

Pseudomonas species and Acinetobacter baumannii associated Urinary tract infection: Antimicrobial resistance patterns and therapeutic alternatives.

ABSTRACT

Background

Pseudomonas species and Acinetobacter **baumanii(spelling)** are uncommon opportunistic pathogens in our environment, they have recently emerged as significant aetiological agents in nosocomial infections particularly in immunocompromised individuals and have become more resistant to antibiotics on a global scale, this is due to the widespread use of broad-spectrum antibiotics, such as latest generation carbapenems and cephalosporins.

This study's goal was to examine changes in antibiotic susceptibility profiles of *A. baumannii* and *Pseudomonas spp isolates* over the course of the one-year study period in our facility.

METHODS

This was a retrospective study that involved a review of the medical microbiology laboratory records for the antimicrobial susceptibility patterns of *Pseudomonas spp* and *Acinetobacter baumannii* isolated from the urinary samples of patients who were been assessed for Urinary tract infection between April 2020 to March 2021. The bacteria were isolated and identified from routine urine samples using standard bacteriological methods and the **API(Expand)**. In vitro antibiotic susceptibility test (AST) to Aztreonam, Piperacillin-tazobactam, Cefoperazone, Levofloxacin, Amikacin, Ceftazidime, Imipenem and Meropenem was routinely performed by the modified Kirby-Bauer disk diffusion test and susceptibility break points determined using the Clinical and Laboratory Standards Institute (CLSI) guidelines.

RESULTS

Acinetobacter baumannii isolates showed the more resistance rate to Ceftazidime (46.2%), Piperacillin-tazobactam (46.1%) and Levofloxacin (53.9%) but had least resistance to Aztreonam (0%), and Amikacin (15.4%). Similarly, *Pseudomonas aeruginosa* isolates were most resistant to Piperacillin-tazobactam (53.3%), followed by Ceftazidime and Cefoperazone (40%) respectively, however 60% of all *Pseudomonas aeruginosa* isolates were susceptible to Ceftazidime and Meropenem, while 46.7% were sensitive to Amikacin.

CONCLUSION

In our setting for the empirical treatment of urinary tract infection (UTI) due to *A. baumannii*, Aztreonam, Amikacin and Meropenem are possible drugs of Choice. While for *Pseudomonas aeruginosa* associated UTIs Meropenem and Ceftazidime can be used for empirical treatment. Finally, with the greater than 20% resistance rates to Carbapenems noticed in *A. baumannii* and some *Pseudomonas species* especially *Pseudomonas aeruginosa*, this emphasizes the need for antibiotic stewardship programme within our facility.

KEYWORDS

Acinetobacter baumannii, *Pseudomonas species*, Imipenem, Meropenem, Levofloxacin, Aztreonam

INTRODUCTION.

Pseudomonas spp are gram-negative, non-glucose-fermenting, strictly aerobic, motile, catalase-positive and cytochrome oxidase-positive bacillus. *Acinetobacter baumannii* is a bacillus that is gram-negative, strictly aerobic, non-glucose-fermenting, not motile, catalase-positive, and cytochrome oxidase-negative [1, 2]. It can colonise the epidermis of the human skin, respiratory, and digestive systems and is extensively spread in nature [3]. Although these bacteria are uncommon opportunistic pathogens in our environment, they have recently emerged as significant aetiological agents in nosocomial infections and are linked to high rates of morbidity and mortality, particularly in weak and immunocompromised individuals [4]. Currently, these pathogens have turned out to be a “red-alert” because of their rapid emergence of resistance following the overuse and misuse of antibiotics and the increased incidence and the worldwide spread of multidrug-resistant (MDR) isolates (5). These microorganisms' antibiotic resistance profile is influenced by a number of mechanisms, including membrane permeability changes, dysregulation of intrinsic resistance mechanisms, acquisition of resistance components from other bacteria, and the emergence of efflux pumps. There have been reports on the presence of **extended-spectrum -lactamases (ESBLs)(beta)**, type D and type B (metallo--lactamases) carbapenemases in *A. baumannii*, as well as porin and efflux pump disorders, but **type A carbapenems(carbapenemases)** have not been reported [6]. This is because of the clinical significance of increased -lactam resistance, particularly to carbapenems. Apart from ceftazidime, *Pseudomonas spp* has an AmpC-type chromosomal cephalosporin that confers resistance to penicillins and to first-, second-, and third generation

cephalosporins. Additionally, it can develop type A, B, or D carbapenemases, modify OprD porin, and exhibit active expulsion mechanisms such MexAB-OprM, which confers carbapenem resistance [7–9)

When *A. baumannii* and *Pseudomonas spp* are carbapenem-susceptible, carbapenems remain the preferred treatment. Although typically used in conjunction with carbapenems, aminoglycosides, particularly amikacin and tobramycin, may be beneficial for therapy [10]. Sulbactam and carbapenems together are frequently used to treat *A. baumannii*. Although some isolates are resistant, ciprofloxacin or levofloxacin has good effectiveness against *P. aeruginosa* while being ineffective against *A. baumannii*. Treatment options are severely limited if the bacterium is resistant to both carbapenems and aminoglycosides, and colistin is typically used as a last resort.

A. baumannii has unfortunately become alarmingly more resistant to antibiotics on a global scale, which is mostly due to the widespread use of broad-spectrum antibiotics, such as latest generation carbapenems and cephalosporins [11]. Therefore, it is not unusual to come across multi-resistant *A. baumannii* isolates that can only be treated with colistin, even though resistance to this antibiotic has also been noted [12]. Concern has been drawn to this problem since this bacterium causes infections in vulnerable patients. Given the danger of nephrotoxicity associated with using colistin, its usage is limited to infections caused by these multiresistant bacteria.

A. baumannii and *P. aeruginosa* are two bacteria that may develop resistance if empirical treatment for urinary tract infections (UTIs) is not started properly. This study's goal was to examine changes in the *A. baumannii* and *Pseudomonas spp isolates* antibiotic susceptibility profiles over the course of the one-year study period in our environment.

MATERIALS AND METHODS.

Study setting:

The study was conducted in the department of medical microbiology of the Lagos State University Teaching Hospital, an 800-bedded tertiary centre located in Ikeja, Lagos southwest Nigeria. The hospital is dedicated to teaching, research and specialist services and serves Lagos State and neighbouring States in southwest Nigeria.

Study design:

This was a retrospective study that involved a review of the medical microbiology laboratory records for the antimicrobial susceptibility patterns of *Pseudomonas* spp and *Acinetobacter baumannii* isolated from the urinary samples of patients who were being assessed for Urinary tract infection between April 2020 to March 2021.

Isolation and antibiotic susceptibility pattern of bacterial isolates:

During the period of the review, urinary sample processing in the Laboratory involved macroscopic and microscopic examination. And then, urinary samples were inoculated into Cystine Lactose Electrolyte Deficient (CLED) and Blood agar plates and incubated aerobically at 35-37⁰C for 18-24 hours. Isolates were identified by conventional biochemical tests and using API and antimicrobial susceptibility testing (AST) was performed using the modified Kirby-Bauer disk diffusion method. The break points for susceptibility were determined using the Clinical and Laboratory Standards Institute (CLSI) guidelines (13).

Ethical considerations

Ethical approval for the study was obtained from Lagos State University Teaching Hospital Research and Ethics Committee. As data were retrospectively obtained from the laboratory records and did not involve contact with patients nor recruitment of patients, informed consent was not deemed necessary. However, privacy and confidentiality of patients' data were ensured.

RESULTS

For the period under consideration, a total number of 2,253 urine samples were processed in the medical microbiology laboratory and 662 (29.4%) samples yielded Positive cultures. (Table 1). *Acinetobacter baumannii* isolate was 26 (3.93%) and *Pseudomonas spp.* 46(6.94%) with *Pseudomonas aeruginosa* accounting for 30(4.53%), *Pseudomonas luteola* 12(1.81%), and *Pseudomonas fluorescens* and *Pseudomonas oryzihabitans* accounting for 2(0.3%) each. Other gram negatives accounted for 63.75% (422) of the positive cultures, while gram positives were 168(25.38%). (Table 2).

Table1. Total urinary sample and culture result.

Total samples	Culture positive	Culture negative
2,253	662 (29.4%)	1,591 (70.6%)

ISOLATE	FREQUENCY	PERCENTAGE
<i>Pseudomonas aeruginosa</i>	30	4.53%
<i>Pseudomonas luteola</i>	12	1.81%
<i>Pseudomonas fluorescens</i>	2	0.30%
<i>Pseudomonas oryzihabitans</i>	2	0.30%
<i>Acinetobacter baumannii</i>	26	3.93%
Other gram negatives	422	63.75%
Gram positive	168	25.38%
	662	100%

Table 2. Isolates and frequency.

Acinetobacter baumannii isolates showed the more resistance rate to Ceftazidime (46.2%), Piperacillin-tazobactam (46.1%) and Levofloxacin (53.9%) but had least resistance to Azteonam (0%), and Amikacin (15.4%). Similarly, *Pseudomonas aeruginosa* isolates were most resistant to Piperacillin-tazobactam (53.3%), followed by Ceftazidime and Cefoperazone (40%) respectively, however 60% of all *Pseudomonas aeruginosa* isolates were susceptible to Ceftazidime and Meropenem, while 46.7% were sensitive to Amikacin.

Pseudomonas luteola low susceptibility for Ceftazidime (16.7%), Cefoperazone (33.3%). Imipenem (33.3%) and Meropenem (33.3%), while Levofloxacin (83.3%), Amikacin (66.7%) and Piperacillin-tazobactam (50%). Were the most active antibiotics invitro. Furthermore, *Pseudomonas oryzihabitans* showed 100% sensitivity to Amikacin, Cefoperazone, Imipenem and Piperacillin-tazobactam, but had complete intermediate sensitivity to Ceftazidime and Levofloxacin, while *Pseudomonas fluorescens* was 100% sensitive to Amikacin, Cefoperazone , Imipenem , Meropenem and Levofloxacin and least susceptible to Ceftazidime (50%).(Table 3).

Table 3. Antibiotic Susceptibility Pattern of *Pseudomonas* spp and *Acinetobacter baumannii*.

Gram Negative	Antibiotics	Sensitivity	Intermediate	Resistant	Total

Organisms					
<i>Pseudomonas aeruginosa</i>	Amikacin (AMK)	14(46.7%)	6	10(33.3%)	30
	Cefoperazone (CFP)	12 (40%)	6 (20%)	12 (40%)	
	Ceftazidime (CFZ)	18 (60%)	—	12 (40%)	
	Imipenem (IMI)	12 (40%)	10	8 (26.7%)	
	Meropenem (MPN)	18 (60%)	2	10 (33.3%)	
	Piperacillin – Tazobactam (PIP-T)	12 (40%)	2	16 (53.3%)	
	Levofloxacin (LVO)	10 (33.3%)	16	4(13.3%)	
<i>Pseudomonas</i>	Amikacin (AMK)	8 (66.7%)	—	4(33.3%)	12

<i>Luteola</i>					
	Cefoperazone (CFP)	4(33.3%)	—	—	
	Ceftazidime (CFZ)	2(16.7%)	2	8(66.7%)	
	Imipenem (IMI)	4(33.3%)	—	8(66.7%)	
	Meropenem (MPN)	4(33.3%)	—	8(66.7%)	
	Piperacillin Tazobactam (PIP-T)	6(50%)	—	6(50%)	
	Levofloxacin (LVO)	10(83.3%)	—	2(16.7%)	
<i>Pseudomonas Fluorescens</i>	Amikacin (AMK)	2(100%)	0	0	2
	Cefoperazone (CFP)	2(100%)	0	0	
	Ceftazidime (CFZ)	0	0	2(100%)	

	Imipenem (IMI)	2(100%)	0	0	
	Piperacillin – Tazobactam (PIP-T)	1(50%)	1(50%)	0	
	Levofloxacin (LVO)	2(100%)	0	0	
	Meropenem MEM	2(100%)	0	0	
<i>Pseudomonas</i> <i>Oryzihabitans</i>	Amikacin (AMK)	2(100%)	—	0	2
	Cefepera Zone (CFP)	2(100%)	—	0	
	Ceftazidime (CFZ)	0	2(100%)	0	
	Imipenem (IMI)	2(100%)	—	0	
	Piperacillin – Tazobactam (PIP-T)	2(100%)	—	0	
	Levofloxacin (LVO)	0	2(100%)	0	

<i>Acinetobacter</i> <i>baumanii</i>	Amikacin (AMK)	20(76.9%)	2	4(15.4%)	26
	Ceftazidime (CFZ)	10(38.5%)	4	12(46.2%)	
	Imipenem (IMI)	16(61.5%)	2	8(30.8%)	
	Meropenem (MPN)	18(69.2%)	2	6(23.1%)	
	Piperacillin– Tazobactam (PIP-T)	14(53.9%)	—	12(46.1%)	
	Levofloxacin (LVO)	10(38.4%)	2(7.7%)	14(53.9%)	
	Aztreonam (AZT)	24(92.3%)	2(7.7%)	0	

DISCUSSION

Gram-negative bacteria, especially Enterobacteriaceae, are becoming increasingly resistant to antibiotics on a global scale. *A. baumannii* and *Pseudomonas species* are impeding the use of effective antibiotics (14-16,17).

Due to the high prevalence of UTIs and the frequent involvement of gram-negative bacilli in their aetiology, which are the primary microorganisms responsible for the acquisition of plasmid-encoded resistance, inappropriate use of antibiotics against UTIs is a significant contributor to the development of resistance mechanisms [18, 19].

A. baumannii has shown a high capacity to acquire resistance mechanisms and to spread these resistant phenotypes among the general population [16]. Multi-resistant *A. baumannii* is highly complicated to treat and has become a global threat over the past few years. The correct use of antibiotics is a key measure in controlling the acquisition of bacterial multi-resistances [20]. Areas with a high incidence of ESBL-producing bacteria, for which carbapenems are the preferred treatment, have been found to exhibit carbapenem resistance [21]. The consumption of carbapenem has significantly increased over the past two decades [22], primarily in poor nations, and the resulting development in carbapenem-resistant gram-negative bacteria has quickly become a global healthcare concern. Therefore, it is crucial to keep an eye on the local *A. baumannii* susceptibility profile and to regulate the dosage of antibiotics used to treat it. The objective is to turn things around and stop the spread of these strains, particularly in hospital areas with more vulnerable patients (such critical care units or haematology departments). Potential microorganisms that have already colonised patients may develop resistance mechanisms because of exposure to specific antibiotics, making it extremely difficult to eradicate them. With minimal limits, cephalosporins and quinolones have long been widely used as the preferred empirical treatment in ICUs (23,24), which may help to explain why it is frequently discovered that critically sick patients have significant resistance rates for pathogens like *A. baumannii* and *P. aeruginosa*.

The present study indicated that Levofloxacin is no longer an appropriate therapeutic option for *Acinetobacter baumannii* which showed a susceptibility of less than 40% or *Pseudomonas aeruginosa* which showed a susceptibility of less than 35%. With respect to Cephalosporins the susceptibility of *Acinetobacter baumannii* was less than 40% for Ceftazidime. *Pseudomonas aeruginosa* isolates had 60% and 40% sensitivity to Cefoperazone and Ceftazidime respectively. Similarly, *Pseudomonas luteola* had less than 20% susceptibility to Ceftazidime and less than 35% susceptibility for Cefoperazone, while *Pseudomonas fluorescens* and *Pseudomonas oryzihabitans* had 100% sensitivity to Cefoperazone. While *Pseudomonas fluorescens* isolates were completely resistant to Ceftazidime, that of *Pseudomonas oryzihabitans* were intermediately sensitive to Ceftazidime. This finding negates the general consideration of Ceftazidime been previously considered as the anti-*Pseudomonas* Cephalosporin of Choice (25). As we can see in this study, this does not apply to all species of *Pseudomonas*.

The high resistance rate of *Acinetobacter baumannii* some *Pseudomonas* spp seen in this study can not overemphasize the need for improve surveillance protocols to avoid the spread of these multi-resistant bacteria in the hospital.

CONCLUSION

In our setting for the empirical treatment of urinary tract infection due to *A.baumannii*, Aztreonam, Amikacin and Meropenem are good options. While for *Pseudomonas aeruginosa* associated UTIs Meropenem and Ceftazidime can be used for empirical treatment.

The only limitation is that none of them may be **idea(l)** for outpatient treatment of Urinary tract infections since they are all injectable.

For *Pseudomonas luteola* and *Pseudomonas oryzihabitans* Amikacin and Levofloxacin can be used for empirical treatment of infection caused by these uropathogens, while for

Pseudomonas fluorescens Amikacin, Meropenem, Imipenem, Cefoperazone and Levofloxacin are possible drugs for empirical therapy for these organisms associated Urinary tract infections.

Finally, with the greater than 20% resistance rates to Carbapenems noticed in *A. baumannii* and some *Pseudomonas species* especially *Pseudomonas aeruginosa*, this emphasizes the importance of antibiotics stewardship programme (26, 27). Strict infection control measures must be put in place to prevent the spread of multi-resistant isolates from patient to patient or from health workers to patients and vice-versa.

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