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DEVELOPMENT OF COMBINATION ANTIBIOGRAM TO START EMPIRICAL THERAPY FOR PSEUDOMONAS AERUGINOSA IN A TERTIARY CARE HOSPITAL.

Microbiology

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ABSTRACT

Introduction Pseudomonas aeruginosa is one of the most common life-threatening bacteria that cause nosocomial infections and is a major cause of morbidity and mortality. Local antibiograms helps in empirical antimicrobial selection based on susceptibility patterns within a distinct patient population. Most of Pseudomonas aeruginosa isolates are multidrug resistant, therefore combination antibiotic therapy has been advised for their management. The aim of study was to develop the local combination antibiogram to help clinicians choosing optimum empirical combination regimen for Pseudomonas aeruginosa infections. **Methods:** A retrospective study was conducted at Dept of Microbiology, RCSM GMC Kolhapur. Pseudomonas aeruginosa strains from all samples received between June 2022 to Oct 2023 were included in study. Kirby-Bauer disk diffusion method was used for susceptibility testing as per the CLSI guidelines for Pseudomonas aeruginosa. While choosing combination regimen susceptibility to at least one of the dual agents was considered. The susceptibility to the antipseudomonal single antibiotics (Piperacillin-Tazobactam, Ceftazidime, Cefepime or Meropenem) or to those administered in combination with an aminoglycoside (Gentamicin or Amikacin) or fluoroquinolone (Ciprofloxacin) was calculated. All analyses were conducted using MS EXCEL. **Results:** A total of 451 Pseudomonas. aeruginosa isolates were included in the study. 58 (12.86%) Isolates were from ICU and 393 (87.14%) from wards. The susceptibility of the isolates to monotherapy beta lactam antibiotics were 49% for Ceftazidime, 76.5% for Meropenem, 52.55% for Cefepime, 68.29% for Piperacillin-Tazobactam and it ranges between 49 to 76.5 %. The combination regimen containing Gentamicin and Meropenem provided the highest coverage rate (85.35%) and the one containing Ciprofloxacin and Ceftazidime (62.08%) provided the lowest coverage rate among all the combination regimens. **Conclusion** Local combination antibiogram should be developed to facilitate clinicians in selecting optimal combination regimen for empirical therapy of infected patients caused by Pseudomonas aeruginosa. Choosing aminoglycosides, especially Amikacin, Gentamicin and fluoroquinolones like Ciprofloxacin as the additive agents can maximize the empirical coverage rate

KEYWORDS

Pseudomonas aeruginosa, Antibiogram, Susceptibility, Combination regimen.

INTRODUCTION

Pseudomonas aeruginosa (PA) is one of the most common life-threatening bacteria that cause nosocomial infections, and is a major cause of morbidity and mortality.[1] Pseudomonas infection is especially prevalent among patients with burn wounds, cystic fibrosis, acute leukemia, organ transplants, and intravenous-drug addiction. *Pseudomonas aeruginosa* is a common nosocomial contaminant, and epidemics have been traced to many items in the hospital environment. Patients who are hospitalized for extended periods are frequently colonized by this organism and are at increased risk of developing infection. The most serious infections include malignant external otitis, endophthalmitis, endocarditis, meningitis, pneumonia, and septicemia.[2] Meta-analysis reported that the decision-making process for selecting an appropriate empirical therapy regimen is key to reduce sepsis-associated mortality.[3]

Piperacillin/tazobactam (PTZ), Cefepime, Ceftazidime, and Meropenem are widely used to treat severe Pseudomonas aeruginosa infections in the intensive care units (ICUs). The excellent bactericidal activity of these b-lactam antibiotics makes them the most crucial empirical option to treat Pseudomonas aeruginosa.[4] Some studies have demonstrated that using combination therapy with different classes of drugs successfully reduces mortality among patients with severe MDR- *Pseudomonas aeruginosa* infections. [5,6]

While there is no international consensus on the definition of multi-drug resistance, most published studies considered that multi-drug resistant as to resistant to at least one drug from three different antibiotic classes, mainly aminoglycosides, antipseudomonal penicillins, cephalosporins, carbapenem and fluoroquinolones. .[7]

The selection of antimicrobial agents for use in *Pseudomonas aeruginosa* empirical therapy should always consider local resistance patterns. Traditional local antibiograms usually help prescribers to select the optimal empirical single-antibiotic treatment; however, they do not reflect the real antimicrobial resistance conditions when two antimicrobial agents are combined. Combination antibiograms should be developed to help physicians in selecting appropriate combinations of antimicrobial agents to expand the coverage of resistant *Pseudomonas aeruginosa*. The aim of our study is to develop the local combined antibiogram to help clinicians choosing optimal empirical combination regimen for *Pseudomonas aeruginosa* infections.

MATERIAL AND METHODS:

A retrospective study was conducted at Dept of Microbiology RCSM GMC and CPR Hospital Kolhapur from Jun 2022 to Oct 2023. All *Pseudomonas aeruginosa* bacterial isolates were included in the study and susceptibility of all the culture isolates were analyzed according to the standard protocol. Kirby-Bauer disk diffusion method was used for susceptibility testing and the isolates were classified as susceptible, resistant, or intermediate according to zone of inhibition value from Clinical and Laboratory Standards Institute (CLSI) guidelines for *Pseudomonas aeruginosa*.[8] The intermediate isolates were considered resistant. The *Pseudomonas aeruginosa* isolates isolated from ICU and from the general ward were categorized into the ICU and non-ICU groups, respectively. The susceptibility to the antipseudomonal single antibiotics (Piperacillin-Tazobactam, Ceftazidime, Cefepime or Meropenem) or to those administered in combination with an aminoglycoside (Gentamicin or Amikacin) or fluoroquinolone (Ciprofloxacin) was calculated. An isolate's susceptibility to a combination regimen was defined as its susceptibility to at least one of the dual agents [7]. All analyses were conducted using MS EXCEL.

RESULT:

A total of 451 *Pseudomonas aeruginosa* isolates were included in our study. 58 (12.86%) Isolates from ICU and 393 (87.14%) from wards. The distribution of the 451 *Pseudomonas aeruginosa* isolates was as following:274 (61%) isolates collected from pus, 71 (16%) from sputum, 43 (9%) from urine, 27 (6%) from blood, 36 (8%) from fluid like pleural, ascites, CSF etc.

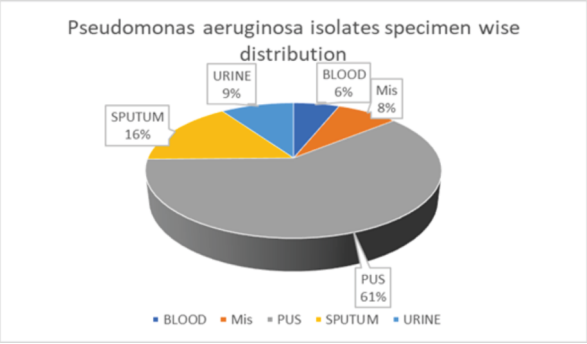

Table no 1 Coverage rates of single antibiotics and combined regimens

	Monotherapy	With Amikacin	With Gentamicin	With Ciprofloxacin
N 451	(%)	291 (64.52)	297 (65.85)	255(56.54)
Ceftazidime	221 (49)	311 (68.96)	318 (70.51)	280 (62.08)
Meropenem	345 (76.5)	378 (83.81)	385 (85.37)	363 (80.49)
Cefepime	237 (52.55)	321 (71.18)	326 (72.28)	283 (62.75)
Piperacillin - Tazobactam	308 (68.29)	326 (72.28)	360 (79.82)	324 (71.84)

Table No.2 Susceptibility rates of single antibiotics and combined regimens ICU patients

N 58	Monotherapy	With Amikacin	With Gentamicin	With Ciprofloxacin
Monotherapy		37 (63.79)	39 (67.24)	37 (63,79)
Ceftazidime	26 (44.83)	37 (63.79)	40 (68.97)	39 (67.24)
Meropenem	39 (67.24)	43 (74.14)	45(77.59)	44 (75.86)
Cefepime	29 (50.00)	40 (68.97)	41 (70.69)	41 (70.69)
Piperacillin-tazobactam	42 (72.41)	50 (86.21)	50 (86.21)	46 (79.31)

Table No. 3 Susceptibility rates of single antibiotics and combined regimens non-ICU patients

N 393	Monotherapy	With Amikacin	With Gentamicin	With Ciprofloxacin
Monotherapy		254 (64.63)	258 (65.65)	218 (55.47)
Ceftazidime	195 (49.62)	274 (69.72)	278 (70.74)	241 (61.32)
Meropenem	306 (77.86)	335 (85.24)	340 (86.51)	320 (81.42)
Cefepime	208 (52.93)	281(71.50)	284 (72.26)	252 (64.12)
Piperacillin-tazobactam	266 (67.68)	306 (77.86)	310 (78.88)	278 (70.74)

- The susceptibility of all the isolates to single beta lactam antibiotics are 49% for Ceftazidime, 76.5% for Meropenem, 52.55% for Cefepime, 68.29% for Piperacillin-Tazobactam and it ranges between 49 to 76.5 %. To expand the empirical coverage rate, we combined the b-lactam agents with aminoglycosides and fluoroquinolones (Table1). The combination regimen containing Gentamicin and Meropenem provided the highest coverage rate (85.35%) and the one containing Ciprofloxacin and Ceftazidime (62.08%) provided the lowest coverage rate among all the combination regimens. All the combined regimens exhibited a greater coverage rate (62 to 86%) than did any of the single b-lactam antibiotics (49 to 76%). In ICU patients Piperacillin-tazobactam showed highest susceptibility rate among all monotherapy drugs as well as in all combined regimens. Adding an aminoglycoside resulted in higher susceptibility rates than adding a fluoroquinolone.

DISCUSSION:

In this study, we focused on the importance of determining appropriate empirical combination regimens to treat *Pseudomonas aeruginosa* infections. Although local antibiograms were available to help us in selecting a proper empirical single b-lactam antibiotic in the hospital, the hospital did not yet have access to an antibiogram capable of assessing the appropriateness of local combination therapies. Combination therapies are developed with consideration given to the susceptibility of bacteria to the single antimicrobial agents used in the therapies. The antibiograms are useful clinical tools for evaluating the antimicrobial coverage of multiple antibiotics to inform the physicians regarding choosing optimal empirical combination regimes. The combination antibiogram could provide more detail and accurate susceptibility information for clinician when they are trying to use empirical combination regimen to treat severe *Pseudomonas aeruginosa* infections. For example, in our study, Meropenem susceptibility to *Pseudomonas aeruginosa* was (76.5%) while expanded to (85.37%) when Gentamicin was combined. Our Study has reported that single antimicrobial agents exhibit low coverage for *Pseudomonas aeruginosa* isolates; using such medications in combination with aminoglycosides (Amikacin or Gentamicin) or fluoroquinolones (Ciprofloxacin) could significantly expand the coverage rates, and aminoglycosides can expand the coverage to a greater extent than can fluoroquinolones. In our study, none of the single b-lactam antibiotic provided coverage of >80% for the ICU isolates. Combination of Meropenem and Amikacin, super-additive effects were observed against *Pseudomonas aeruginosa* infections. With regard to the clinical efficacy and prevention of antibiotic resistance, Meropenem combination therapy with aminoglycoside is the most superior treatment for pseudomonal infections, and the findings in this study suggest that Meropenem is still clinically very useful but combination therapy with aminoglycoside would be preferable for better coverage.[9]

CONCLUSION

Local combination antibiogram should be developed to facilitate clinicians in selecting optimal combination regimen for empirical therapy of infected patients caused by *Pseudomonas aeruginosa*. Choosing aminoglycosides, especially Amikacin, Gentamicin and fluoroquinolones like Ciprofloxacin as the additive agents can maximize the empirical coverage rate.

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