ethics guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

REFERENCES

1. Kerr KG, Snelling AM. *Pseudomonas aeruginosa*: a formidable and ever-present adversary. J Hosp Infect. 2009;73:338–44.

2. Chatzinikolaou I, Abi-Said D, Bodey GP, Rolston KV, Tarrand JJ, Samonis G. Recent experience with *Pseudomonas aeruginosa* bacteremia in patients with cancer: retrospective analysis of 245 episodes. Arch Intern Med. 2000;160:501–9.

3. Culshaw N, Glover G, Whiteley C, et al. Healthcare-associated bloodstream infections in critically ill patients: descriptive cross-sectional database study evaluating concordance with clinical site isolates. Ann Intensive Care. 2014;4:34.

4. Maschmeyer G, Braveny I. Review of the incidence and prognosis of *Pseudomonas aeruginosa* infections in cancer patients in the 1990s. Eur J Clin Microbiol Infect Dis. 2000;19:915–25.

5. Mesaros N, Nordmann P, Plesiat P, et al. *Pseudomonas aeruginosa*: resistance and therapeutic options at the turn of the new millennium. Clin Microbiol Infect. 2007;13:560–78.

6. Dellit TH, Owens RC, McGowan JE Jr, 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.

7. Hsueh PR, Chen WH, Luh KT. Relationships between antimicrobial use and antimicrobial resistance in Gram-negative bacteria causing nosocomial infections from 1991–2003 at a university hospital in Taiwan. Int J Antimicrob Agents. 2005;26:463–72.

8. Xu J, Duan X, Wu H, Zhou Q. Surveillance and correlation of antimicrobial usage and resistance of *Pseudomonas aeruginosa*: a hospital population-based study. PLoS One. 2013;8:e78604.

9. Fukushima Y, Fukushima F, Kamiya K, et al. Relation between the antimicrobial susceptibility of clinical isolates of *Pseudomonas aeruginosa* from respiratory specimens and antimicrobial use density (AUD) from 2005 through 2008. Intern Med (Tokyo, Japan). 2010;49:1333–40.

10. Mutnick AH, Rhomberg PR, Sader HS, Jones RN. Antimicrobial usage and resistance trend relationships from the MYSTIC programme in North America (1999–2001). J Antimicrob Chemother. 2004;53:290–6.

11. Clinical Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Third Informational Supplement. CLSI document M100-S23. Wayne: Clinical and Laboratory Standards Institute; 2013.

12. WHO Collaborating Centre for drug statistics methodology, definition and general considerations. http://www.whocc.no/ddd/definition_and_general_considera/. Accessed May 7, 2015.

13. Nakamura A, Miyake K, Misawa S, et al. Meropenem as predictive risk factor for isolation of multidrug-resistant *Pseudomonas aeruginosa*. J Hosp Infect. 2013;83:153–5.

14. Tacconelli E, Cataldo MA, Dancer SJ, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect. 2014;20(Suppl 1):1–55.

15. Loeffler JM, Garbino J, Lew D, Harbarth S, Rohner P. Antibiotic consumption, bacterial resistance and their correlation in a Swiss university hospital and its adult intensive care units. Scand J Infect Dis. 2003;35:843–50.

16. Slain D, Sarwari AR, Petros KO, et al. Impact of a multimodal antimicrobial stewardship program on *Pseudomonas aeruginosa* susceptibility and antimicrobial use in the intensive care unit setting. Crit Care Res Pract. 2011;2011:416426.

17. Jonas D, Meyer E, Schwab F, Grundmann H. Genodiversity of resistant *Pseudomonas aeruginosa* isolates in relation to antimicrobial usage density and resistance rates in intensive care units. Infect Control Hosp Epidemiol. 2008;29:350–7.