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Original Article

Correlation between antibiotic consumption and resistance of *Pseudomonas aeruginosa* in a teaching hospital implementing an antimicrobial stewardship program: A longitudinal observational study

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KEYWORDS
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Abstract *Background/purpose:* The rapid emergence of *Pseudomonas aeruginosa* resistance made selecting antibiotics more challenge. Antimicrobial stewardship programs (ASPs) are urging to implant to control the *P. aeruginosa* resistance. The purpose of this study is to evaluate the relationship between antimicrobial consumption and *P. aeruginosa* resistance, the impact of ASPs implemented during the 14-year study period.

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Pseudomonas aeruginosa (P. *aeruginosa*);
Resistance;
Antibiotics consumption;
Extended-infusion therapy

Methods: A total 14,852 *P. aeruginosa* isolates were included in our study. The resistant rate and antimicrobial consumption were investigated every six months. Linear regression analysis was conducted to examine the trends in antibiotics consumption and antimicrobial resistance over time. The relationship between *P. aeruginosa* resistance and antimicrobial consumption were using Pearson correlation coefficient to analysis. The trend of resistance before and after ASPs implanted is evaluated by segment regression analysis.
Results: P. aeruginosa resistance to ceftazidime, gentamicin, amikacin, ciprofloxacin and levofloxacin significantly decreased during the study period; piperacillin/tazobactam (PTZ), cefepime, imipenem/cilastatin and meropenem remained stable. The *P. aeruginosa* resistance to ciprofloxacin and levofloxacin increasing initial then decreased after strictly controlled the use of levofloxacin since 2007. As the first choice antibiotic to treat *P. aeruginosa*, the consumption and resistance to PTZ increase yearly and resistance became stable since extended-infusion therapy policy implant in 2009.
Conclusion: Our ASP intervention strategy, which included extended infusion of PTZ and restrict use of levofloxacin, may be used to control antimicrobial resistance of *P. aeruginosa* in medical practice.

Introduction

Pseudomonas aeruginosa (*P. aeruginosa*), a ubiquitous gram-negative bacillus, is one of the most common causes of nosocomial infections worldwide.[1] In the United States, *P. aeruginosa* was found to be the fourth most common pathogen causing hospital-acquired infections (HAIs), particularly ventilator-associated pneumonia and catheter-related urinary tract infections.[2] Moreover, it was responsible for 6.9%—11.0% of HAIs in Taiwan from 2012 to 2021, as reported by the Taiwan Healthcare-Associated Infection and Antimicrobial Resistance Surveillance System established by the Centers for Disease Control. The global increase in antibiotic-resistant *P. aeruginosa* infections for over a decade has become a health-care concern.[3–5] Notably, antibiotic-resistant *P. aeruginosa* strains were responsible for 84,600 deaths in 2019.[6] The rapid emergence of *P. aeruginosa* antimicrobial resistance has made selecting effective antibiotics more challenging.[7] Study has reported a positive correlation between antibiotic consumption and resistance in *P. aeruginosa*.[8]

Implementation of antimicrobial stewardship programs (ASPs) to address local trends in antibacterial resistance is a key strategy for controlling bacterial resistance.[9] This study investigated the relationship between consumption of different antipseudomonal agents and antimicrobial resistance over a 14-year ASP intervention period at a university hospital in Taipei, Taiwan.

Methods

Hospital setting

Taipei Medical University Hospital is a private, tertiary care, university-affiliated teaching hospital in Taipei, Taiwan. This hospital had 350 beds in 2004, 560 beds in 2008, 702 beds in 2010, and 743 beds in 2017. The hospital has medical, surgical, neonatal, and pediatric intensive care units and an emergency room.

Bacterial isolates, susceptibility testing, and antimicrobial resistance rate

All *P. aeruginosa* strains isolated from inpatients and outpatients at our hospital from 2004 to 2017 were included in this study. Susceptibility data were obtained from the Clinical Microbiology Laboratory Department. A broth microdilution method (Phoenix; Becton Dickinson, Sparks, MD) was used for susceptibility testing, and the breakpoints for determining susceptibility of each antibiotics was interpreted according to the criteria suggested by the Clinical and Laboratory Standards Institute.[10]

Antibiotic consumption and ASPs

The antipseudomonal agents examined in this study comprised penicillins (piperacillin-tazobactam (PTZ)), cephalosporins (ceftazidime and cefepime), carbapenems (imipenem-cilastatin and meropenem), aminoglycosides (gentamicin and amikacin), and fluoroquinolones (ciprofloxacin and levofloxacin) applied on inpatient and outpatient at our institution from 2004 to 2017. The amounts of antibiotic consumption were presented as defined daily doses (DDDs) per 1000 patient days (PD) (DID = DDDs/1000 PD). And the DDDs of each antibiotics was defined depended on the World Health Organization Collaborating Centre for Drug Statistics Methodology.

In our hospital, ASPs are led by infectious disease (ID) physicians, infection control nurse (ICN), clinical laboratory technologist and pharmacists with ID training are also deeply involved in the programs. We regularly hold educational program and advocate the guideline, enforce facility-specific clinical practice on treatment, provide prior authorization for the use of restricted antibiotics

within 24 h, conduct prospective audit and provide feedback, verify dose and optimal duration. Furthermore, we hold regular conference to monitor and rectify inadequate antibiotic use monthly, report and feedback on facility-specific antibiotic susceptibility rate and infection rate to prescriber and medical staff quarterly.

Strategies implemented as part of our hospital's ASP to control *P. aeruginosa* antimicrobial resistance from 2004 to 2017 included the following (and Supplementary Fig. 1):

(1) Strict regulation of carbapenem prescriptions since 2004, comprising (a) requiring prior authorization—consisting of a real-time consultation using a computer-generated alert system and confirmation by and ID specialist— for carbapenem prescriptions and (b) monitoring carbapenem consumption and *P. aeruginosa* resistance to carbapenem every six months.
(2) Use of PTZ, rather than ceftazidime or cefepime, as to the first-choice treatment for *P. aeruginosa* infections since 2004 due to increasing usage of 3rd and 4th cephalosporins since 2003, comprising (a) Education: prescribers have been advised the empirical use of PTZ for severe hospital-acquired infection leading by *P. aeruginosa*, (b) Preprescription approval: Mandate formal ID consultation for prescribing of ceftazidime, cefepime and PTZ and (c) Monitoring ceftazidime and cefepime consumption monthly.
(3) Strict regulation of levofloxacin prescriptions since July 2007 due to a surging rate of Fluoroquinolone-resistant *P. aeruginosa* was observed since 2006, comprising (a) Education: Staff members have been advised against the empirical use of Fluoroquinolones, and the recommendation of optimal dose has been provided to all physicians, (b) Pre-authorization: each levofloxacin prescriptions need to be applied through electronic medical system (indication documented) and verified by pharmacists and (c) Monitoring levofloxacin consumption monthly and resistance to levofloxacin every six months.
(4) Implementation of PTZ extended-infusion therapy since 2009, initial started from intensive care units and promoted throughout our hospital gradually, comprising (a) The recommended dosage is 4500 mg Q8H infusion over 4 h for patients with normal renal function. The dose and extended-infusion time are adjusted according to renal function. And compatibility was also reviewed by ID pharmacist (Supplementary Fig. 2), (b)Advocate institution updated guideline: all prescribers and staff members (application of infusion pump) were instructed by ID physicians and linking nurse and (c)Set protocol at electronic physician order entry system.

Correlation between antimicrobial resistance rate and antibiotic consumption

The relationship between antimicrobial resistance rate and antibiotic consumption was investigated every six months. The change in *P. aeruginosa* resistance to PTZ from pre-intervention to postintervention was used to evaluate the effectiveness of the PTZ extended-infusion strategy to control *P. aeruginosa* antimicrobial resistance.

Statistical analysis

The trends in antibiotic resistance and antibiotic consumption and medical were analyzed by linear regression analysis. A Pearson correlation coefficient was conducted to determine the relationship between the consumption of each antibiotic and the antimicrobial resistance rate with SPSS statistical software (Version 19.0; SPSS Inc. Armonk, NY, USA). The effect of the intervention on the implementation of PTZ extended-infusion strategy since 2019 and bacterial resistance was assessed using Segment regression analysis. Analyses was performed using R statistical software version 3.1.2. A p value of <0.05 was considered statistically significant for all tests.

Results

Trends in antimicrobial resistance and consumption of selected antibiotics

A total 14,852 *P. aeruginosa* isolates were isolated at Taipei Medical University Hospital from 2004 to 2017. The number of *P. aeruginosa* isolates in each half-year period ranged from 293 to 726. Table 1 shows the trends of antibiotic resistance of these isolates over the 14-year period.

Table 1 The trend of Antibiotic resistance to *Pseudomonas aeruginosa* rate (%) at Taipei Medical University Hospital from 2004 to 2017.

Antimicrobial agent	Median resistance rate (%)	Interquartile Range	Gradient (95% CI)	Trend	*p*-value
Piperacillin/tazobactam	15	(12–17)	0.253 (−0.067, 0.574)	Stable	0.116
Ceftazidime	13.5	(11–19.5)	−0.426 (−0.637, −0.215)	Decreasing	<0.0001*
Cefepime	29	(24–34)	−0.128 (−0.379, 0.123)	Stable	0.304
Imipenem/cilastatin	13	(11–15)	0.391 (−0.124, 0.906)	Stable	0.131
Meropenem	11	(10–14)	0.090 (−0.470, 0.649)	Stable	0.745
Gentamicin	19	(12–26.5)	−0.381 (−0.490, −0.272)	Decreasing	<0.0001*
Amikacin	6	(2–10)	−0.662 (−0.864, −0.460)	Decreasing	<0.0001*
Ciprofloxacin	19.5	(17.5–24)	−0.367 (−0.587,-0.147)	Decreasing	0.002*
Levofloxacin	23	(20.5–26)	−0.307 (−0.582,-0.033)	Decreasing	0.03*

* $p < 0.05$, Statistically significant.

Table 2 The trend of Antibiotic consumption (DID) at Taipei Medical University Hospital from 2004 to 2017.

Antimicrobial agent	Median use (DID)	Interquartile Range	Gradient (95% CI)	Trend	*p*-value
Piperacillin/tazobactam	22.25	(20.95–25.1)	0.718 (0.512, 0.924)	Increasing	<0.0001*
Ceftazidime	2.94	(1.99–4.265)	0.783 (0.271, 1.295)	Increasing	0.004*
Cefepime	6.06	(2.285–16.7)	0.447 (0.335, 0.558)	Increasing	<0.0001*
Imipenem/cilastatin	2.55	(1.7–3.2)	−1.923 (−3.105, −0.764)	Decreasing	0.002*
Meropenem	6.3	(3.85–9.75)	0.739 (0.452, 1.026)	Increasing	<0.001*
Gentamicin	42.65	(35.85–51.55)	−0.347 (−0.435, −0.259)	Decreasing	<0.0001*
Amikacin	20.9	(17.05–24.5)	−0.539 (−0.775,-0.302)	Decreasing	<0.0001*
Ciprofloxacin	25.3	(22.8–31.05)	0.393 (0.076, 0.709)	Increasing	0.017*
Levofloxacin	7.1	(5.95–9.55)	−0.402 (−0.743, −0.062)	Decreasing	0.022*

* $p<0.05$, Statistically significant.

Resistance rates for all nine selected antimicrobials decreased significantly or remained stable. The consumption of PTZ, ceftazidime, cefepime, meropenem, and ciprofloxacin increased significantly over time. By contrast, the consumption of imipenem/cilastatin, gentamicin, amikacin, and levofloxacin decreased significantly (Table 2).

Correlation of antibiotic consumption and resistance rate

Table 3 presents the relationship between the consumption of each antipseudomonal agent and the resistance rate. PTZ, gentamicin, amikacin, and levofloxacin consumption exhibited a significant positive correlation with antimicrobial resistance; meropenem, imipenem/cilastatin, and ciprofloxacin consumption exhibited no correlation; and ceftazidime and cefepime consumption exhibited a significant negative correlation.

Effect of control of levofloxacin use on *P. aeruginosa* resistance to fluoroquinolones

P. aeruginosa resistance to ciprofloxacin and levofloxacin increased to 37% and 36%, respectively, in the first half of 2006, during which the consumption of fluoroquinolones also increased. Our hospital has strictly controlled the use of levofloxacin since the second half of 2007. The consumption of total levofloxacin decreased significantly from 14.12 ± 5.37 to 6.86 ± 1.92 (p = 0.011), and *P. aeruginosa* resistance to ciprofloxacin and levofloxacin decreased to 18% and 21% in 2017, separately (Tables 1–2).

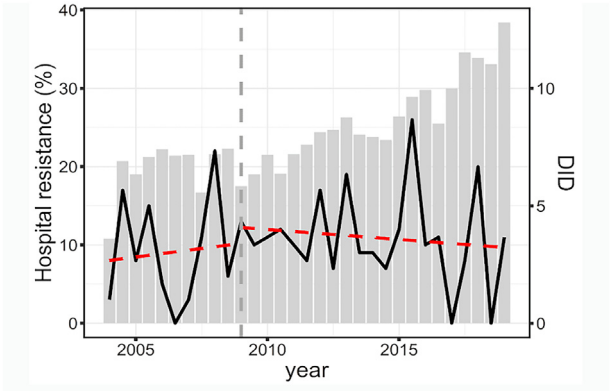
Table 3 Correlations between consumption of each antibiotic agent and resistance rate at Taipei Medical University Hospital.

Antimicrobial agent	Coefficient (r^2)	Coefficient (r)	*p*-value
Piperacillin/ tazobactam	0.221	0.470	0.012*
Ceftazidime	0.191	−0.440	0.019*
Cefepime	0.112	−0.416	0.028*
Imipenem/cilastatin	0.132	−0.358	0.061*
Meropenem	0.018	−0.134	0.498
Gentamicin	0.573	0.757	<0.0001*
Amikacin	0.487	0.697	<0.0001*
Ciprofloxacin	0.135	−0.367	0.055
Levofloxacin	0.517	0.719	<0.0001*

* $p < 0.05$, Statistically significant.

Effect of PTZ extended-infusion therapy on *P. aeruginosa* resistance to PTZ

The incidence rate of *P. aeruginosa* resistance to PTZ increased to 28% in the second half of 2006 and nosocomial infections related to PTZ-resistant *P. aeruginosa* also raised to 24%. Extended-infusion therapy policy was implemented



Parameter	Odds ratio (Standard Error)	95% CI for odds ratio	p value
Preintervention slope	0.0012 (0.004012)	(0.0092, −0.0068)	0.767
Change in intercept (intermediate effect)	2.226 (5.434413)	(13.10, −8.643)	0.686
Postintervention slope	-0.00083 (0.004368)	(0.0067, −0.0067)	0.646

Figure 1. *Pseudomonas aeruginosa* resistance to Piperacillin/tazobactam(PTZ) before and after implementation of the extended-infusion therapy policy in 2009 and change in PTZ slope before and after policy implementation. (Gray bar: PTZ consumption (DID), black line: PTZ resistance rate (%), red dotted line: PTZ resistance trend, gray dotted line: PTZ extended-infusion strategy implementation).

since 2009. The consumption (DID) of total PTZ increased from 19.74 ± 3.39 to 24.63 ± 4.20 during study period. But the resistance slope was 0.0012 and −0.00083 before and after implementation of the extended-infusion therapy policy, respectively; no significant difference ($p = 0.646$) was identified between the two stages (Fig. 1).

Discussion

Our study evaluated the association between consumption of different antipseudomonal agents and the antibiotic resistance of *P. aeruginosa* in a teaching hospital over a 14-year ASP intervention period. Under long-term ASP strategies on targeted antibiotics management, our antibiogram of *P. aeruginosa* was more susceptible to similar university-affiliated hospitals. Hence, we will focus on management of specific antibiotics in the following discussion.

Fluoroquinolones are antibiotics with broad-spectrum activity, high potency, and favorable bioavailability, which make them convenient treatment options for various clinical indications, including pseudomonas infections.[11] However, the overuse of quinolones has contributes to increasing the resistance of *P. aeruginosa* to quinolones worldwide.[12–14] The Clinical and Laboratory Standards Institute (CLSI) has even lowered the Fluoroquinolon antimicrobial susceptibility breakpoints for *P. aeruginosa* on the basis of pharmacokinetic and pharmacodynamic findings.[15] Several retrospective observational studies identified a positive correlation between quinolone use and the antimicrobial resistance of *P. aeruginosa*, especially to levofloxacin.[16–18] This finding could partly be explained by pharmacodynamic principles. Ciprofloxacin has higher antibacterial efficacy against *P. aeruginosa* than does levofloxacin because it has a lower minimum inhibitory concentration (MIC). And the mutant selection window (MSW) concept may help explain this phenomenon. This window is the concentration range between the MIC and the MIC of the least drug-susceptible mutant subpopulation and is known as the mutant prevention concentration (MPC).[19,20] Fluoroquinolones exposures within this window have been shown to promote the emergence of resistant populations. Hansen et al. reported that the MPC for ciprofloxacin was approximately three to four times lower than that for levofloxacin, indicating a narrowed MSW and lower possibility of inducing a mutation.[21] In our previous study, strictly restricting levofloxacin consumption resulted in a 20% decrease in the incidence of Fluoroquinolones -resistant *P. aeruginosa* infections[22]; therefore, levofloxacin prescriptions have been strictly regulated since the second half of 2007, and ciprofloxacin, instead of levofloxacin, is used to treat pseudomonas infections if indicated. Since the implementation of the ASP, a significant decrease in levofloxacin consumption was noted over 10 years. Concurrently, the incidence of Fluoroquinolones -resistant *P. aeruginosa* also decreased.

Studies have demonstrated that β-lactam resistance is positively correlated with the consumption of β-lactam agents, and that PTZ is less likely than β-lactam antibiotics to induce β-lactam resistance in *P. aeruginosa*.[23–25] Studies have also mentioned that reducing the use of extended-spectrum cephalosporin and replacing it with PTZ could control antimicrobial resistance in bacteria, such as extended-spectrum β-lactamase (ESBL) resistance in Enterobacteriaceae, β-lactam resistance in *P. aeruginosa*, and vancomycin resistance in Enterococcus and *Clostridioides difficile*.[26,27] In fact, both ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates associated with nosocomial infections were arising since 2003 (from 9.6% to 12.5% and from 23.52% to 31.5%, respectively) was found in our hospital. After implementing our outline ASP strategy of using PTZ instead of broad-spectrum cephalosporins, the amount of ceftazidime consumed in our hospital decreased dramatically from 12.7 DID in 2003 to 5.6 DID in 2004; during the study period, the average amount consumed was approximately 3.68 DID. The amount of cefepime consumed remained below 5 DID until the second half of 2010 (8.2 DID), when it increased due to improved *P. aeruginosa* sensitivity to cefepime.

However, because PTZ became the first-choice treatment for *P. aeruginosa* infections, its consumption increased dramatically. Since the first half of 2006 and still lasted for years, an increasing rate of *P. aeruginosa* resistance to PTZ was observed. We developed PTZ extended infusion guidance to solve these issues through literature review which concentrated on its pharmacokinetic/pharmacodynamic (PK/PD). The specific β-lactam antibiotics have short elimination half-lives, and all exhibit time-dependent bactericidal activity. According to the characteristics above, the best predictor of bactericidal effect is achieved by the free drug concentration exceeds the MIC of the bacterial pathogen (%fT > MIC) by approximately fourfold for 40 to 60 percent of the dosing interval. In critically ill patients, more aggressive PK/PD targets up to 100%fT > 4–5 × MIC was required. Extended infusion of PTZ may exert stronger antimicrobial effects than intermittent infusion due to providing high probabilities of target attainment.[28] Thereby reduce the mortality rate of *P. aeruginosa* infections and achieved higher microbiological cure rates.[29–31] Furthermore, it may couple with the economic benefits of fewer daily doses. Regarding emergence of resistance, Gatti et al. also noted trough concentration (Cmin)/MIC ratios ranging >3.8 and the ratio between steady-state concentration and MIC ratio >5 were significantly associated with bacteria regrowth prevention.[32] Continuous and extended infusion may represent better administration mode in preventing microbiological failure. However, some systemic review and meta-analysis demonstrated no difference in development of resistance between extended infusion and short-term intravenous infusion.[29–31] But cited randomized controlled trials have high heterogeneity and small sample size. In present study, although PTZ consumption increased, the results of the analysis indicated that *P. aeruginosa* resistance to PTZ remained unchanged. Notedly, PTZ still had a susceptibility rate of >80% in our hospital, higher than other epidemiological and microbiological studies in Taiwan.[33] Our study was the first observational study to demonstrate that PTZ-resistant *P. aeruginosa* remained stable might be related to extended-infusion strategies.

Carbapenem use is among the most significant factors contributing to the development of carbapenem-resistant enterobacteria and other gram-negative Bacilli.[34,35] According to Taiwan Surveillance of Antimicrobial Resistance program and The Study for Monitoring Antimicrobial

Resistance Trends, the prevalence rates of carbapenem-resistant *Pseudomonas aeruginosa* are on the rise in this decade.[36,37] And carbapenem resistance will increase hospitalization costs and day than in carbapenem-susceptible *P. aeruginosa* patients.[38,39] Strictly controlling carbapenem use is key to controlling antimicrobial resistance; once the consumption is below 15 DID, carbapenem use is likely not responsible for the problem of antimicrobial resistance.[23] The consumption of meropenem was 6.3 (3.85—9.75) DID from 2004 to 2017; the values was far below 15 DID. Furthermore, the carbapenem-resistant *P. aeruginosa* rate remained stable and below 15% during the 14-year ASP intervention period. Strict control of carbapenem as a treatment for *P. aeruginosa* infections is necessary to control *P. aeruginosa* resistance to carbapenem.

Our study has some limitations. First, it was a single-center, retrospective, observational study that used aggregate data with an inherent risk of bias. Second, we were not able to investigate whether restrictive use of antibiotics was associated with any mortality benefit or length of stay shortening. Third, the phenomenon antibiotic-resistant bacteria is the combined result of antibiotic use causing the development of resistant organisms and horizontal gene transfer.[40] Both antibiotic control and infection control are key to ASP strategies for combatting antibiotic-resistant organisms. Our retrospective study did not analyze the effect of infection control methods, such as hand hygiene, bundle care, isolation and de-colonization policy for multi-drug resistant organisms on the control of antibiotic-resistant *P. aeruginosa*. In addition, epidemiological genotypic and molecular analysis of our *P. aeruginosa* strains to determine the mechanisms underlying antimicrobial resistance were not performed in this study.

Because few new antibiotics are being developed, the proper use of the available antibiotics to avoid increasing antibiotic resistance is crucial. Our ASP intervention strategy, which included extended infusion of PTZ and restrict use of levofloxacin, may be used to control antimicrobial resistance of *P. aeruginosa* in medical practice. In conclusion, regulating antibiotic consumption, monitoring antimicrobial resistance, and developing appropriate ASPs in a timely manner are the key to controlling the populations of multidrug-resistant organisms.

Declaration of competing interest

None.

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None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.08.017.