*IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)*
*e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 16, Issue 1 Ser. I (Jan. –Feb. 2021), PP 55-58*
*www.Iosrjournals.Org*

# Resistance Patterns *Pseudomonas aeruginosa* to Beta-lactam AntibioticsIsolated from ClinicalSamples. A Review

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***Abstract:***
***Background****: Pseudomonas aeruginosa is a Gram-negative pathogenic bacterium that attacks immunocompromised patients and it causes of morbidity and mortality in hospitalized patients. The emergence of P. aeruginosa bacteria resistance to beta-lactam antibiotics is one of the problems in the treatment of infectious diseases. Understanding about bacterial resistance to antibiotics is currently very important in clinical practice, due to changing patterns of bacterium resistance. This review aims to examine the scientific literature related to research on the resistance pattern of P. aeruginosa to beta-lactam antibiotics from clinical samples in various hospitals with Kirby Bauer agar diffusion method.*
***Materials and Methods****: The method that usedin this literature studies by finding sources in the form of primary data from international journals in the last 10 years (2010-2020).*
***Results****: From the results of the resistance pattern of P. aeruginosa to beta-lactam antibiotics, obtained that P. aeruginosa isolates were isolated from clinical samples in various hospitals and tested on 10 antibiotics with the following results: (1) Amoxicillin 88,8%, (2) Ampicillin 95%, (3) Piperacillin 64,87%, (4) Cefazolin 85,33%, (5) Cefuroxime 89,90%, (6) Ceftazidim 78,16%, (7) Ceftriaxone 80,09%, (8) Cefixime 98,33%, (9) Ceftizoxim 88,63%, (10) Imipenem 54,06%.*
***Conclusion:****The highest level of resistance was cefixime with 98,33% and the lowest was Imipenem at 54,06%.*
***Key Word****:P. aeruginosa, betalactam antibiotics, resistance, clinical sample.*

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Date of Submission: 06-01-2021 Date of Acceptance: 21-01-2021

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## I. Introduction

*P. aeruginosa* is an opportunistic Gram-negative bacterium that can cause various infections, which are difficult to treat because *P. aeruginosa* has developed resistance to several antibiotics(1). *P. aeruginosa* has intrinsic and acquired resistance to many antibiotics. In addition, it can also occur due to irrational use of antibiotics. The hydrolysis of beta lactam antibiotics by beta lactamase is the most common resistance mechanism against this group of antibiotics in Gram negative bacteria(2).

*P. aeruginosa* can cause infection in immunocompromisedpatients(3). These bacteria can invade the bloodstream, resulting in a systemic infection called bacteremia. The condition of *P. aeruginosa* infection is also commonly found in patients with severe burns, diabetes, cancer, organ transplants, respiratory tract, urinary tract, stomach, and wounds(4). In several therapies using antibiotics, *P. aeruginosa* has shown the ability to develop resistant strains(5).

Therapy that can be used in *P. aeruginosa* infection are penicillin, gentamicin, meropenem, imipenem, doripenem, aztreonam, polymixin E, and ciprofloxacin. However, over time, some antibiotics experience resistance followed by evolution from bacteria(6). Infection due to *P. aeruginosa* is difficult to treat, because of the increased intrinsic resistance of the bacteria as well as the ability to become resistant to different antibiotics(7).The use of antibiotics is currently quite wide accompanied by low knowledge about the use of appropriate antibiotics so that it can cause resistance.

In general, the mechanisms of antibiotic resistance to *P. aeruginosa* can be divided intrinsically and acquired. Intrinsic refers to a resistance mechanism that is genetically coded and acquired refers to resistancethrough the acquisition of additional mechanisms or is a consequence of a mutation event under selective pressure(8).The basic mechanism of *P. aeruginosa* resistance to beta-lactam antibiotics involves the production of extended spectrum beta lactamases (ESBLs) enzymes(9).ESBL is an enzyme produced by bacteria that has the ability to hydrolyze penicillin, cephalosporin, and monobactam antibiotics and cause resistance to all of these antibiotics(10).

Bacterial resistance to beta-lactam antibiotics is caused by enzymatic inactivation of the antibiotics, namely by producing the enzyme betalactamase which hydrolyzes the beta-lactam ring so that the antibiotic becomes inactive. The widespread use and misuse of antibiotics by people with the improper practice of unskilled healthcare practitioners has led to increased resistance(9).

## II. Methods

In making this review article, the technique used is literature study by searching for sources or literature in the form of primary data in the official books and international journals from the last 10 years (2010-2020). In addition, data searches in this review article use online media through trusted sites such as IJCMAS, ScienceDirect, Research Gate, Pubmed, Semantic scholar and AJOMR. The preparation of this article was carried out by searching for data using the keywords "Resistance Patterns *Pseudomonas aeruginosa*" and "Betalactam antibiotics".

## III. Result

**Table No.1: Results of *P. aeruginosa* bacteria resistance to beta-lactam antibiotics.**

| Antibiotics | Location | Source of Isolates | | | | | | | | | | | | | | | | | | | | Number of Isolates | Resistance of Isolates | % Resistance | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | B | P | SS | S | FE | U | ES | T | F | T | L | E | TS | V | W | B | H | C | E | A | O | | | | |
| Amoxicilin | Teaching Hospital in Nepal | 5 | 17 | 4 | 10 | 2 | 13 | 5 | - | - | - | - | - | 3 | 2 | - | - | - | - | - | - | 2 | 63 | 29 | 83% | (11) |
| | Azadi Teaching Hospital in the city of Kirkuk, Iraq | - | - | - | - | - | 5 | - | - | - | - | - | - | - | 10 | 11 | 14 | - | - | - | - | - | 40 | 37 | 92,5% | (12) |
| | Ahmadu Bello University Education, Zaria, Nigeria | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 11 | - | - | - | - | - | 11 | 10 | 90,9% | (13) |
| Ampicillin | Azadi Teaching Hospital in the city of Kirkuk, Iraq | - | - | - | - | - | 5 | - | - | - | - | - | - | - | 10 | 11 | 14 | - | - | - | - | - | 40 | 38 | 95% | (12) |
| | Hospital in Islamabad | 4 | 41 | - | 5 | - | 32 | 3 | - | - | - | - | - | - | - | - | - | 4 | 3 | 8 | - | - | 100 | 100 | 100% | (14) |
| | Intensive Care Unit (ICU) RSUP in Sanglah | - | 3 | - | 5 | - | 2 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 5 | 15 | 10 | 90% | (1) |
| Piperacillin | Teaching Hospital in Nepal | 16 | 38 | - | 9 | - | 18 | 2 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 83 | 33 | 60% | (15) |
| | Pakistani | 24 | 50 | - | 10 | - | 24 | - | 50 | 14 | 6 | - | - | 16 | - | 6 | - | - | - | - | - | - | 200 | 12 | 75% | (16) |
| | Institute of Medical Sciences, Islamabad, Pakistan | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Kanchipuram Tertiary Care Hospital, Tamil Nadu, India | 4 | 49 | - | 38 | - | 13 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 104 | 62 | 59,61% | (17) |
| Cefazolin | Hospital in Islamabad | 4 | 41 | - | 5 | - | 32 | 3 | - | - | - | - | - | - | - | - | - | 4 | 3 | 8 | - | - | 100 | 99 | 99% | (14) |
| | Burns patient in Guilan, Iran | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 86 | - | - | - | - | - | - | 86 | 76 | 83,7% | (18) |
| | A wound infection patient in Pattukkottai, Tamil Nadu, India | - | - | - | - | - | - | - | - | - | - | - | - | - | 30 | - | - | - | - | - | - | - | 30 | 22 | 73,3% | (19) |
| Cefuroxime | Teaching Hospital in Nepal | 5 | 17 | 4 | 10 | 2 | 13 | 5 | - | - | - | - | - | 3 | 2 | - | - | - | - | - | - | 2 | 63 | 42 | 84% | (11) |
| | Hospital in Islamabad | 4 | 41 | - | 5 | - | 32 | 3 | - | - | - | - | - | - | - | - | - | 4 | 3 | 8 | - | - | 100 | 100 | 100% | (14) |
| | Tertiary care teaching hospital in Tripura | - | - | - | 7 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 7 | 6 | 85,71% | (20) |
| Ceftazidime | Teaching Hospital in Nepal | 16 | 38 | - | 9 | - | 18 | 2 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 83 | 53 | 89,83% | (15) |
| | Ekiti State University Teaching Hospital, Ado-Ekiti, Ekiti State Nigeria | - | - | - | - | - | 17 | 4 | - | - | - | - | - | - | - | 13 | - | - | - | - | - | 8 | 42 | 34 | 80,95% | (21) |
| | Sya'ban and Khatam-Ul-Anbiya Hospitals, Tehran Azhar Clinic, Tehran | 7 | 6 | - | - | - | 36 | 4 | 24 | - | - | 9 | 2 | - | - | - | - | - | - | - | - | - | 138 | 88 | 63,7% | (22) |
| Ceftriaxone | Teaching Hospital in Nepal | 16 | 38 | - | 9 | - | 18 | 2 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 83 | 13 | 72,23% | (15) |
| | Ekiti State University Teaching Hospital, Ado-Ekiti, Ekiti | - | - | - | - | - | 18 | 5 | - | - | - | - | = | - | - | 11 | - | - | - | - | - | 8 | 42 | 34 | 80,95% | (21) |

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | State Nigeria | | | | | | | | | | | | | | | | | | | | | | | |
| | Pakistani Institute of Medical Sciences, Islamabad, Pakistan | 24 | 50 | - | 10 | - | 24 | - | 50 | 14 | 6 | - | - | 16 | - | 6 | - | - | - | - | - | - | 200 | 27 | 87,1% | (16) |
| Cefixime | Azadi Teaching Hospital in the city of Kirkuk, Iraq | - | - | - | - | - | 5 | - | - | - | - | - | - | - | 10 | 11 | 14 | - | - | - | - | - | 40 | 38 | 95% | (12) |
| | Southwest Nigeria Ibadan Hospital | - | - | - | - | - | - | 23 | - | - | - | - | - | - | - | 47 | 30 | - | - | - | - | - | 100 | 100 | 100% | (9) |
| | Tertiary Hospital in Ogbomoso, Southwest Nigeria | 2 | - | - | 5 | - | 2 | 6 | - | - | - | - | 1 | - | 4 | 10 | - | - | - | - | 1 | - | 31 | 31 | 100% | (23) |
| Ceftizoxime | Sya'ban and Khatam-Ul-Anbiya Hospitals, Tehran Azhar Clinic, Tehran | 10 | 9 | - | - | - | 35 | 5 | 24 | - | - | 21 | 5 | - | - | - | - | - | - | - | - | - | 109 | 109 | 78,9% | (22) |
| | Clinical laboratory in Karachi, Pakistan | - | 14 | - | 5 | 3 | 65 | 5 | - | - | - | - | - | - | 4 | - | - | - | - | - | - | - | 96 | 9 | 91% | (24) |
| | Tehran ShahidMotahari Burns Hospital, Iran | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 50 | - | - | - | - | - | 50 | 48 | 96% | (25) |
| Imipenem | Intensive Care Unit (ICU) RSUP in Sanglah | - | 3 | - | 5 | - | 2 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 5 | 15 | 8 | 63% | (1) |
| | Sya'ban and Khatam-Ul-Anbiya Hospitals, Tehran Azhar Clinic, Tehran | 4 | 3 | - | - | - | 34 | 1 | 18 | - | - | 9 | 2 | - | - | - | - | - | - | - | - | - | 71 | 71 | 51,4% | (22) |
| | Pakistani Institute of Medical Sciences, Islamabad, Pakistan | 24 | 50 | - | 10 | - | 24 | - | 50 | 14 | 6 | - | - | 16 | - | 6 | - | - | - | - | - | - | 200 | 11 | 47,8% | (16) |

Note : B (blood), P (pus), SS (skin scratches), S (sputum), F(feses), U(urine), ES (ear swab), T (trachea), F (fluid), T (tissue), L (lession), E (eye), TS (throat swab), V (vagina), W (wound), B (burn), H (hand), C (catheter), EN (environment), A (abscess), O (other).

## IV. Discussion

*P. aeruginosa* is an opportunistic pathogenic bacterium that causes infection in critically ill patients and patients with very low levels of immunity. Difficulty in treating *P. aeruginosa* bacterial infection also occurs due to bacterial resistance to beta-lactam antibiotics. Several studies have been conducted to address the problem of antibiotic resistance. The resistance pattern of *P. aeruginosa* bacteria was tested using several methods, but most of the methods used were *Kirby Bauer* agar diffusion. *Kirby-Bauer* disc diffusion is a standard procedure for testing the sensitivity of bacterial isolates, the standard medium used is Mueller-Hinton agar (MHA). This test was carried out by incubating the bacterial isolate at 37 ° C for 24 hours(26).

Beta-lactam antibiotics are pharmacological therapies that are often given to infected patients. However, cases of bacterial resistance to antibiotics in this class are also increasing. Continued exposure to beta-lactam antibiotics causes the production and mutation of the enzyme beta lactamase in some bacteria, such as *P. aeruginosa*(27).*P. aeruginosa* is an opportunistic bacterium and has been resistant to betalactam antibiotics, making it difficult to administer therapy to patients infected with these bacteria (7). The mechanism of action of the beta-lactamase enzyme is by hydrolyzing the beta-lactam ring in the antibiotic which causes the ring to break, so that the antibiotic cannot inhibit the work of the transpeptidase enzyme which forms peptidoglycan which is needed for the formation of bacterial cell walls, so that bacteria are not susceptible to antibiotics and continue to grow(28). *P. aeruginosa* isolate resistance was found to be 13% and 10.3%, respectively, in the US and Europe. Resistance is the ability of bacteria to neutralize and weaken the working power of antibiotics so that bacteria become less susceptible to antibiotics, so this can cause patient morbidity and mortality(29).

In Table 1, it shows that the 10 beta-lactam antibiotics were tested showed various results as indicated by the percentage. From the number of isolates in several hospitals in various countries that were tested, each had different results. *P. aeruginosa* isolates have developed resistance to beta-lactam antibiotics. The results obtained were the percentage of *P. aeruginosa* bacteria resistance to beta-lactam antibiotics obtained from three sampling locations, namely as follows: Amoxicillin (83%, 92.5%, 90.9%), Ampicillin (95%, 100%, 90 %), Piperacillin (60%, 75%, 59.61%), Cefzolin (99%, 83.7%, 73.3%), Cefuroxime (84%, 100%, 85.71%), Ceftazidime (89 , 83%, 80.95%, 63.7%), Ceftriaxone (72.23%, 80.95%, 87.1%), Cefixime (95%, 100%, 100%), Ceftizoxime (78,9 %, 91%, 96%), Imipenem (63%, 51.4%, 47.8%). Obtained an average value for the percentage of resistance, namely Amoxicillin (88.8%), Ampicillin (95%), Piperacillin (64.87%), Cefzolin (85.33%), Cefuroxime (89.90%), Ceftazidime (78, 16%), Ceftriaxone (80.09%), Cefixime (98.33%), Ceftizoxime (88.63%), Imipenem (54.06%). From all the data, the highest level of resistance to beta-lactam is the antibiotic cefixime 98.33%. Meanwhile, imipenem showed the lowest resistance at 54.06%.

The difference in the percentage of *P. aeruginosa* bacteria resistant to beta-lactam antibiotics between places and countries was caused by irrational use of antibiotics. Irrational use of antibiotics is a major cause of

increasing antibiotic resistance(30).Improper administration of antibiotics is a risk factor that will make the bacteria mutate and become resistant. In addition, antibiotic resistance can also be caused by a lack of patient compliance in using antibiotic drugs, as well as a lack of patient information and knowledge about these antibiotics (31).

## V. Conclusion

The resistance pattern of *P. aeruginosa* isolates in several hospitals showed the highest level of resistance to cefixime antibiotics 98,33% and imipenem showed the lowest resistance 54,06%.

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