Full Length Research Paper

Trend of antibiotics susceptibility of multidrugs resistance *Pseudomonas aeruginosa* in Jakarta and surrounding areas from 2004 to 2010

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*Pseudomonas aeruginosa* is an opportunistic Gram negative microorganism, usually related to serious infections within hospital environment and causes significant increase in patient’s morbidity and mortality. This study aimed to report antibiotic susceptibility of *P. aeruginosa* originated from all kind of specimens received at Clinical Microbiology Laboratory of the Faculty of Medicine, University of Indonesia, Jakarta, from 2004 to 2010, and evaluate their trend of susceptibility to certain antibiotics. Culture and identification of specimens were performed according to standard microbiology procedures. Antibiotic susceptibility tests were carried out according to performance standards for antimicrobial susceptibility testing from the Clinical and Laboratory Standards Institute. The data was processed using WHO-NET Version 5.6 program. *P. aeruginosa* was constantly found between 12 to 19% among other Gram negative bacteria. A significant decrease of susceptibility against ceftazidim, cefepime, cefoperazone, gentamicin, amikacin, tobramycin, ciprofloxacin, levofloxacin, meropenem and imipenem was observed. Susceptibility to aztreonam and piperacilline-tazobactam was decreased, though it was not statistically significant. In 2010, among the anti-pseudomonas antibiotics, imipenem showed good activity (80%). Overall, declining trend of susceptibility to all antibiotic tested was significantly observed. Imipenem was found to be the only anti-pseudomonas antibiotic with good activity (80%).

**Key words:** Gram negative bacteria, *Pseudomonas aeruginosa* and antibiotic susceptibility.

**INTRODUCTION**

Bacterial infections are becoming more difficult to treat. At present, 70% of nosocomial infections are resistant to at least one antimicrobial drug that previously was effective for the causative pathogens. Microbes that are notorious for their virulence and able to develop resistance include *Staphylococcus aureus*, *Enterococcus* spp., members of the *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter* species (Carmeli, 2008). Recent data from the U.S. National Healthcare Safety Network indicated that Gram negative bacteria was responsible for more than 30% of health care associated infection (HAI), and these bacteria were found predominately in cases of ventilator-associated pneumonia (47%) and urinary tract infections (45%) (Peleg and Hooper, 2010). A multicenter study showed an increasing number of Gram negative bacteria isolated from blood both from hospital and community acquired infection cases. Of the 12,781 causative organisms, Gram negative aerobic bacteria...
were 47.4%, whereas Gram positives accounted for 43.9% (Luzzaro et al., 2011). Likewise a study carried out by Moehario et al. (2009) in Jakarta found that P. aeruginosa was the second most isolated after Acinetobacter anitratus from blood specimen. Among all positive isolates from blood specimen, Gram negative bacteria was found approximately 68% with eight most frequent species isolated were A. anitratus (25.8%), P. aeruginosa (19.5%), Klebsiella pneumoniae subsp. pneumoniae (14.5%), Enterobacter aerogenes (8%), Salmonella Typhi (7.5%), Escherichia coli (6.2%), Alcaligenes faecalis (5.6%) and Klebsiella oxytoca (3.2%). This earlier study also showed P. aeruginosa resistant to antibiotic ceftriaxone, cefotaxime, amikacin, gentamycin, and susceptible to ciprofloxacin (77.8%), levofloxacin (92.2%) and cefepime (88.9%)(Moehario et al., 2009).

P. aeruginosa is an opportunistic pathogen and most commonly present serious infection and therapeutic threat within hospital environment. Infections caused by multidrug resistance (MDR) P. aeruginosa have been associated with significant increase in patients' morbidity and mortality, length of hospital stay, requirement for additional medical procedure and surgery, chronic care, and overall cost (Lister and Wolter, 2011). As persist elsewhere, more and more cases due to the MDR P. aeruginosa occur in hospitals in Jakarta and the adjacent areas and give rise to serious problems. Thus, information on antibiotics for treatment of these patients is seriously needed. Empirical therapy should, however, be in line with local condition.

This study aimed to report antibiotic susceptibility of P. aeruginosa originated from all kind of specimens received in our laboratory in 2004 to 2010, and evaluate their trend of resistance to certain antibiotics.

MATERIALS AND METHODS

Specimens

All kinds of specimens, that is, blood, sputum, pus, urine and throat swab were received in the laboratory of Clinical Microbiology, Faculty of Medicine, University of Indonesia (CML-FMUI). The specimens' derived from hospitals, among other was National Hospital Cipto Mangunkusumo (a tertiary general public hospital), private practices and individuals.

Cultures and antibiotic susceptibility tests

Cultures and susceptibility tests to antibiotics were performed according to CML-FMUI standard practices (CML-FMUI, 2004, 2009) and performance standards for antimicrobial susceptibility testing from the Clinical and Laboratory Standards Institute (CLSI, 2012). Cultures were performed using Bectec 9050 (Becton Dickinson) and microorganism identification was determined using standard biochemical reactions; in recent years API20E biochemical identification system (BioMerieux) was used instead. The susceptibility of microorganisms to antibiotics was assessed using disc diffusion method. Antimicrobial susceptibility results were categorized in to three groups: sensitive (S), intermediate (I) and resistant (R) according to CLSI. The antibiotics susceptibility data was processed and analyzed using WHO-NET Version 5.6 program.

Antibiotics

Not all antibiotic discs were tested in all consecutive years due to inconsistent availability (stock shortage and laboratory policy). The following antibiotic discs were used continuously from 2004 to 2010: cefepime (FEP) 30 μg, ciprofloxacin (CIP) 5 μg, amikacin (AMK) 30 μg, gentamicin (GEN) 10 μg and meropenem (MEM) 10 μg. In 2006 to 2010, ceftazidime (CAZ) 30 μg, cefoperazone (CFP) 75 μg, tobramycin (TOB) 10 μg, levofloxacin (LVX) 5 μg, piperacillin-tazobactam (TZP) 110 μg, and imipenem (IPM) 10 μg were also tested. Aztreonam (ATM) 30 μg was evaluated for two years, 2009-2010. Susceptibility of P. aeruginosa to antibiotics were tabulated and good activity in vitro was defined by antimicrobial susceptibility of 80% or greater.

Statistical analysis

Chi-square test was employed to analyze the significant decrease or increase susceptibility to particular antibiotics between years using space plans systems (SPS) version 16.

RESULTS

P. aeruginosa countinuously persisted, 12 to19% from all specimens of total Gram negative bacteria (Figure 1). Among all Gram negative microorganisms isolated from 2004 to 2010, eight most frequent ones were presented in Table 1. Overall, P. aeruginosa was in the big five most frequent Gram negative bacteria found in all specimens. It was the second most frequent in 2004, the third in 2005, 2007 to 2009, and the fourth in 2006 and 2010. Antipseudomonas antibiotics were tested against all P. aeruginosa isolates, and the susceptibility patterns in 2010 was presented in Figure 2. It appeared that only antibiotic imipenem had good activity in-vitro, that is 80%, while meropenem, amikacin and piperacillin-tazobactam were less active.

Over period of 7 years until 2010, antibiotic susceptibility patterns of P. Aeruginosa showed declining trend to most antibiotic tested except for gentamicin and ciprofloxacin (Figure 3). Some fluctuation of susceptibility were observed within those periods for cefepime, amikacin, gentamicin, ciprofloxacin, meropenem. Statistically, however, either the increase or the decreasesusceptibility of each antibiotics was significant that is AMK p = 0.000, GEN p = 0.002, CIP p = 0.003, FEP p = 0.000, MEM p = 0.000. Despite the apparent increase trend of susceptibility observed for GEN and CIP from 2007 to 2010, there was a significant decrease of susceptibility of these antibiotics (Figure 3).

Susceptibility of P.aeruginosa to cephalosporins as presented in Figure 4 showed decreasing trend of susceptibility for ceftazidime and cefepime of more than 10%, and was statistically significant (CAZ p = 0.000 and FEP p = 0.006). Interestingly, for cefoperazone there was
Figure 1. Percentage of *P. aeruginosa* isolates compared to other Gram negative bacteria from 2004 to 2010.

Table 1. Eight most frequent Gram negative bacteria isolates in 2004 to 2010.

<table>
<thead>
<tr>
<th>Year</th>
<th>Isolates</th>
<th>No. of isolates</th>
<th>Year</th>
<th>Isolates</th>
<th>No. of isolates</th>
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<th>Isolates</th>
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<th>Year</th>
<th>Isolates</th>
<th>No. of isolates</th>
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<tr>
<td></td>
<td><em>P. aeruginosa</em></td>
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<td></td>
<td><em>E. coli</em></td>
<td>106</td>
<td></td>
<td><em>E. coli</em></td>
<td>103</td>
<td></td>
<td><em>K. pneumoniae</em> ss. Pneumoniae</td>
<td>98</td>
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<td><em>E. coli</em></td>
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<td>71</td>
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<td><em>P. aeruginosa</em></td>
<td>95</td>
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<td><em>P. aeruginosa</em></td>
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<td><em>P. aeruginosa</em></td>
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<td><em>P. aeruginosa</em></td>
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<td><em>K. oxytoca</em></td>
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<td><em>S. odorifer</em></td>
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**Figure 2.** Susceptibility of *P. aeruginosa* to antipseudomonas tested in 2010.

**Figure 3.** Changing pattern of *P. aeruginosa* susceptibility to antipseudomonas antibiotics used from 2004 to 2010.
up and down patterns in which a significant decrease of susceptibility occurred from 2008 to 2009 (p = 0.000). In 2010, an increase of susceptibility was apparent but statistically was not significant (p = 0.753). Ceftazidime and cefepime showed good activities in 2008 that is 84 and 83%. These antibiotics became less active in 2009 to 2010, that is 68 and 70%. Susceptibility of P. aeruginosa to ceftazidime and cefepime was similar, but higher than cefoperazone.

Antibiotic susceptibility patterns of P. aeruginosa to aminoglycosides was shown in Figure 5. It showed decrease susceptibility for all three aminoglycosides tested which statistically significant (AMK p = 0.000; GEN p = 0.002; TOB p = 0.000). The microorganism appeared to be more susceptible to amikacin than gentamicin. Earlier in 2008, amikacin was less active compared to tobramycin, however, it had better activity in 2009 and 2010. Amikacin showed better activity than gentamicin and tobramycin, that is 75% versus 68 and 65%, respectively in 2010. Susceptibility patterns of P. aeruginosa to ciprofloxacin and levofloxacin was rather similar in three consecutive years from 2008 to 2010, that is 63, 60 and 56% versus 66, 62 and 54%, respectively; significant declining susceptibilities were observed that is CIP p = 0.003, LVX p = 0.000 (Figure 6). In carbapenem group, depletion of susceptibility for both meropenem and imipenem in 2008 to 2009 was significant (p = 0.000), however, an insignificant increase of susceptibility of these antibiotics was observed in later years (p = 0.692) (Figure 7). Imipenem showed better activity than meropenem in 2010 which was 80% against 75%. Susceptibility of P. aeruginosa to piperacillin-tazobactam and aztreonam was shown in Figure 8. A declining trend was observed for both antibiotics from 2008 to 2010 which was not significant statistically (TZP p = 0.055, and ATM p = 0.346). In 2010, piperacillin-tazobactam showed nearly good activity, that is 75%.

**DISCUSSION**

Our study showed P. aeruginosa was constantly present as one of the most Gram negative bacteria isolated from clinical specimens in 2004 to 2010. Despite much lesser specimen received in our laboratory in recent years due to more microbiology laboratories available in the area, P. aeruginosa isolates found were rather consistent that is 12 to 19%. The same condition was reported by one private hospital in Jakarta in 2005 and 2010 (Soebandrio, 7th National Symposium of Indonesia Antimicrobial Resistance Watch Symposium, Jakarta, 2011), and also by one hospital in Solo, Central Java (Priyambodo and Saptawati, Dr. Moewardi General Hospital - Solo, Indonesia, unpublished, 2010). Though many more hospitals detected high occurrence of MDR P. aeruginosa in our country, published data is hardly available. The
Figure 5. Trend of *P. aeruginosa* susceptibility to Aminoglycosides from 2008 to 2010.

Figure 6. Trend of *P. aeruginosa* susceptibility to Quinolones from 2008 to 2010.
Figure 7. Trend of P. aeruginosa susceptibility to Carbapenem from 2008 to 2010.

Figure 8. Trend of P. aeruginosa susceptibility to Aztreonam and Piperacillin-Tazobactam from 2008 to 2010.
In the present study was similar to that reported by Pathmanathan et al. (2009) from Malaysia. Better susceptibility to ceftazidime than cefoperazone observed in our study was also found in Sudan (Saeed and Awad, 2009). Superiority of amikacin compared to gentamicin found in 2008 to 2010 (Figure 5) was confirmed by Mohanasoundaram (2011) which reported that susceptibility to amikacin was higher as compared to gentamicin that is 63, 41 and 46% versus 36, 32 and 32%, respectively. In 2009 and 2010, amikacin remained superior in comparison to tobramycin, and this was similar to that of Gad et al. (2010).

In quinolone group, the susceptibility of *P. aeruginosa* to ciprofloxacin and levofloxacin in the present study was higher compared to that of Javiya et al. (2006) which was only 26.76 and 35.71% for ciprofloxacin and levofloxacin, respectively. Adhikari et al. (2010) reported 47.76 and 44.78% susceptibility to those antibiotics. Activity of imipenem and meropenem to *P. Aeruginosa* shown in our study correlated with others which found imipenem had a better activity than meropenem (Gupta et al., 2006). Nonetheless, it was not in agreement to that reported by Tan et al. (2008), who found that meropenem was better than imipenem. In 2010, piperacillin-tazobactam showed nearly good activity that is 75% despite other study performed by Tan et al. (2008) which demonstrated 88.3%. The susceptibility of *P. aeruginosa* to aztreonam was 54%, which in fact was higher than the one reported by Pieboji et al. (2006) which is 33%.

**CONCLUSION**

In the past seven years until 2010, *P. aeruginosa* was one of the most Gram negative bacteria found from all kind of specimens received in CML-FMUI, Jakarta. Overall, there was a tendency of decrease susceptibility to all antibiotic tested. In 2010, the only anti-pseudomonas antibiotic showed good activity (80%) was imipenem, and so was suggested as drug of choice in pseudomonas infection.

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