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Original article

Resistant patterns of *Pseudomonas aeruginosa* in a Malaysian teaching hospital

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Abstract

Objective: *Pseudomonas aeruginosa* is an opportunistic pathogen and the leading cause of nosocomial infections. Currently a notable increase in the prevalence of multidrug-resistant *P. aeruginosa* worldwide has been reported in hospitalized patients and was associated with high morbidity and mortality. **Methods**: A retrospective laboratory based analysis regarding the spectrum and distribution of *P. aeruginosa* from a wide range of clinical samples in Hospital Universiti Sains Malaysia since January 2003 to December 2007 was done. **Results**: Altogether, there were 2 308 clinical isolates analyzed. The main sources of *P. aeruginosa* were from swab, respiratory, urine and blood specimens which accounted for 28.2 %, 21.8 %, 13.2 % and 12.8 % respectively. Results showed significant reduction in percentage of resistant towards three antibiotic namely ciprofloxacin, ceftazidime and imipenem. However the percentage of pan-resistant *P. aeruginosa* increased steadily over these years. **Conclusion**: This data is helpful to the clinician in guiding the choice of appropriate antibiotic to treat *P. aeruginosa* infection. At the same time, it warrants a more aggressive infection control activity to be implemented to control the spread of pan resistant strain in this centre.

Keywords: *Pseudomonas aeruginosa*; Resistant pattern; Infection

INTRODUCTION

Pseudomonas aeruginosa is the most frequent nosocomial pathogen that responsible for infections and outbreak in intensive care units (ICUs)[1-3]. It is generally acquired from the environment, and person-to-person spread occurs rarely[4]. Nosocomial infection is an important cause of morbidity, mortality and indirectly increased total hospital cost. However, case fatality rate of *P. aeruginosa* bacteraemia varies, depending on studies conducted. It ranged from 30.6 % to 77.0 %[5,6]. Of concern today is the increasing trend of *P.* aeruginosa that are resistant to a commonly used antipseudomonal agents[7-9]. The prevalence of resistant *P. aeruginosa* varies among countries, depending on confounding factors such as the antibiotics usage, antibiotic policies and effectiveness of infection control practise in the particular hospital. A study of resistant pattern of Gram negative bacteria including *P. aeruginosa* in two hospitals in Iran showed imipenem was the most active agent with overall susceptibility rate of 73.4% compared to ceftazidime (28.1 %), cefepime (33.3%) and ciprofloxacin (33.3 %)[8]. In a Malaysian study, the sensitivity of *P. aeruginosa* isolates were 90.1 % for imipenem compared to ceftazidime (89.1%), cefepime (61.1 %), ciprofloxacin (79.0%) and meropenem (63.2%)[10]. Therefore, identifying the local resistance pattern of *P. aeruginosa* is a key to success in predicting appropriate empirical treatment. The aim of this study

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was to determine the antibiotic susceptibility pattern of *P. aeruginosa* isolated from clinical specimens in Hospital Universiti Sains, Malaysia. It is hoped that the results will guide the clinician in choosing a more effective empirical antipseudomonal therapy in our hospital.

MATERIALS AND METHODS

Data collection

A retrospective laboratory based analysis regarding the spectrum and distribution of *P. aeruginosa* from a wide range of clinical samples in Hospital Universiti Sains Malaysia from January 2003 to December 2007 was done. The hospital has 700 beds, with two adult ICUs (medical and surgical), one neonatal ICU, 28 medical wards and 11 surgical wards, including two oncology wards. The data was extracted from the Microbiology Laboratory Survey electronic data base. *P. aeruginosa* was identified based on colony appearance, basic chemical tests, pigment production, positive oxidase reaction and also commercialized identification system, API-20 NE system (bioMerieux, France) if needed. Antimicrobial susceptibility was determined using disc diffusion method and interpreted according to Clinical and Laboratory Standards Institute (CLSI).

Statistical analysis

SPSS Version 12.0 was used for data entry and analysis. Descriptive statistics and cross-tabulations were used to explore all data. Categorical data were analyzed using chi-square tests, or Fisher's exact tests as appropriate, to test for the significance of association between variables. The level of significance was taken at 0.05.

RESULTS

Altogether, there were 2 308 clinical isolates analyzed. Of 2 308 isolates, 453 (19.6 %) were from the surgical patients and 357 (15.5 %) were from patients in medical wards. Other isolates were from patients in general ICU (307,13.3 %), orthopedic ward (299, 13.0 %), neurosurgical ICU (280, 12.1%), ophthalmology ward (184,8.0 %), neonatal ICU (100,4.3 %), pediatrics (77,3.3 %) and other wards/clinics (351,15.2 %). Majority of *P. aeruginosa* were isolated from swab specimens, followed by respiratory, urine, blood and tissue which accounted for 28.2 %, 21.8 %, 13.2 % 12.8 % and 10.3 % respectively. *P. aeruginosa* was also isolated from other types of specimens but less frequent such as eye (117,5.1 %), ear (48, 2.1%), wound (32 ,1.4 %) and other specimens (120,5.2 %).

Further analysis of specimen types and wards location showed 51.2 % of the swabs specimens were from surgical and orthopaedic wards, 66.8 % of the respiratory specimens were from ICU and neurosurgical ICU, 55.0 % of the urine specimens were from surgical wards and neurosurgical ICU and 40 % of the blood specimens came from medical wards, ICU and neonatal ICU (data not shown).

Table 1 demonstrated the susceptibility pattern of *P. aeruginosa* isolated from clinical specimens. Overall antimicrobial susceptibility results indicated that *P. aeruginosa* isolated in our hospital for the past five years had inconsistent level of resistant towards ten antibiotics tested namely cefepime, cefoperazone, ceftazidime, ciprofloxacin, piperacillin-tazobactam, imipenem, gentamicin, amikacin and netilmicin.

Table 1 Resistant pattern of *Pseudomonas aeruginosa* isolated from 2003-2007.

Year	No. isolates	percent (%) of isolates resistance									
		CFP	CAZ	FEP	CIP	GEN	AMK	NET	IPM	MEM	TZP
2003	483	30.0	18.0	2.3	21.5	23.6	21.1	21.7	19.7	10.6	17.4
2004	384	25.0	16.7	1.3	16.1	27.1	15.4	14.3	14.6	12.2	14.6
2005	407	22.1	18.4	3.7	14.3	34.4	13.0	15.7	13.5	5.7	9.3
2006	567	19.8	13.8	14.6	14.1	15.7	10.8	12.9	13.8	11.5	10.4
2007	467	26.6	13.1	17.1	11.6	12.8	10.5	12.2	11.1	13.3	10.5

CFP = cefoperazone, CAZ = ceftazidime, FEP = cefepime, CIP = ciprofloxacin, GEN = gentamicin, AMK = amikacin, NET = netilmycin, IPM = imipemen, MEM = meropenem, TZP = piperacillin – tazobactam.

DISCUSSION

This tertiary teaching hospital received patients from various districts hospitals of the state including the State General Hospital, Kota Bharu. It has a special burn unit, urology subspeciality in surgical unit, and a neurosurgical ICU which gave rise to certain types of samples that were frequently received by the

Microbiology Laboratory. In this study, majority of *P. aeruginosa* is isolated from swab specimens of patients from surgical and orthopaedic wards while the respiratory samples particularly endotracheal tube secretion were contributed by ventilated patients. The finding is in keeping with the fact that this organism was among the commonest pathogen associated with hospital acquired pneumonia [11,12].

In a 6 year surveillance in the United Kingdom and Ireland, *P. aeruginosa* bacteraemia were detected in 1 226 cases with 62 % of the episodes detected among patients who were hospitalized for more than 48H. Majority of the cases were from general medicine 20 %; haematology/oncology 17 %; ICU 14 %; surgery 13 % [13]. Major source of *P.* aeruginosa bacteraemia; unknown 36 %; lines 18 %; genitourinary tract 17 %; respiratory tract 13% [13]. Bacteraemia from *P. aeruginosa* reported in the United Kingdom and Ireland study (Year 2000-2006) ranged from 4.2 to 4.6 % which was lower compared to this study, 12.8 % [14].

Drug-susceptible strains showed a few mechanisms of resistance such as present of inducible AmpC b-lactamase which confers inherent resistant to those b-lactams that induce this enzyme, production of porin channel and efflux pump system that removes b-lactams, chloramphenicol, fluoroquinolones, macrolides, novobiocin, sulfonamides, tetracycline, and trimethoprim[15]. *P. aeruginosa* can develop pan-resistance, most often by successive mutations that: (i) up-regulate efflux and AmpC b-lactamases; (ii) alter quinolone targets; and (iii) down-regulate permeability, but occasionally by acquisition of plasmids encoding metallo-b-lactamases and multiple aminoglycoside modifying enzymes[13].

P. aeruginosa is a uniquely problematic pathogen because of the following capability; the species´ inherent resistance to many drug classes; its ability to acquire resistance, via mutations, to all relevant treatments; its high and increasing rates of resistance locally[15]. The resistant pattern of this pathogen is persistently changed over time. National survey of antibiotic resistance conducted by the London Hospital Medical College in 1982 showed resistance frequencies detected by MIC were: carbenicillin 9.6%, azlocillin 3.9 %, cefotaxime 1.9 %, cefoperazone 4.3 %, ceftazidime 0.3 %, amikacin 3.8 %, and gentamicin 5.5 % [16]. However, in a similar survey done by the same institution in 1993 found that the frequency of resistance to the aminoglycosides increased ($P < 0.005$) as had those to the penicillins and ceftazidime ($P < 0.001$) ranges from 8-12 %. Ciprofloxacin and the carbapenems were not tested in 1982, but in the current survey, imipenem and meropenem had a resistant pattern of 2.5 % and 1.1 % respectively[17].

In this study, cefoperazone resistance fluctuated, peaked at 30 % in 2003 and returned to 19.8 % in 2006 and increased up to 26.6 % in 2007. *P. aeruginosa* resistance to cefepime was markedly increased in year 2006 (14.6 %) and 2007 (17.1%) compared to previous years. However, the susceptibility results in year 2005 showed a significant reduction in resistant pattern even though slight differences was observed towards seven antibiotics tested (ceftazidime, ciprofloxacin, piperacillin-tazobactam, imipenem, amikacin and netilmicin) compared to year 2003. Reductions in the percentage of resistance for those antibiotics were ranging between 5-11 %. A 6 year review of data from British Society for Antimicrobial Chemotherapy bacteraemia surveillance together with the Health Protection Agency concluded that, among *P. aeruginosa*, non-susceptibility rates to b-lactams and gentamicin fluctuated, without trend, below 10 %; those to ciprofloxacin ranged from 16 % to 22 % [14].

The type of resistance towards antibiotic is categorized into mono resistance, multi resistance or pan resistance. These classification is not standardized thus data of previous studies were not comparable. Certain studies define MDR *P. aeruginosa* as resistant to three or more antipseudomonal drugs where as others had define as resistant to three or more classes of antipseudomonal drugs[18]. In our study, MDR *P. aeruginosa* was defined as resistant to three or more core drugs tested. The prevalence of MDR and pan resistant in this study were 18.5 % and 1.6 % respectively. Though the percentage of pan-resistant was only 1.6 %, but the rising trend was worrying. The unnecessary use of multiple broad-spectrum antibiotics has been documented to be a major factor[15,19] due to competitive eradication of normal flora and to the selective emergence of resistant strains. In other study, treatment with broad-spectrum cephalosporins and aminoglycosides has been proven to be important risk factors for acquiring these strains[19]. Further more, active infection control measures such as cohorting of infected patients, continuous surveillance and contact precaution were crucial to prevent dissemination of the resistant strains[19]. In a Surveillance Network Database USA, 16 % of isolates now resistant to three or more of the core drugs (amikacin, ceftazidime, ciproflox-

acin, gentamicin, imipenem, and piperacillin-ticarcillin) and with 1% resistant to all 6 of these agents[15].

In conclusion, *P. aeruginosa* isolates in our setting were still susceptible to majority of core drugs tested, except for cefoperazone and gentamicin which demonstrated about 20 % to 30 % resistance rate. Thus, antipseudomonal drugs from cephalosporins, fluoroquinolones or carbapenem groups are acceptable for empirical treatment to treat *P. aeruginosa* infections in our local setting. Further choices would depend on other factors such as severity of clinical conditions, types of infections and local antibiotic guidelines produced by the institution.

Currently available surveillance system should be fully utilized and closely monitored. This will help us to give an immediate response towards any changes in the pattern of antimicrobial resistance in this local setting. The lack of consistent long-term surveillance of microbial resistance would aggravate the existing problems. The infection control team should be strengthened in terms of manpower and strategies to curb the emergence of MDR and pan resistant organisms in our setting.

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