



Urinary Tract Infections by Multidrug Resistant *Acinetobacter* species- A Retrospective Analysis

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Abstract

Background: *Acinetobacter* species have emerged as important cause of nosocomial infections like pneumonia and urinary tract infections. *Acinetobacter* species are known to be highly resistant to commonly used antimicrobial agents. Since *Acinetobacter* species are ubiquitous and have tremendous colonizing capacity, it is difficult to explain the role of *Acinetobacter* acquisition in the ICU and medical wards. The objective of this study was to determine the frequency of urinary tract infection (UTI) caused by different *Acinetobacter* species in hospitalized patients and in the community and to analyze their antimicrobial susceptibility pattern.

Materials and Methods: This is a retrospective analysis from January 2016 to December 2017. Urine samples collected in appropriate sterile manner were screened for polymorphonuclear leucocytes and bacteria by routine microscopic examination. This was followed by plating on MacConkey's agar and Blood agar. Isolated *Acinetobacter* strains which are oxidase negative and non-lactose fermenters from MacConkey's agar were identified with Matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) to confirm the identification. Antibiotic susceptibility was performed by Vitek Compact™ 2 (Biomeuriux, France) as per CLSI standards establishing MIC (Minimum Inhibitory Concentration).

Results: Of the 429 isolates of *Acinetobacter* species from urinary tract, *Acinetobacter baumannii* complex (78%) found to be the most common species followed by *Acinetobacter junii* (10%) and *Acinetobacter baumannii* (8%). Of the 334 (78%) isolates of *Acinetobacter baumannii* complex from urinary tract, 73 (21.85%) isolates were resistant with doripenem, 62 (18.56%) with imipenem and 59 (17.66%) were resistant with meropenem with MIC values $\geq 8 \mu\text{g/ml}$. The rest of the isolates like *Acinetobacter junii*, *Acinetobacter johnsonii*, and *Acinetobacter lwoffii* are found to be more sensitive with carbapenems with lower MIC values.

Discussion: The treatment of multidrug-resistant bacteria in hospitalized patients continues to be a challenge for the clinician's in routine practice. *Acinetobacter baumannii* complex has proven to be an important pathogen in health care associated infections with significant mortality and morbidity. The drug resistant nature of the pathogen and its unpredictable susceptibility patterns make empirical and therapeutic decisions even more difficult.

Conclusion: *A. baumannii* is an important opportunistic agent of nosocomial UTI, especially in patients with longer hospitalization, antibiotic exposure, urinary catheterization and decreased immunity. High antimicrobial resistance and patient co-morbidities limit therapeutic choices. Hence, alternative therapeutic options are urgently needed to treat a patient with *A. baumannii* infection.

Keywords: Nosocomial Infections; *Acinetobacter baumannii* Complex; MALDI-TOF MS; Urinary Catheterization

Introduction

Acinetobacter species have emerged as important cause of nosocomial infections like pneumonia and urinary tract infections. These species have been known to cause different kinds of opportunistic infections. *Acinetobacter baumannii* is now recognized to be the *Acinetobacter* genomic species of great clinical importance [1]. *Acinetobacter* species are known to be highly resistant to com-

monly used antimicrobial agents [2]. *Acinetobacter* species cause a wide variety of illness in debilitated and hospitalized patients especially in intensive care units (ICU). These bacteria survive for long time in the hospital environment. There is substantial increase in the opportunity for cross infection [3]. Lower respiratory tract and urinary tract are more commonly affected sites with *Acinetobacter* species, and these distributions are very similar

to that of other nosocomial pathogens [4]. As neonates are highly susceptible to infections with opportunistic pathogens, bacteremia and septicemia due to *Acinetobacter* species is gaining importance in neonates [5]. Because of frequent resistance to aminoglycoside's, fluoroquinolone's, ureidopenicillin's and third generation cephalosporins, carbapenem are important agents in managing *Acinetobacter* infections. In the recent years there has been an alarming increase in carbapenem resistance in *Acinetobacter* species [6,7]. Since *Acinetobacter* species are ubiquitous and have tremendous colonizing capacity, it is difficult to explain the role of *Acinetobacter* acquisition in the ICU and medical wards. In addition, the risk factors for *Acinetobacter* acquisition may vary in different set up with epidemic, outbreak of infection or endemic colonization [8]. The risk factors that are involved in acquisition of *Acinetobacter* infection, as reported by other investigators, are assisted ventilation, use of broad spectrum antimicrobial therapy, endotracheal intubation, parenteral nutrition and urinary and intravascular catheterization.

Objective of the Study

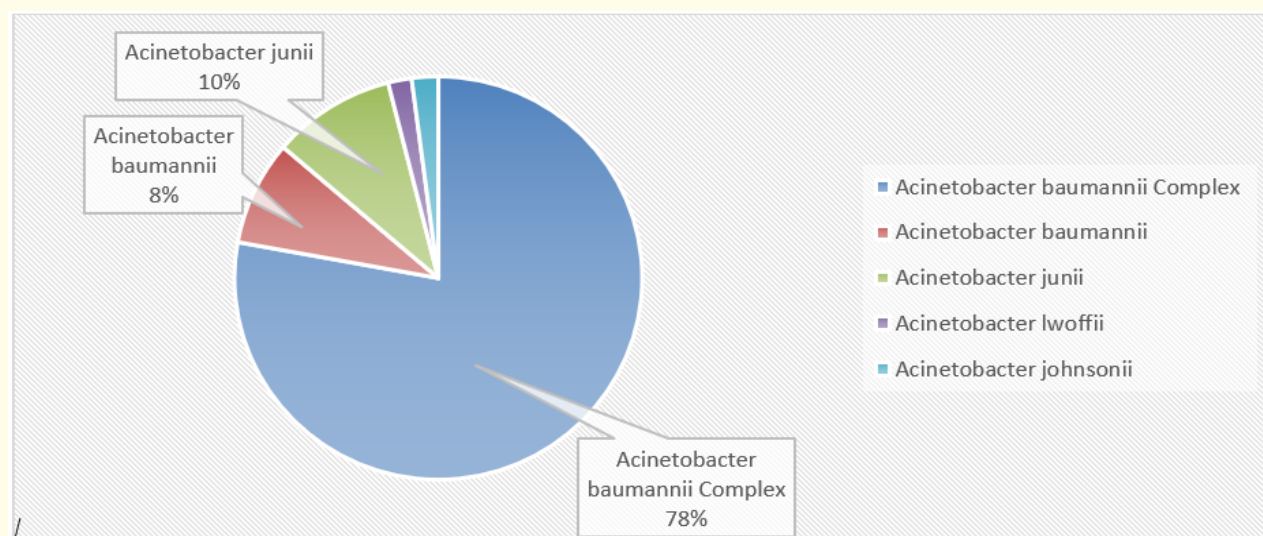
The objective of this study was to determine the frequency of urinary tract infection (UTI) caused by different *Acinetobacter* species in hospitalized patients and in the community and to analyze their antimicrobial susceptibility pattern.

Materials and Methods

All the urine (midstream, catheterized and suprapubic aspiration) specimens collected from patients with suspected UTI were cultured on blood agar and MacConkey's agar in the Department of Microbiology, Metropolis healthcare limited, Mumbai, India. During the study period (January 2016 to December 2017), Gram negative, oxidase negative, non-lactose fermenting coccobacilli isolated in significant counts ($> 1 \times 10^5$ cfu/ml) in pure culture were

included in the study. UTI was defined as the presence of any one of the following symptoms: fever, burning, urgency, frequency of micturition, supra pubic tenderness and growth of $\geq 1 \times 10^5$ cfu/ml of *Acinetobacter* species from urine specimen. Patients with suprapubic aspiration, even less colony count ($< 1 \times 10^5$ cfu/ml) with presence of polymorphonuclear leucocytes was considered significant and included in the study. The objective of this study was to determine the antibiotic susceptibility pattern of the isolated strains of *Acinetobacter* species with special reference to cephalosporin's and carbapenem resistance and to guide clinicians for appropriate antimicrobial therapy for reduction of morbidity and mortality in hospitalized patients. This study was performed with patients admitted in a tertiary care hospital, developing symptoms of UTI at least after 48 hours of admission. Some patients from community acquired infection with symptoms of UTI have also been included in the study. Cases of urinary tract infection with established nonbacterial aetiology (fungal UTI) excluded from the study. Urine samples collected in appropriate sterile precautions were screened for pus cells and bacteria by routine microscopic examination. This was followed by plating on MacConkey's agar and Blood agar by T streaking method with an inoculating loop of 4 mm diameter (10 μ l of un-centrifuged urine specimen). Inoculated plates were incubated overnight at 37°C. Isolated *Acinetobacter* strains (Gram negative coccobacilli) which are oxidase negative and non-lactose fermenters from MacConkey's agar were identified with Matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) to confirm the identification and speciation. Antibiotic susceptibility was performed by Vitek Compact™ 2 (Biomeuriux, France) as per CLSI guidelines establishing MIC (Minimum Inhibitory Concentration) of the tested antibiotics.

Results



Graph 1: Percentage proportion of different species of *Acinetobacter* isolated from urinary tract.

Antimicrobial	MIC g/ml			Comments
	S	I	R	
Doripenem	<=2	4	>=8	Breakpoints for doripenem are based on a dosage regimen of 500 mg every 8h.
Imipenem	<=2	4	>=8	Breakpoints for imipenem are based on a dosage regimen of 500 mg every 6h.
Meropenem	<=2	4	>=8	Breakpoints for meropenem are based on a dosage regimen of 1 g every 8h or 500 mg every 6h.
Colistin	<=2	-	>=4	Colistin should generally be given with a loading dose and at maximum recommended doses, and used in combination with other agents. Applies to <i>A. baumannii</i> complex only. (The only approved MIC method for testing is broth micro dilution. Disk diffusion and gradient diffusion should not be performed-2018 CLSI).
Polymyxin B	<=2	-	>=4	-
Gentamicin	<=4	8	>=16	-
Amikacin	<=16	32	>=64	
Piperacillin-tazobactam	<=16/4	32/4 - 64/4	>=128/4	-
Ceftazidime	<=8	16	>=32	
Cefepime	<=8	16	>=32	
Cefotaxime	<=8	16 - 32	>=64	
Ceftriaxone	<=8	16 - 32	>=64	
Ciprofloxacin	<=1	2	>=4	
Levofloxacin	<=2	4	>=8	-
Trimethoprim-sulfamethoxazole	<=2/38	-	>=4/76	-

Table 1: Minimum inhibitory concentrations of antimicrobials used for *Acinetobacter* species causing urinary tract infections adapted from CLSI. Performance Standards for Antimicrobial Susceptibility Testing, 27th edition. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.

S: Susceptible; I: Intermediate; R: Resistant.

Of the 429 isolates of *Acinetobacter* species from urinary tract, *Acinetobacter baumannii* complex (78%) found to be the most common species followed by *Acinetobacter junii* (10%) and *Acinetobacter baumannii* (8%).

Of the 334 (78%) isolates of *Acinetobacter baumannii* complex from urinary tract, 73 (21.85%) isolates were resistant with doripenem, 62 (18.56%) with imipenem and 59 (17.66%) were resistant with meropenem with MIC values ≥ 8 $\mu\text{g/ml}$. The rest of the isolates like *Acinetobacter junii*, *Acinetobacter johnsonii*, and *Acinetobacter lwoffii* are found to be more sensitive with carbapenems with lower MIC values.

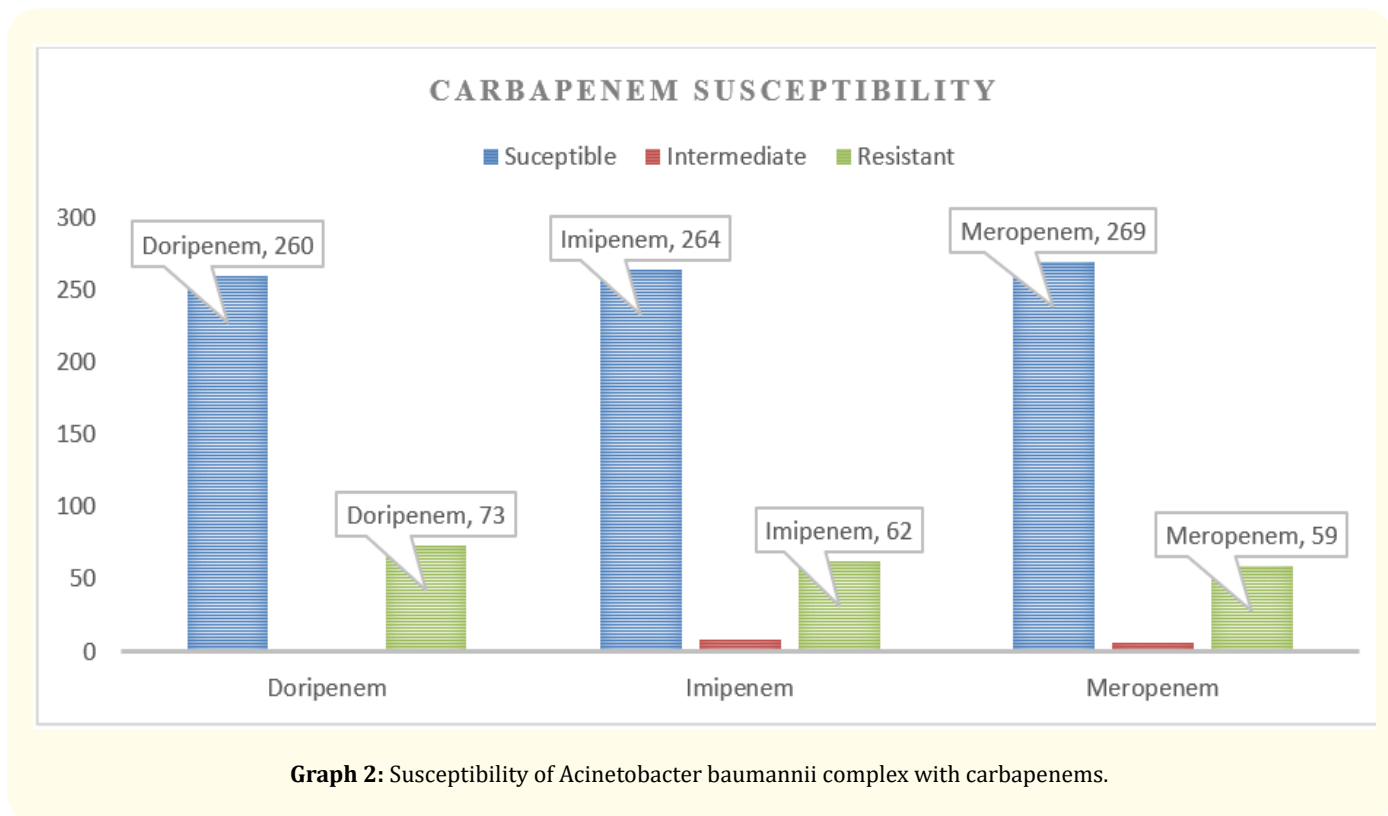
Of the 370 isolates of *Acinetobacter baumannii* and *Acinetobacter baumannii* complex, 9(2.43%) isolates were found resistant to both polymyxin B and colistin with MIC ≥ 4 $\mu\text{g/ml}$. Colistin should generally be given with a loading dose and at maximum recommended doses, and used in combination with other agents. Applies to *A. baumannii* complex only. The only approved MIC method for testing is broth micro dilution. Disk diffusion and gradient diffusion should not be performed.

Of the 334 (78%) isolates of *Acinetobacter baumannii* complex, 123 (36.82%) isolates were resistant with Trimethoprim-sulfamethoxazole. The rest of the isolates like *Acinetobacter junii*, *Acinetobacter johnsonii*, and *Acinetobacter lwoffii* are found more sensitive with Trimethoprim-sulfamethoxazole.

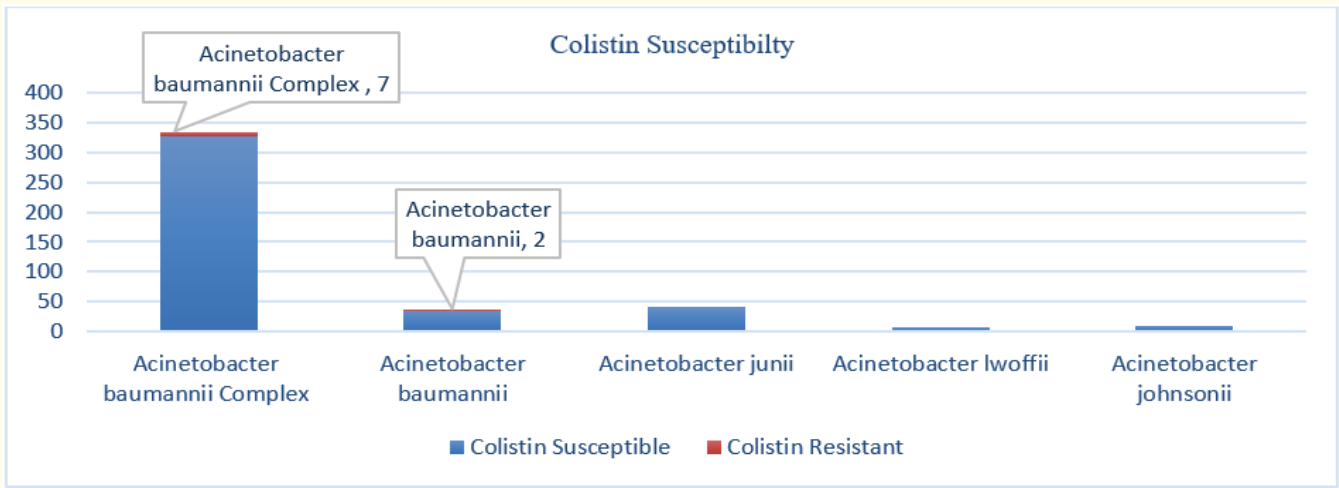
Organism (N=429)/ Antibiotic	<i>Acinetobacter baumannii</i> Complex (N = 334)			<i>Acinetobacter baumannii</i> (N = 36)			<i>Acinetobacter junii</i> (N = 42)			<i>Acinetobacter lwoffii</i> (N = 8)			<i>Acinetobacter johnsonii</i> (N = 9)		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Doripenem	260	1	73	30	0	6	39	1	2	7	0	1	6	1	2
Imipenem	264	8	62	28	1	7	38	1	3	7	0	1	7	1	1
Meropenem	269	6	59	29	1	6	40	1	1	7	0	1	7	1	1
Colistin	327	-	7	34	-	2	42	0	0	8	-	0	9	-	0
Polymyxin B	327	-	7	34	-	2	42	0	0	8	-	0	9	-	0
Gentamicin	243	11	80	27	0	9	38	0	4	8	0	0	6	2	1
Amikacin	245	7	82	23	2	11	36	1	5	8	0	0	6	1	2
Piperacillin-tazobactam	246	6	82	24	0	12	36	2	4	8	0	0	7	1	1
Ceftazidime	212	26	96	20	4	12	35	3	4	7	0	1	7	1	1
Cefepime	227	20	87	24	3	9	39	1	2	8	0	0	9	0	0
Cefotaxime	223	18	93	21	2	13	36	1	5	7	0	1	7	1	1
Ceftriaxone	228	8	98	21	1	14	36	1	5	7	0	1	7	1	1
Ciprofloxacin	197	9	128	26	0	10	32	4	6	5	1	2	5	1	3
Levofloxacin	205	8	121	28	0	8	34	3	5	6	1	1	5	1	3
Trimethoprim-sulfamethoxazole	211	-	123	25	-	11	38	-	4	6	-	2	7	-	2

Table 2: Susceptibility pattern of different species of *Acinetobacter* from urinary tract isolates.

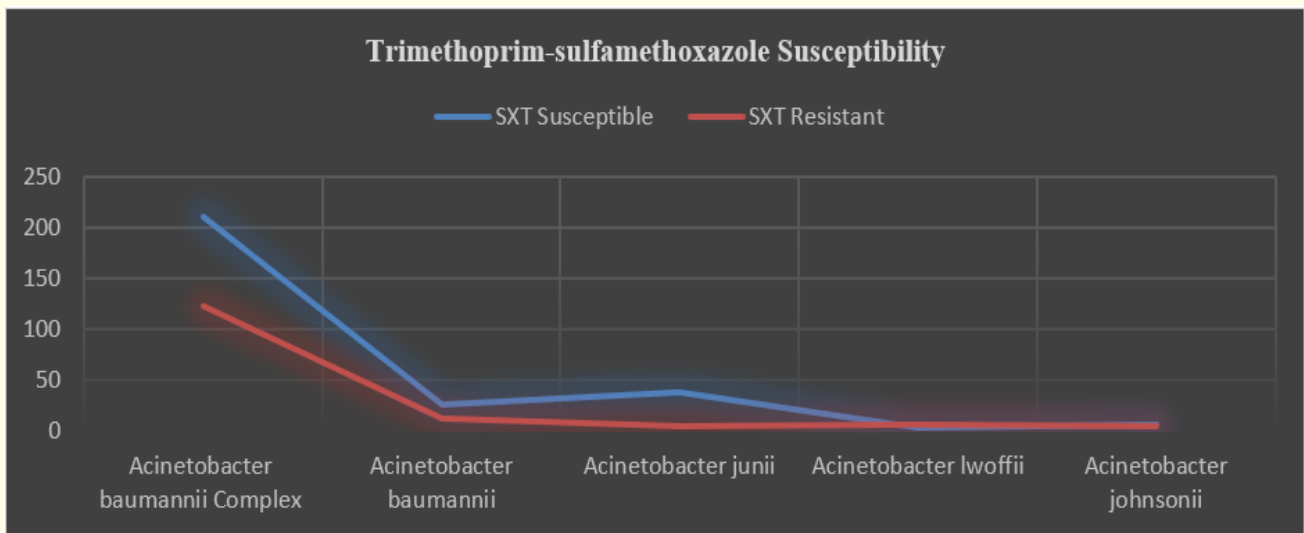
S: Susceptible; I: Intermediate; R: Resistant



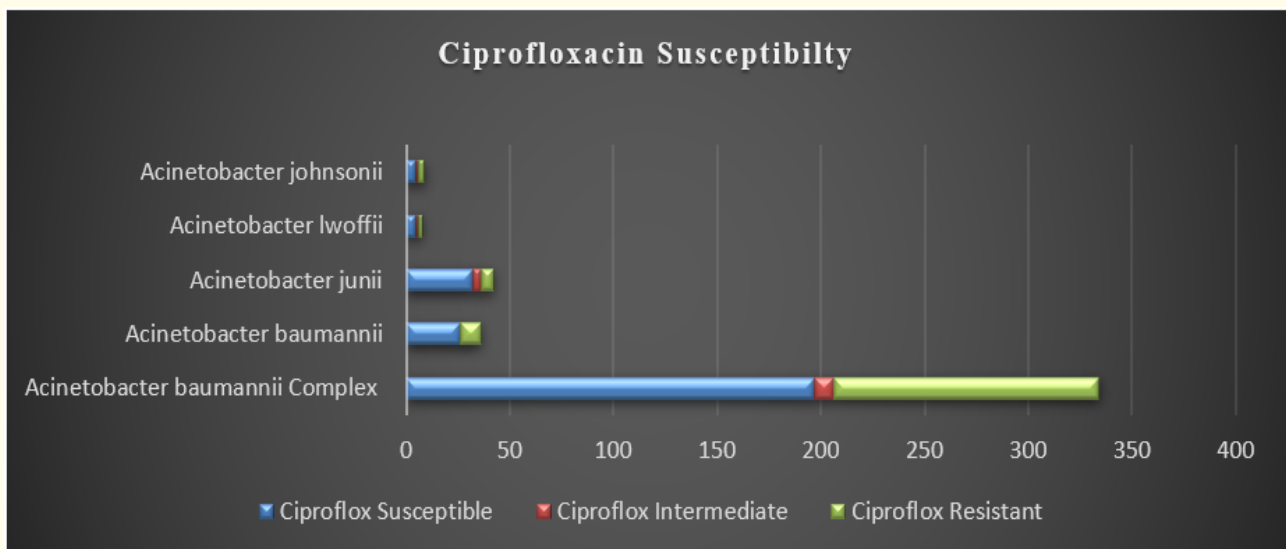
Graph 2: Susceptibility of *Acinetobacter baumannii* complex with carbapenems.



Graph 3: Susceptibility of *Acinetobacter* species with polymixin B and colistin.



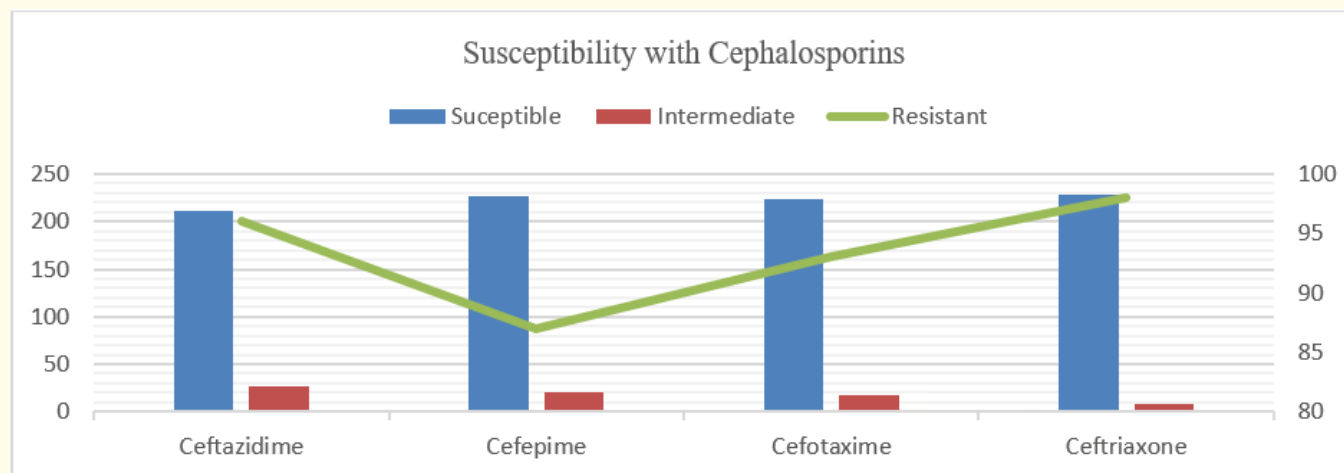
Graph 4: Susceptibility of *Acinetobacter* species with Trimethoprim-sulfamethoxazole.



Graph 5: Susceptibility of *Acinetobacter* species with Fluoroquinolones.

Of the 334 (78%) isolates of *Acinetobacter baumannii* complex, 128 (38.32%) isolates were resistant with ciprofloxacin and 121 (36.22%) were resistant with levofloxacin. With the rest of the isolates like *Acinetobacter junii*, *Acinetobacter johnsonii* and *Acinetobacter lwoffii*, there was no significant difference found between ciprofloxacin and levofloxacin susceptibility.

Of the 334 (78%) isolates of *Acinetobacter baumannii* complex, 212 isolates were susceptible, 26 were intermediate and 96(28.74%) isolates were resistant with ceftazidime. Of the 334 (78%) isolates of *Acinetobacter baumannii* complex, 227 isolates were susceptible, 20 were intermediate and 87(26%) isolates were resistant with cefepime. In general, there was no significant difference in susceptibility was found between various cephalosporins like ceftazidime, cefotaxime, ceftriaxone and cefepime.



Graph 5: Susceptibility of *Acinetobacter baumannii* complex with cephalosporins.

Discussion

The *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex consists of four genotypically distinct but phenotypically very similar bacterial species or DNA groups: *A. calcoaceticus* (DNA group 1), *A. baumannii* (DNA group 2), unnamed [9] DNA group 3 and unnamed [10] DNA group 13. The treatment of multidrug-resistant bacteria in hospitalized patients continues to be a challenge for the clinician's in routine practice. *Acinetobacter baumannii* complex has proven to be an important pathogen in health care associated infections with significant morbidity. The drug resistant nature of the pathogen and its unpredictable susceptibility patterns make empirical and therapeutic decisions even more difficult. The association of *A. baumannii* with pneumonia, bacteremia, and septicemia especially in neonates in ICU, wound infections, urinary tract infections, and meningitis has been well described as a nosocomial pathogen [11]. Risk factors associated with colonization or infection (which can be difficult to distinguish) include prolonged hospitalization, assisted ventilation, intensive care unit admission, recent surgical procedures, antimicrobial agent exposure, central venous catheter use, prior hospitalization, nursing home residence, and local colonization pressure on susceptible patients [12,13]. *A. baumannii* has adapted to survive for extended periods on environ-

mental surfaces. This phenomenon is of great important for transmission of organism within the health care setting. Health care associated infections with *A. baumannii* are usually multidrug resistant due to prolonged exposure of antimicrobial agents and prolonged hospitalization. The impressive number of acquired mechanisms of resistance makes selection of an appropriate empirical antimicrobial agent exceedingly difficult. The mechanisms of drug of resistance in *A. baumannii* nosocomial infections is beyond the scope of this study but can be reviewed in Peleg AY, *et al* [14]. Degradation enzymes against β -lactams splitting β -lactam ring, modification enzymes against aminoglycosides like aminoglycosides modifying enzyme (AME), altered binding sites for quinolones, and a variety of efflux mechanisms and changes in outer membrane proteins have been reported. All of these mechanisms of drug resistance can be combined which may result in a highly drug-resistant pathogen, and at times pan-resistant opportunistic pathogen. Attributable mortality has been difficult to assess for an organism that appears to be as much a colonizer as it is a true pathogen. We do not know the pathogenicity of this organism causing urinary tract infections, but only those urine samples showing significant polymorphonuclear leucocytes (PMNL) and

patients with suprapubic aspiration of urine have been included in the study. *A. baumannii* is often identified in the sputum samples of patients with mechanical ventilation and in urinary catheterized patients. This quandary of pathogenicity has added to the difficulty of treating these highly resistant organisms, because many therapeutic strategies are associated with significant toxicity. The in-hospital attributable mortality appears to be 8% - 23%, but for the intensive care unit, it was found to be 10% - 43% [15,16]. Strains of *A. baumannii* have acquired multiple drug resistance to newly developed antimicrobials in the last 30 years. These strains are known as multidrug resistant (MDR) *A. baumannii*. It is prevalent in many hospitals all over the world. Recently, it has been recognized as a leading nosocomial pathogen with significant mortality and morbidity in hospital settings [17]. Terminologies like multidrug resistant (MDR), extensive drug resistant (XDR), and pan-drug resistant (PDR) have been used with various definitions to describe the degree of antimicrobial resistance for *Acinetobacter* species. MDR *Acinetobacter* species can refer to being resistant to a minimum of three classes of antimicrobial agents e.g. all penicillins and cephalosporins fluoroquinolones, and aminoglycosides [18]. Another specific definition of multidrug resistance is whenever there is resistance to more than two of the following five drug classes: antipseudomonal cephalosporins (ceftazidime or cefepime), antipseudomonal carbapenems (imipenem or meropenem), ampicillin-sulbactam, fluoroquinolones (ciprofloxacin or levofloxacin), and aminoglycosides (gentamicin, tobramycin, or amikacin) [19]. MDR *Acinetobacter* strains which show additional resistant to carbapenems are defined as XDR. PDR *Acinetobacter* species is a term given to the XDR *Acinetobacter* species that is also resistant to polymyxins (polymyxin B and colistin) and tigecycline. These categorizations help to define the extent of resistance and rational antimicrobial therapy in a clear way [20]. Enzymatic degradation by β lactamases is the most prevailing mechanism of β lactam resistance in *A. baumannii*. β lactamases are divided into 4 molecular groups: Ambler class A, Ambler class B (metallo enzymes), Class C β lactamases, and Ambler class D (oxacillinases). These enzymes, at least partially, hydrolyze carbapenems along with other β -lactams [21]. Extended-spectrum β lactamases (ESBLs) from the Ambler class A group have been described for *A. baumannii*. Many ESBLs were identified in *A. baumannii* including TEM-92 and 116 from Italy and Netherlands respectively, and SHV-12 from China and the Netherlands. In addition, CTX-M-2 and CTX-M-43 have been reported from Japan and Bolivia correspondingly. Seven different Penicillin binding protein (PBPs) (1a, 1c, 2, 3, 4, 4b and 5) in *A. baumannii* were found. The resistance of *A. baumannii* to carbapenems is related to decreased drug uptake because of porin deficiency, and diminished affinity for the drug due to modification of the PBP's by mutations which is described by a reduced expression of PBP-2, as shown in isolates from Seville, Spain [22]. Of the 334 (78%) isolates of *Acinetobacter baumannii* complex, 212 isolates were susceptible, 26 were intermediate and 96(28.74%) isolates were resistant with

ceftazidime. Of the 334 (78%) isolates of *Acinetobacter baumannii* complex, 227 isolates were susceptible, 20 were intermediate and 87 (26%) isolates were resistant with cefepime. In general, there was no significant difference in susceptibility was found between various cephalosporins like ceftazidime, cefotaxime, ceftriaxone and cefepime. Carbapenems (imipenem and meropenem) resistance *Acinetobacter* is increasingly reported, making MDR *Acinetobacter* infections difficult to treat. However, carbapenems continue to be the treatment of choice in cases where isolates are still susceptible to this antimicrobial class. Of the 334 (78%) isolates of *Acinetobacter baumannii* complex from urinary tract, 73 (21.85%) isolates were resistant with doripenem, 62 (18.56%) with imipenem and 59 (17.66%) were resistant with meropenem with MIC values ≥ 8 $\mu\text{g/ml}$. The rest of the isolates like *Acinetobacter junii*, *Acinetobacter johnsonii* and *Acinetobacter lwoffii* are found to be more sensitive with carbapenems with lower MIC values. Alteration in the structure of DNA gyrase or topoisomerase IV through mutations in the quinolones resistance-determining regions of the *gyrA* and *parC* genes is the main cause for resistance of *A. baumannii* to fluoroquinolones. These changes decrease the affinity of the quinolones binding to the enzyme-DNA complex. Another mechanism of resistance to the quinolones is caused by efflux systems that reduce intracellular drug accumulation comprising RND-type pump AdeABC and multi antimicrobial extrusion protein MATE pump AbeM. Until now, *qnr* genes and plasmid mediated quinolones resistance has not been reported for *A. baumannii* [23]. In the present study, of the 334 (78%) isolates of *Acinetobacter baumannii* complex, 128 (38.32%) isolates were resistant with ciprofloxacin and 121(36.22%) were resistant with levofloxacin. With the rest of the isolates like *Acinetobacter junii*, *Acinetobacter johnsonii* and *Acinetobacter lwoffii*, there was no significant difference found between ciprofloxacin and levofloxacin susceptibility. Tigecycline derivative of minocycline and has bacteriostatic activity against MDR *A. baumannii* [24]. High-level resistance to tigecycline has been reported for some multidrug-resistant *A. baumannii* isolates, with a concern that this organism can quickly escape this antimicrobial mediated efflux pumps. Over expression of a multidrug efflux pump in *A. baumannii* isolates with reduced susceptibility to tigecycline has been described [11]. Tigecycline is a good therapeutic option for treatment of life threatening MDR *A. baumannii* infections. Its role has been studied in bone and soft tissue infections, blood stream and gastrointestinal infections. However its antimicrobial activity in treating urinary tract infection is questionable. In the present study we did not test any isolate of *A. baumannii* complex against tigecycline. Amikacin and gentamicin are some of the aminoglycoside agents used as therapeutic options in cases of infection with multidrug-resistant *A. baumannii* isolates that retain susceptibility. These options are typically used in combination with another active antimicrobial agent. Many multidrug-resistant *A. baumannii* isolates maintain an intermediate susceptibility to amikacin or gentamicin to which resistance is

highly correlated with aminoglycoside modifying enzymes (AME) or efflux pump mechanisms [25]. Of the 334 isolates of *A. baumannii* complex 245 (73.35%) isolates were susceptible with amikacin and 82 (24.55%) were resistant and 7 (2%) isolates have shown intermediate susceptibility. There was no significant difference in susceptibility between amikacin and gentamicin. Other isolates of *Acinetobacter* like *A. junii*, *A. johnsonii* and *A. lwoffii* were found to be more sensitive to aminoglycosides but significance of these organisms in causing urinary tract infection needs to be further evaluated. Colistin, a cationic polypeptide. It is part of the polymyxin family (colistimethate or colistin sulfomethate or polymyxin E). It is an old potent broad spectrum antimicrobial agent. This agent was originally used in the 1960s and 1970. Because of concerns with nephrotoxicity and neurotoxicity, this agent was not prescribed frequently in clinical practice. Clinicians are going back to the use of polymyxin B or polymyxin E (colistin) for highly drug-resistant *A. baumannii* infections. Observational studies have shown a rate of 57 - 77% of cure or improvement among severely ill patients with multidrug-resistant *A. baumannii* infections treated with colistin. These infections included pneumonia, bacteremia, sepsis, intra-abdominal, and Central Nerves System infection [26]. Of the 370 isolates of *Acinetobacter baumannii* and *Acinetobacter baumannii* complex, 9 (2.43%) isolates were found resistant to both polymyxin B and colistin with MIC ≥ 4 $\mu\text{g/ml}$. Colistin should generally be given with a loading dose and at maximum recommended doses, and used in combination with other agents. As per recent CLSI guidelines 2018, colistin testing applies to *A. baumannii* complex only and no other *Acinetobacter* species. The only approved MIC method for colistin testing is broth micro dilution. Disk diffusion and gradient diffusion should not be performed. The nine strains of *Acinetobacter* which were found resistant with colistin were rechecked with Vitek Compact™ 2 automated susceptibility system (Biomérieux, France). However we did not do any manual broth micro dilution method for testing colistin resistance.

Conclusion

A. baumannii is an important opportunistic and emerging pathogen that can lead to serious nosocomial infections especially in patients with longer hospitalization, antibiotic exposure, urinary catheterization and decreased immunity. Its pathogenic potential includes the ability to adhere to surfaces, form biofilms, display antimicrobial resistance and acquire genetic material from unrelated genera, making it a versatile and difficult adversary to control and eliminate. High antimicrobial resistance and patient co-morbidities limit therapeutic choices. The optimal treatment for *A. baumannii*, especially nosocomial infections resulting from multiple resistant strains, remains to be established. It is thus a clinical imperative that well-designed procedures are put in place to help guide clinicians on decisions regarding the current best therapeutic practice.

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Conflict of Interest

Author declares no conflicts of interest.

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Ethical Approval

Not applicable.

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