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RESEARCH ARTICLE

Antibiotic use and antibiotic resistance profile of bacteria isolated from out-patients of Pakem primary health care Yogyakarta

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Abstract

Background: The use of antibiotics is one of the procedures in the treatment of infectious diseases. Antibiotic are given to kill or inhibit the growth of infectious bacteria within the host's system. Inappropriate use of antibiotics may lead to antibiotic resistance where the bacteria able to resist the effect of the drugs. **Objective:** The purpose of this study was to determine the pattern of antibiotic use and antibiotic resistance in out-patients at the Pakem Health Center, Yogyakarta. **Method:** This study employed a descriptive research design using the data of patients with bacterial infections. Twenty-six patients were the subjects of the study with predetermined characteristics, namely age, gender, occupation, and antibiotics given. **Result:** The result showed the five (5) common types of infections were pyoderma, pharyngitis, abscess, bronchitis, and wound infection. Meanwhile, the infectious bacteria found were *Staphylococcus aureus, Streptococcus pyogenes, Klebsiela pneumoniae, Acinetobacter baumannii, Klebsiella oxytoca, Pseudomonas aeruginosa*, and *Streptococcus betahaemolyticus*. The prescribed antibiotics included amoxicilin (73.33%), metronidazole (16.67%), gentamicin (6.67%), and ciprofloxacin (3.33%). The antibiotic resistant bacteria were *Acinetobacter baumannii, Klebsiela pneumoniae*, *Klebsiella oxytoca*, and *Staphylococcus aureus*. Among the test bacteria, several groups showed multiple-drug resistance. The five highest antibiotic resistance found were penicillin (52.9%), ampicillin (40.0%), tetracycline (33.3%), cefuroxime (33.3%), and amikacin (33.3%). **Conclusion:** The most common type of infection was pyoderma and the antibiotic treatment given to most occurring cases of infection was amoxicillin.

Introduction

One of the procedures to handle infectious diseases is antimicrobial therapy, which aims to kill or inhibit the growth of infectious bacteria in the body (Kemenkes, 2017; Ho & Ip, 2019). More than 90% of cases of respiratory tract infection and pharyngitis were administered antibiotics which resulted in an increased number of antibiotic prescriptions (Apsari *et al.*, 2017). Moreover, in America, the use of antibiotics increased among adult patients (about 192-198 million) in 2014 (Ho & Ip, 2019).

Antibiotics are powerful medicines that are taken to kill or inhibit the growth of bacteria in the body. However, the excessive use of antibiotics may trigger the emergence of antibiotic resistance (Humaida, 2014). Excessive use of antibiotics has an impact not only in terms of resistance but also affects the level of effectiveness and efficiency (Friedman *et al.*, 2016). This is because it is associated with increased morbidity, mortality, length of treatment, and care costs (Sinto, 2020). The resistant bacteria tend to cause the failure of infectious disease therapy because they have become resistant to antibiotics (Mahdani *et al.*, 2020). Antibiotic resistance in ESCAPE organisms (*Enterococcus, Staphylococcus. aureus, Klebsiella pneumoniae, Acinetobacter. baumannii, Pseudomonas aeruginosa*, and *Enterobacter* sp) is frequently linked to significantly higher rates of morbidity, mortality, and fiscal burden (Zhen *et al*., 2019).

Antibiotic resistance has become a major global problem (Murray *et al.*, 2022). In 2009, Indonesia was ranked 8th out of 27 countries with the highest multidrug-resistant predicate in the world (Estiningsih *et al.*, 2016). Bacteria can be resistant to an antibiotic due to several factors, such as the lack of cell organelles that are the target of antibiotics, certain bacterial species having cell walls which are not permeable to certain antibiotics, and a population of bacterial species do not necessarily have the same level of sensitivity to an antibiotic (Kemenkes, 2017). One way to lower the incidence of antibiotic resistance is to reduce the number of antibiotic prescriptions (Apsari *et al.*, 2017).

Appropriate use of antibiotics may reduce adverse events. The differences in the resistance patterns of bacteria determine the antibiotic prescription. Hence, this study aims to determine the antibiotic use and antibiotic resistance patterns of infectious bacteria associated with the out-patients within the primary health care at Pakem, to aid the effectiveness and efficiency of antibiotic prescription.

Methods

Design

This research employed a descriptive study with prospective data collection carried out by analysing patients' medical record data obtained from the Pakem primary health care, Yogyakarta.

Materials

The instrument used in this study was the research data form. The material used was the medical records of the patients and the specimen taken from patients according to the infection.

Inclusion and exclusion criteria

The inclusion criteria included out-patients in Pakem primary health care, Yogyakarta, who were diagnosed with infections and received antibiotic therapies, patients who were not undergoing haemodialysis, patients who were not treated from the hospital for at least 30 days, and patients that were willing to become probandi in this study. Meanwhile, the exclusion criterion was vegetarian patients.

Results

A total of 26 patient data were analysed. Patients who participated in the study were dominated by those in the late adolescent age (30.8%), followed by the early adolescents (15.4%), late adults (15.4%), early elderly (15.4%), late elderly (15.4%) and the early adults (7.7%) as shown in Table I.

Table I: Age characteristics of patients

Age	n	%
Early adolescence (12 - 16 years old)	4	15.4
Late adolescence (17 - 25 years old)	8	30.8
Early adult (26 - 35 years old)	2	7.7
Late adult (36- 45 years old)	4	15.4
Early elderly (46 - 55 years old)	4	15.4
Late elderly (56 - 65 years old)	4	15.4
Total	**26**	**100**

The results of the study obtained from the 26 patients showed various types of infections, most of which were pyoderma (19.3%), pharyngitis (15.4%), abscess (11.5%), bronchitis (11.5%), wound infectious (7.7%), otitis media (7.69%), cellulitis (3.9%), and sinusitis (3.9%) (Figure 1).

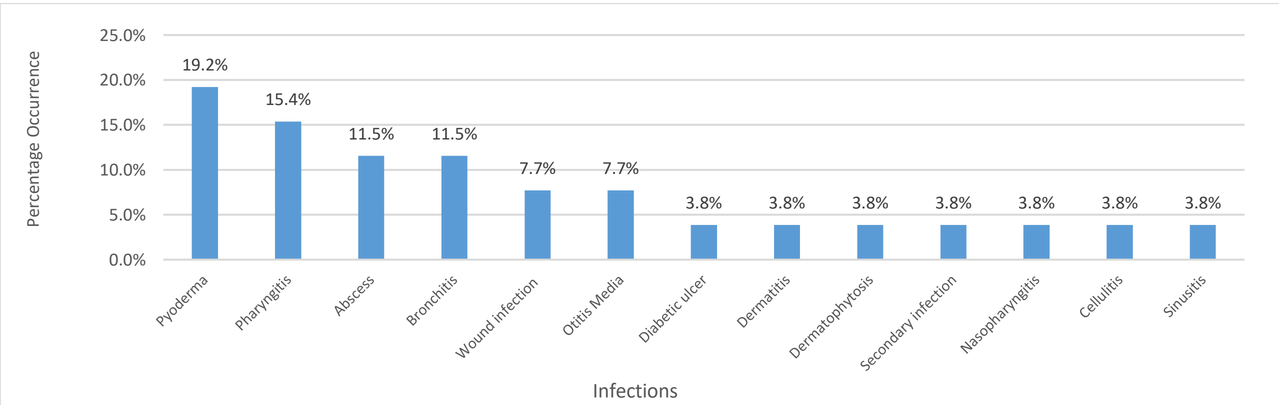

Figure 1: Percentage of infection type

Infections were caused by several types of bacteria with the largest percentage in *Staphylococcus aureus* (45.8%) followed by *Streptococcus pyogenes* (25%), *Klebsiella pneumonia* (12.5%), *A.baumannii* (4.2%), *Klebsiella oxytoca* (4.2%), *P.aeruginosa* (4.2%) and *Streptococcus betahaemolyticus* (4.2%) (Table II).

Table II: Bacteria causing infections

Bacteria	Total	%
Staphylococcus aureus	11	45.8
Streptococcus pyogenes	6	25.0
Klebsiella pneumoniae	3	12.5
Pseudomonas aeruginosa	1	4.2
Acinetobacter baumannii	1	4.2
Streptococcus betahaemolyticus	1	4.2
Klebsiella oxytoca	1	4.2
Total	**24**	**100**

In this study, data on the use of antibiotics for treatment were also obtained. The data showed that the most widely utilised antibiotics were amoxicillin 500 mg tablets (73.3%), metronidazole tablets (16.7%), then gentamicin (6.7%), and ciprofloxacin 500 mg tablets (3.3%) (Table III). Most amoxicillin was prescribed to infectious patients, especially those diagnosed with pharyngitis, followed by other types of infections such as dermatitis, abscesses, infectious wounds, and otitis media. Amoxicillin is a β-lactam antibiotic that has a broad spectrum and it is often used to treat various infectious diseases caused even by gram-positive and gram-negative bacteria, such as ear infections, pneumonia, streptococcal pharyngitis, skin infections, urinary tract infections, Salmonella infections, Chlamydia infections and Lyme disease (Benjamin, 2019). Amoxicillin is also a type of antibiotic that has been listed in the Indonesian National Formulary so that patients are guaranteed to get the right, efficacious, quality, safe, and affordable medicines (Apsari *et al*., 2017).

Table III: Antibiotic use

Antibiotic	Total	%
Amoxicillin	22	73.3
Metronidazole	5	16.7
Gentamicin	2	6.7
Ciprofloxacin	1	3. 3
Total	**30**	**100**

Based on the patient's data, antimicrobial susceptibility testing (AST) was then carried out to determine antibiotic sensitivity. The result revealed the diversity in the bacterial resistance pattern to the test antibiotics (Figure 2; Table IV).

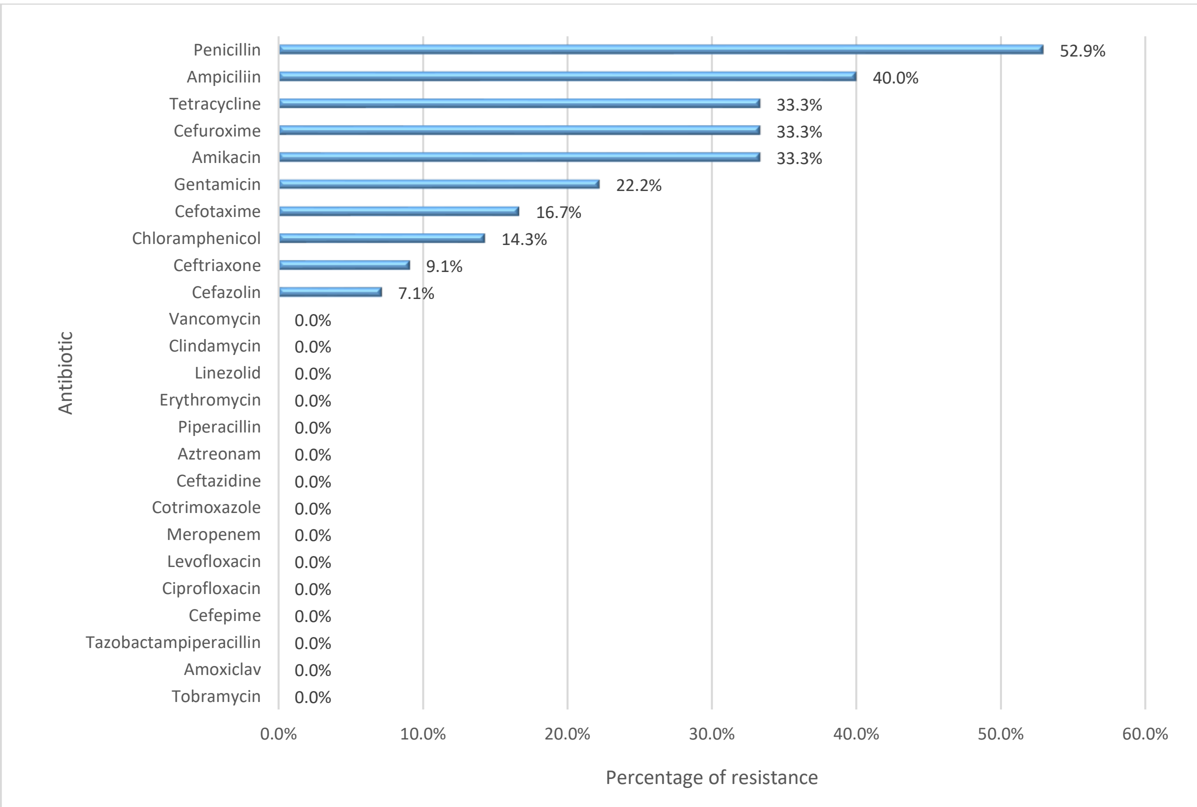

Figure 2: Antibiotic resistance (%)

Table IV: Antibiotic sensitivity test results

Group	Antibiotic	Bacteria (% resistant)						
		A	B	C	D	E	F	G
Aminoglycosides	Gentamicin	100	0	0	0	33.3	-	-
	Tobramycin	0	0	0	0	-	-	-
	Amikacin	100	33.3	0	0	-	-	-
Β-lactam + β lactamase inhibitor	Ampi-sulbactam	0	-	-	-	-	-	-
	Amoxiclav	-	0	0	-	-	-	-
Piperacillin + tazobactam	Tazobactapiperacillin	0	0	0	0	-	-	-
Cephalosporin	Cefazolin	-	0	100	-	0	-	-
	Cefuroxime	-	33.3	0	-	-	-	-
	Cefepime	0	0	0	0	-	0	0
	Ceftriaxone	100	0	0	-	-	0	0
	Ceftazidime	0	-	-	0	-	-	-
	Cefotaxime	100	-	-	-	-	0	0
Fluoroquinolone	Ciprofloxacin	0	0	0	0	9.1	-	-
	Levofloxacin	0	0	0	0	-	0	0
Carbapenem	Meropenem	0	0	0	0	-	-	-
Cotrimoxazole	Cotrimoxazole	0	0	0	-	0	-	-
Monobactam	Aztreonam	-	-	-	0	-	-	-
Penicilin	Ampicillin	-	100	100	-	-	0	0
	Piperacillin	-	-	-	0	-	-	-
	Penicillin	-	-	-	-	81.8	0	0
Macrolides	Erythromycin	-	-	-	-	0	0	0
Oxazolidinone	Linezolid	-	-	-	-	0	-	-
Tetracycline	Tetracycline	-	-	-	-	36.4	-	0
Lincosamide	Clindamycin	-	-	-	-	0	0	0
Glycopeptide	Vancomycin	-	-	-	-	-	0	0
Chloramphenicol	Chloramphenicol	-	-	-	-	25.0	0	0

Note: **A:** (*Acinetobacter baumannii*); **B**: (*Klebsiella pneumoniae*); **C:** (*Klebsiella oxytoca*); **D:** (*Pseudomonas aeruginosa*); **E:** (*Staphylococcus aureus*); **F:** (*Streptococcus betahaemolyticus*); **G:** (*Streptococcus pyogenes*)

Discussion

Based on the result of the antibiotic sensitivity test, *A. baumannii* showed 100% resistance to gentamicin and amikacin (aminoglycosides). The most studied mechanism of resistance to aminoglycoside antibiotics in strain *A. baumannii* is the production of aminoglycotic-modifying enzymes (AMEs) (Kyriakidis *et al*., 2021). In this study, *A. baumannii* also showed absolute resistance to ceftriaxone (100%) and Cefotaxime (100%). Additionally, based on the result of antibiotic susceptibility testing (AST) between 1995 and 2004, it was also confirmed that there was an increase in the percentage of resistance to all antibiotics in four main classes, namely fluoroquinolones (50-73%), aminoglycosides (19-31%), *β-lactam* (39-66%), and carbapenems (9-39%)(Vázquez-López *et al*., 2020). This indicates that the bacteria have developed resistance to survive.

Klebsiella pneumoniae showed similar low resistance to amikacin and cefuroxime (33.3%), while to Penicillin by 100%. Moreover, it is also reported in other studies where most of the *K. pneumoniae* isolates were classified as multidrug-resistant (MDR) with high levels of resistance to a broad spectrum of drugs including β-lactams, aminoglycosides, and quinolones (Fair & Tor, 2014). Antibiotics from the β-lactam group are commonly prescribed worldwide including penicillins, cephalosporins, monobactams, and carbapenems (Ur Rahman *et al*., 2018). The resistance mechanism of β-lactam antibiotics-resistant bacteria is the production of β-lactamase enzymes in the presence of cell wall transpeptides (Igrejas *et al*., 2019).

Klebsiella oxytoca showed 100% resistance to cefazolin and ampicillin. Other studies also mentioned the presence of *K. oxytoca* carrying a constitutive β-lactamase low resistance to penicillin but susceptible to other β-lactams (Fenosa *et al*., 2009). Furthermore, *Staphylococcus aureus* was resistant to several antibiotics and the largest percentage was to a penicillin (81.8%). *S. aureus* resistance to penicillin is associated with Methicillin-Resistant *Staphylococcus Aureus* (MRSA) (Laux *et al.*, 2019). It can produce penicillinase which can rehydrate the *β-lactam* ring of penicillin, causing the antibiotic to be insensitive. MRSA is a kind of multi-drug resistant "*super bacteria*" that are resistant to penicillin, cephalosporin, chloramphenicol, lincomycin, aminoglycosides, tetracycline, macrolides, quinophthalones, sulfonamides and rifampicin. Such is a very difficult problem in clinical medicine (Guo *et al*., 2020). In addition, *S. aureus* showed resistance to tetracycline (36.4%), gentamicin (33.3%), chloramphenicol (25%) and ciprofloxacin (9.1%). Meanwhile, *P. aeruginosa*, *Streptococcus betahaemolyticus*, and *Streptococcus pyogenes* were not resistant to any antibiotics in this study.

The result of the sensitivity test showed that several bacteria in this study belong to the multidrug-resistant organisms (MDRO) category (**Table III**). MDRO is a microorganism, especially bacteria that show resistance to at least one type of antibiotic from in ≥3 antibiotic group (Siegel *et al.*, 2017) This study showed that *Staphylococcus aureus* showed resistance to five (n=5) groups of antibiotics, one of which was the Penicillin group (Penicillin). This resistance might be due to the production of penicillinase which is in charge of degrading penicillin in the extracellular space by hydrolyzing the ring β-lactam (Ho & Ip, 2019). In addition, *Klebsiella pneumonia* was also resistant to three (n=3) types of antibiotic groups, namely aminoglycosides (amikacin), cephalosporins (cefuroxime), and penicillin (penicillin).

In most cases, infections caused by resistant bacteria result in twice higher adverse outcomes as those caused by susceptible bacteria (Cosgrove & Carmeli, 2003). These negative effects could be clinical (death or therapy failure) or economic (cost of treatment or length of stay). Additionally, it makes a note of delayed therapy and antibiotic treatment failures to eradicate the infection (Friedman *et al*., 2016). The published MDROs restrain guidance remarks ongoing debate areas on optimal control strategies (Siegel *et al*., 2017). Moreover, various approaches have diminished MDROs rates. Thus, intervention options for controlling MDRO transmission must be based on local problem assessments, the prevalence of various MDROs and feasibility (Siegel *et al*., 2017). Furthermore, individuals ought to seek proper guidance as well as adopt effective measures that care for their needs and circumstances (Siegel *et al*., 2017). The management of patients infected with resistant bacteria is conducted by providing appropriate antibiotics; considering their clinical efficacy, sensitivity, patient clinical condition, cost, prioritizing first-line/narrow-spectrum antibiotics, and their availability in healthcare facilities (Kemenkes, 2011)

This study showed that most of the isolates resistant to antibiotics were gram-negative where *A. baumannii* had the highest percentage (30.8%), followed by *Staphylococcus aureus* (18.6%), *Klebsiella oxytoca* (14.3%), and *Klebsiella pneumoniae* (11.9%). Our research findings can be compared to a study carried out in hospitals in India, *Staphylococcus aureus* also showed a relatively high occurrence (53%) *(Mogasale et al.,* 2021). In another study, *A. baumannii* and *K. pneumoniae* were the most common gram-negative isolates and had 89% and 81% of possible extensive drug resistance (P-XDR), respectively (Vaithiyam *et al.*, 2020). Among gram-positive pathogens *S. aureus,* 63% of isolates were MDR followed by P-XDR (22%) and only 15% showed non-multidrug-resistant (NMDR) pattern (Vaithiyam *et al*., 2020). Furthermore, a study conducted in Tanzania also reported that *Staphylococcus aureus* (n=100; 22.8%), *was* the most commonly isolated bacteria. Seventy-eight (78) isolates of *Staphylococcus aureus* were obtained and from the antibiotic sensitivity test results, 27 (34.6%) were identified as methicillin-resistant Staphylococcus aureus (MRSA) (Moremi *et al.*, 2016). The resistance rate of *Klebsiella pneumoniae* to third-generation cephalosporins was 38.5% (Moremi *et al*., 2016)

Increased levels of antibiotic resistance can be attributed to various causes: (i) there could be a direct relationship between the emergence of resistant strains and the magnitude of antibiotic consumption, (ii) the usage level of amoxicillin and ampicillin in Indonesia is getting to an alarming stage, (iii) the inappropriate doses use and therapy timing potentially increase resistance (Murniati, 2012). In a recent research on a serious infection of children in South-East Asia, 17% of blood culture isolates were not susceptible to ampicillin, penicillin, gentamicin, or a combination of these drugs (Frost *et al*., 2018). In this study, overall antibiotic resistance was relatively low. As shown in **Figure 2**, with a cutting score of 50%, all the tested antibiotics still appear potent, except for penicillin. However, using these drugs needs to be based on the bacteria's sensitivity to antibiotics.

Resistance mechanisms can be transmitted from one bacterium to another either vertically, when inherited from relatives, or horizontally, through plasmids, which potentially transfer resistance among different species (Vázquez-López *et al*., 2020). The primary cause of resistance is the misuse of antibiotics (Ghosh *et al*., 2020). This consequently has an impact on treatment efforts, more difficulties and higher health costs. As reported by the World Health Organisation infections by resistant bacteria result in ineffective treatment, and increased risk of infection spread to others (WHO, 2015).

Conclusion

The most common type of infection observed in this study was pyoderma and the antibiotic treatment administered to most occurring cases of infection was amoxicillin. In addition, several groups of bacteria were resistant to multiple groups of antibiotics. According to the antibiotic sensitivity test result, the level of resistance from the highest percentage to the least is as follows: penicillin> ampicillin> tetracycline> cefuroxime> amikacin> gentamicin> cefotaxime> chloramphenicol> ceftriaxone> cefazolin.

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