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A Review: The Resistance Patterns of Bacteria *Staphylococcus aureus* toward Beta-Lactam Antibiotics

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Abstract
Background: *Staphylococcus aureus bacteria are Gram positive bacteria that cause infection in tropical areas such as Indonesia due to dusty air conditions, warm temperatures, and humidity. Various diseases caused by S. aureus range from food poisoning, skin and soft tissue infections, serious and even fatal infections acquired in the hospital (nosocomial infections) to severe life-threatening infections. Treatment of S. aureus infection is done by administering antibiotics, such as beta-lactam antibiotics, polypeptides, aminoglycosides, chloramphenicol, tetracycline, macrolides and fluoroquinolones. Beta-lactam antibiotics are the most commonly used drugs because they are the first line of antibiotic therapy for treating bacterial infections, but the level of bacterial resistance to beta-lactam antibiotics continues to increase. This review article discusses the resistance pattern of S. aureus bacteria to beta-lactam antibiotics using the Kirby-Bauer agar diffusion method. The aim of this study is to examine the scientific literature regarding the resistance pattern of S. aureus bacteria to beta-lactam antibiotics from clinical samples in various hospitals.*
Materials and Method: *This literature review uses a method by collecting various literatures in the form of primary data in the form of international journals from the last 10 years (2010-2020) using online media through several official websites.*
Results: *S. aureus is resistant to 10 types of beta-lactam antibiotics. The tested antibiotics consisted of penicillin G with an average percentage of resistance 96.6%, oxacillin 61.2%, ampicillin 84.4%, amoxicillin 64.9%, cefoxitin 49.8%, cefuroxime 39.2%, cefalotin 22.4%, cefotaxime 60.4%, ceftriaxone 36.7%, and imipenem 17.9%. The resistance results were obtained from three sampling locations.*
Conclusion: *The highest level of resistance was found in penicillin G antibiotics, namely 96.6%, while the lowest level of resistance was in the antibiotic imipenem at 17.9%.*
Key Word: *Staphylococcus aureus bacteria, Beta-lactam antibiotics, Resistance.*

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I. Introduction

Staphylococcus aureus is a Gram-positive spherical bacterium, usually arranged in irregular shapes like grapes, not forming spores and flagella. *S. aureus* contains polysaccharides and proteins that function as antigens and are important substances in the cell wall structure (1). *S. aureus* is a normal flora of the human body which is an opportunistic pathogen. *S. aureus* bacteria are known as cause various diseases ranging from food poisoning, skin and soft tissue infections, serious and even fatal infections acquired in hospital (nosocomial infections) to severe life-threatening infections (2).

Treatment of *S. aureus* infection by administering antibiotics, such as beta-lactam antibiotics, polypeptides (vancomycin), aminoglycosides (gentamycin, kanamycin, amikacin), chloramphenicol, tetracycline, macrolides (erythromycin) and fluoroquinolone (ciprofloxacin). Beta-lactam antibiotics are the most commonly used drugs because they are the first line of antibiotic therapy for treating bacterial infections, but the level of bacterial resistance to beta-lactam antibiotics continues to increase (3).

The general mechanism of antibiotics by inhibiting cell wall synthesis, inhibiting protein synthesis, folate antagonists and influencing the synthesis or metabolism of bacterial nucleic acids (4). Beta-lactam antibiotics have a mechanism by inhibiting cell wall synthesis, where the beta-lactam ring inhibits the action of the transpeptidase enzyme which is used by bacteria to form peptidoglycan (a component of bacterial cell walls) (5). About 40-62% of antibiotics are used inappropriately for diseases should not require antibiotics. In various hospitals it is found that 30% -80% of antibiotic uses is not based on indications which is one of the causes of bacterial resistance to antibiotics. To reduce resistance, the choice of antibiotics must be appropriate for the bacteria causes the infection (6).

Antibiotic resistance is a condition when bacteria develop the ability to defeat antibiotics designed to kill them, it does not mean the body is resistant to these antibiotics (7). Bacterial resistance to antibiotics is a problem in the world, especially in developing countries where the use of antibiotics has not been properly

monitored (8). Antibiotic resistance occurs through 3 mechanisms, namely the drug cannot reach its working place, drug inactivation and microbes change the antibiotic binding site (3).

The resistance of *S. aureus* bacteria to beta-lactam antibiotics continues to grow (9). The resistance of *S. aureus* to beta-lactam antibiotics is because *S. aureus* bacteria produce the beta lactamase enzyme which hydrolyzes the beta lactam ring, causing the antibiotic unable to inhibit the work of the transpeptidase enzyme, which is used by bacteria to form peptidoglycan (a component of bacterial cell walls), so the bacteria are unsusceptible to antibiotics and continue to thrive (5). Resistance of *S. aureus* to antibiotics occurred in the 1940s when *S. aureus* was first reported to be resistant to penicillin (10).

Several factors cause bacterial resistance are the use of inappropriate antibiotics, the emergence of bacterial strains that are resistant to antibiotics and the spread of these strains to other bacteria. Factors need to be considered are the presence of host (intrinsic) such as the location of infection, the ability of antibiotics to reach the target organ of infection according to the concentration of the therapeutic dose, the patient's normal flora and environmental ecology (11).

II. Material and Methods

The search for data in this review article was carried out by collecting various literatures of primary data in the form of official books and international journals from the last 10 years (2010-2020). Using online media through websites such as Academic Journals, ResearchGate, ScienceDirect, Semantic Scholar, PubMed, and the Journal of Advances in Microbiology by using the keywords "*Staphylococcus aureus* bacteria", "Beta lactam antibiotics", "*S. aureus* resistance to antibiotics", "*S. aureus* resistance to beta-lactam antibiotics".

III. Result

Tabel 1. The Resistance Patterns of *S. aureus* toward Beta-Lactam Antibiotics

Antibiotics	Sampling Location	Sampling Type	Number of Isolates	Resistant Isolates	% Resistance	Reference
Penicillin G	Kist Medical College Hospital, Lalitpur	Urine, blood, pus, sputum, swabs, bodily fluids and tips	100	100	100%	(12)
	HIV patient YRG CARE, a tertiary HIV care center in Chennai, India	Urine, pus, sputum and body fluids	396	380	95.2%	(13)
	Chitwan Chitwan Medical University Teaching Hospital, Nepal	Pus, blood, urine and sputum	306	290	94.7%	(14)
Oxacillin	Abia State University Teaching Hospital, Aba Southeast Nigeria	Blood, swab (ear, throat, wound, vaginal high) pus and urine	104	68	65.4%	(15)
	From chronic sinusitis patients in Northern Iran.	Nose swab	10	6	60%	(16)
Oxacillin	Cotonou National University Hospital (Benin)	Urine, sperm, urethral dan vaginal	24	14	58.3%	(17)
	Midnapore Medical College Hospital, Midnapore, West	Burns swab	100	96	96%	(18)

Ampicillin	Bengal, India					
	Debre Markos Referral Hospital, Amhara Region, Ethiopia	Surgical scars swab	73	60	82.2%	(19)
	Kist Medical College Hospital, Lalitpur	Urine, blood, pus, sputum, swabs, body fluids and tips	100	75	75%	(12)
Amoxicillin	Cotonou National University Hospital (Benin)	Urine, sperm, urethral dan vaginal	24	20	83.3%	(17)
	Debre Markos Referral Hospital, Amhara Region, Ethiopia	Surgical scars swab	73	60	82.2%	(19)
	Gondar University Hospital	Blood	17	5	29.4%	(20)
Cefoxitin	Midnapore Medical College Hospital, Midnapore, West Bengal, India	Burn swab	100	70	70%	(18)
	Chitwan Chitwan Medical University Teaching Hospital, Nepal	Pus, blood, urine and sputum	306	132	43.1%	(14)
	Local hospital in northern Jordan	Blood, swab (ear, eye, nose, wound), abscess, semen, sputum, catheter tip, and urine	358	130	36.3%	(21)
Cefuroxime	Okitipupa Specialist Hospital, in Ondo State, Nigeria	Skin swab, nostrils, wound exudates or umbilical cord excision sites of hospitalized patients	17	12	70.6%	(22)
Cefuroxime	Various hospitals and clinical wards in Pattukkottai, Tamil Nadu State, India	Sputum and throat swab	81	22	27%	(23)
	Chronic sinusitis patient in Northern Iran	Nose swab	10	2	20%	(16)

Cefalotin	Jimma University Specialized Hospital (JUSH), Ethiopia	Wound swabs (Surgical scars, trauma, abscesses, boils, burns and diabetic foot ulcers)	47	14	29.8%	(24)
	Yekatit 12 Hospital Medical College, Addis Ababa, Ethiopia	Pus/abscess, swab (nose, throat, eye), vaginal discharge, urine, body fluids, ear fluid, feces and sputum	194	37	19.1%	(25)
	Hawassa University Comprehensive Specialized Hospital	Ear swabs	33	6	18.2%	(26)
Cefotaxime	Brazzaville Hospital, Congo	Wound swab	42	42	100%	(27)
	Abia State University Teaching Hospital, Aba Southeast Nigeria	Blood, swab (ear, throat, wound, vaginal high) pus and urine	104	44	42.3%	(15)
	Three referral hospitals namely Milad, Motahary and Loghman	Urine, feces, sputum, nasopharyngeal swab and blood	98	38	39%	(28)
Ceftriaxone	Burns unit at Dhaka Medical College Hospital, Dhaka, Bangladesh	Burns swab	29	17	60%	(29)
	Gondar University Hospital, Northwestern Ethiopia	Blood	17	6	35.3%	(20)
	Jimma University specialized hospital(JUSH), Ethiopia	Wound swabs (Surgical scars, trauma, abscesses, boils, burns and diabetic foot ulcers)	47	7	14.9%	(24)
Imipenem	Brazzaville Hospital, Congo	Wound Swab	42	13	30.9%	(27)
	Three referral hospitals namely Milad, Motahary and Loghman	Urine, feces, sputum, nasopharyngeal and blood swabs	98	12	13%	(28)
	Burns unit at Dhaka Medical College Hospital, Dhaka, Bangladesh	Burns swab	29	3	10%	(29)

IV. Discussion

Infectious diseases caused by bacteria are increasingly reported in Indonesia which cause a decrease in the quality of human health, for example *Staphylococcus aureus. S. aureus* bacteria have the ability to be resistant to an antibiotic. As a result of this resistance, handling of bacteria becomes difficult and the choice of therapy is limited so that the quality of treatment and health decreases. Actually, treatment of infection is not too difficult if we know the cause and the medicine to anticipate it. Treatment of *S. aureus* infection carried out by administering antibiotics. Resistance occurs due to inappropriate administration of antibiotics. Antibiotic resistance occurs when bacteria develop the ability to defeat the antibiotics designed to kill them, which does not mean that the body is resistant to them (7).

Based on the results of the literature, the researchers conducted a study to determine the resistance and susceptibility of *S. aureus*, whose isolates came from clinical samples of patients in the hospital such as wound swabs, burn swabs, surgical scars swab, diabetic foot ulcer swabs, nostril swab, nose swab, throat swab, eye swab, ear swab, nasopharyngeal swab, high vaginal swab, skin swab, wound exudate or umbilical cord excision, urine, pus, boil, abscess, vaginal discharge, blood, body fluids, ear fluid, feces, earwax, sputum, semen, sperm, vaginal, urethral and catheter tip.

Antibiotic susceptibility testing was carried out by using the agar diffusion method (Kirby-Bauer). This method is very commonly used because it is a standard procedure for testing the sensitivity of bacterial isolates. The standard medium used was Mueller-Hinton agar (MHA). This test was carried out by incubating the bacterial isolate at 37°C for 24 hours (31). Kirby-Bauer agar diffusion is carried out by placing a disk containing antimicrobial compounds on the surface of the test microbial inoculated medium. During incubation, these antimicrobial compounds will diffuse into the agar medium. The effectiveness of antimicrobial compounds after the event in the presence of an inhibition zone that forms around the disk. The wider the inhibition zone, the more sensitive the compound is (10).

Currently *S. aureus* is resistant to several types of beta-lactam antibiotics. According to the results of the literature review, which are shown in Table 1, *S. aureus* is resistant to 10 types of beta-lactam antibiotics. Resistance results were obtained from three sampling locations. The tested antibiotics consisted of penicillin G with a resistance percentage of 100%; 95.2%; 94.7%, oxacillin 65.4%; 60%; 58.3%, ampicillin 96%; 82.2%; 75%, amoxicillin 83.3%; 82.2%; 29.4%, cefoxitin 70%; 43.1%; 36.3%, cefuroxime 70.6%; 27%; 20%, cefalotin 29.8%; 19.1%; 18.2%, cefotaxime 100%; 42.3%; 39%, ceftriaxone 60%; 35.3%; 14.9%, and imipenem 30.9%; 13%; 10%. The average values obtained for the percentage of resistance were penicillin G 96.6%, oxacillin 61.2%, ampicillin 84.4%, amoxicillin 64.9%, cefoxitin 49.8%, cefuroxime 39.2%, cefalotin 22.4%, cefotaxime 60.4%, ceftriaxone 36.7%, and imipenem 17.9%. From the average value obtained, the highest level of resistance was penicillin G, which was 96.6%, while the lowest resistance level was imipenem antibiotic at 17.9%.

Penicillin G and oxacillin antibiotics are actively against Gram positive bacteria but rapidly hydrolyzed by beta lactamase so they are not effective against *S. aureus*. Ampicillin is also actively against certain Gram positive and negative bacteria, but can be inactivated by beta lactamase. Almost all *Staphylococcus* are resistant to ampicillin. Amoxicillin is an ampiciliin derivative that has the same antibacterial spectrum. Available in a fixed combination form, namely amoxicillin and clavulanic acid (Co-Amoxiclav), which is only given to infections suspected to be caused by strains that produce beta lactamase and are resistant to amoxicillin (4). Clavulanic acid is a beta lactamase inhibitor that can protect amoxicillin from hydrolysis caused by beta lactamase. However, the resistance mechanism is not only through the production of the beta lactamase enzyme by bacteria that can destroy beta-lactam antibiotics, but also through changes in penicillin binding protein (PBP) (11).

Cefalotin is the first generation of cephalosporins that are effective against Gram positive bacteria (*S. aureus*), but also can be resistant to these bacteria due to the beta lactamase enzyme. Cefoxitin and cefuroxime are second generation cephalosporins that are less effective in treating Gram-positive bacterial (*S. aureus*) infections than the first-generation of cephalosporins. Meanwhile, compared to the first and second generations, cefotaxime and ceftriaxone, which are third generation cephalosporins, are less effective against Gram positive bacteria (*S. aureus*) (4).

Imipenem is a derivative of carbapenem. This antibiotic is bactericidal, has broad spectrum activity, which is sensitive to all types of bacteria, both Gram positive and Gram negative bacteria, both aerobic and anaerobic (4).

The resistance of *S. aureus* to beta-lactam antibiotics is because *S. aureus* bacteria produce the beta lactamase enzyme which hydrolyzes the beta lactam ring, causing the antibiotic unable to inhibit the work of the transpeptidase enzyme, which the enzyme is used by bacteria to form peptidoglycan (a component of bacterial cell walls), so that bacteria are not susceptible to antibiotics and continue to thrive (5).

The main cause of bacterial resistance to antibiotics is generally due to their widespread and irrational use. More than half of the patients in hospital receive antibiotics as therapy or prophylaxis. About 80% of

antibiotic consumption is used for human purposes and at least 40% is based on inaccurate indications, for example virus infection (3).

In addition, education for patients is also important. Education can be delivered through counseling, seminars and media such as television, newspapers, radio, social media. Not all diseases are treated with antibiotics. If necessary, the use of antibiotics must be in accordance with the doctor's instructions, both the dose used and the range of therapy. Antibiotics must be given in appropriate doses to minimize the occurrence of bacterial resistance to antibiotics.

V. Conclusion

The resistance pattern of *S. aureus* bacteria isolates towards beta-lactam antibiotics in several hospitals found that the highest resistance was penicillin G antibiotics, namely 96.6%, while the lowest resistance level was imipenem antibiotics at 17.9%.

References

[1]. Jawetz, Melnick, Adelberg's. Medical Microbiology. 26th ed. The McGraw-Hill. 2013.
[2]. Santosaningsih D, Zuhriyah L, P MN. *Staphylococcus aureus* pada Komunitas Lebih Resisten terhadap Ampisilin dibandingkan Isolat Rumah Sakit. J Kedokt Brawijaya. 2011;26(4):204–7.
[3]. Triana D. Frekuensi β-Lactamase Hasil *Staphylococcus aureus* Secara Iodometri Di Laboratorium Mikrobiologi Fakultas Kedokteran Universitas Andalas. J Gradien. 2014;10(2):992–5.
[4]. Team Medical Mini Notes. Basic Pharmacology & Drug Notes. MMN Publishing; 2017. 1–396 p.
[5]. Van Bambeke F, Mingeot-Leclercq M-P, Glupczynski Y, Tulkens PM. Mechanisms of Action. In: Anti-infective Therapy. 2017. p. 1162-1180.e1.
[6]. Nurmala N, Virgiandhy I, Andriani A, Liana DF. Resistensi dan Sensitivitas Bakteri terhadap Antibiotik di RSU dr. Soedarso Pontianak Tahun 2011-2013. eJournal Kedokt Indones. 2015;3(1).
[7]. CDC. Antibiotic resistance threats in the United States 2019. Cent Dis Control Prev. 2019;1–148.
[8]. Lestari ES, Duerink DO, Hadi U, Severin JA, Nagelkerke NJD, Kuntaman K, et al. Determinants of carriage of resistant *Staphylococcus aureus* among *S. aureus* carriers in the Indonesian population inside and outside hospitals. Trop Med Int Heal. 2010;15(10):1235–43.
[9]. Firizki. F. Pattern Sensitivity of *Escherichia coli* and *Klebsiella* Sp. to Antibiotic Sefalosporin Period of Year 2008-2013 Di Bandar Lampung. Med Fac Lampung Univ Abstr. 2014;64–73.
[10]. Parastan R, Kargar M, Solhjoo K, Kafilzadeh F. *Staphylococcus aureus* biofilms: Structures, antibiotic resistance, inhibition, and vaccines. Gene Reports. 2020;20.
[11]. Pratiwi RH. Mekanisme Pertahanan Bakteri Patogen Terhadap Antibiotik. J Pro-Life. 2017;4(3):418–29.
[12]. CP Bhatt, BMS Karki, B Baral, S Gautam, A Shah, A Chaudhary. Antibiotic susceptibility pattern of Staphylococcus aureus and methicillin-resistant staphylococcus aureus in a tertiary care hospital. J Pathol Nepal. 2014;4:548–51.
[13]. Chinnambedu RS, Marimuthu RR, Sunil SS, Amrose P, Ramachandran V, Pachamuthu B. Changing antibiotic resistance profile of Staphylococcus aureus isolated from HIV patients (2012–2017) in Southern India. J Infect Public Health. 2019;13(1):1–5.
[14]. Ansari S, Nepal HP, Gautam R, Rayamajhi N, Shrestha S, Upadhyay G, et al. Threat of drug resistant Staphylococcus aureus to health in Nepal. BMC Infect Dis. 2014;14(157):1–5.
[15]. Nsofor CA, Nwokenkwo VN, Ohale CU. Prevalence and Antibiotic Susceptibility Pattern of Staphylococcus aureus Isolated from Various Clinical Specimens in South East Nigeria. MOJ Cell Sci Rep. 2016;13(2).
[16]. Rezai MS, Pourmousa R, Dadashzadeh R, Ahangarkani F. Multidrug resistance pattern of bacterial agents isolated from patient with chronic sinusitis. Casp J Intern Med. 2016;7(2):114–9.
[17]. Sina H, Semassa JA, Dougnon VT, Adjile AA, Baba-Moussa F, Bankole HS, et al. Antibiotics Resistance Profile of Staphylococci Isolated from Urogenital Infections and Toxins Production of Staphylococcus aureus Strains. Ann Med Health Sci Res. 2018;8(1):29-34.
[18]. Karmakar A, Dua P, Ghosh C. Biochemical and Molecular Analysis of Staphylococcus aureus Clinical Isolates from Hospitalized Patients. Can J Infect Dis Med Microbiol. 2016;7.
[19]. Kahsay A, Mihret A, Abebe T, Andualem T. Isolation and antimicrobial susceptibility pattern of Staphylococcus aureus in patients with surgical site infection at Debre Markos Referral Hospital, Amhara Region, Ethiopia. Arch Public Heal. 2014;72(16):1–7.
[20]. Dagnew M, Yismaw G, Gizachew M, Gadisa A, Abebe T, Tadesse T, et al. Bacterial profile and antimicrobial susceptibility pattern in septicemia suspected patients attending Gondar University Hospital, Northwest Ethiopia. BMC Res Notes. 2013;6(283):1–7.
[21]. Al-Zoubi MS, Al-Tayyar IA, Hussein E, Al Jabali A, Khudairat S. Antimicrobial susceptibility pattern of Staphylococcus aureus isolated from clinical specimens in Northern area of Jordan. Iran J Microbiol. 2015;7(5):265–72.
[22]. Eucharia EN. Isolation and Antibiogram of Staphylococcus aureus from Patients Admitted at Specialist Hospital Okitipupa, Ondo State, Nigeria. Br Microbiol Res J. 2016;14(6):1–8.
[23]. Manikandan C, Amsath A. Antibiotic susceptibility of bacterial strains isolated from patients with respiratory tract infections. Int J Pure Appl Zool. 2013;1(1):61–9.
[24]. Mama M, Abdissa A, Sewunet T. Antimicrobial susceptibility pattern of bacterial isolates from wound infection and their sensitivity to alternative topical agents at Jimma University Specialized Hospital, South-West Ethiopia. Ann Clin Microbiol Antimicrob. 2014;13(14):1–10.
[25]. Dilnessa T, Bitew A. Prevalence and antimicrobial susceptibility pattern of methicillin resistant Staphylococcus aureus isolated from clinical samples at Yekatit 12 Hospital Medical College, Addis Ababa, Ethiopia. BMC Infect Dis. 2016;16(398):1–9.
[26]. Deyno S, Toma A, Worku M, Bekele M. Antimicrobial resistance profile of Staphylococcus aureus isolates isolated from ear discharges of patients at University of Hawassa comprehensive specialized hospital. BMC Pharmacol Toxicol. 2017;18(35):1–7.
[27]. Moyen R, Ahombo G, Nguimbi E, Ontsira NE, Niama RF, Yala GC, et al. Activity of beta-lactam antibiotics and production of beta-lactamases in bacteria isolated from wound infections in Brazzaville, Congo. African J Microbiol Res. 2014;8(23):2290–4.
[28]. Armin S, Karimi A, Fallah F, Tabatabaei SR, Alfatemi MH, Khiabani P, et al. Antimicrobial resistance patterns of Acinetobacter baumannii, Pseudomonas aeruginosa and Staphylococcus aureus isolated from patients with nosocomial infections admitted to Tehran hospitals. Arch Pediatr Infect Dis. 2015;3(4).

[29]. Hasan R, Acharjee M, Noor R. Prevalence of vancomycin resistant Staphylococcus aureus (VRSA) in methicillin resistant S. aureus (MRSA) strains isolated from burn wound infections. Tzu Chi Med J. 2016;28(2):49–53.
[30]. Nassar MSM, Hazzah WA, Bakr WMK. Evaluation of antibiotic susceptibility test results: How guilty a laboratory could be? J Egypt Public Health Assoc. 2019;94(4):1–5.

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