Sensitive, resistant and multi-drug resistant *Acinetobacter baumanii* at Saudi Arabia hospital eastern region

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Abstract: Since the Physicians start use of antibiotics long ago with un-notice drug resistance. However actual problem was recognized about 85 years ago. Antibiotic resistant and Multi-drug resistant bacterial strains are at rise throughout the world. It is physicians and researchers to take scientific research based appropriate action to overcome this ever-spreading problem. This study is designed to find out sensitive (S), resistant (R) and multi-drug resistant (MDR) *Acinetobacter baumanii* strain along with other isolates in the resident patients of Eastern Region of Saudi Arabia. *Pseudomonas aeruginosa* is excluded from other gram-negative organisms isolated from different sites as it will be dealt separately. This study is based in was retrospective observations designed to collect data of different stains of *Acinetobacter baumanii* with reference to their Sensitivity (S), Resistance (R), Multi-Drug Resistance (MDR) along with other Gram negative isolated from different sites (from 1st January 2004 to 31st December 2011) at King Abdulaziz Hospital located Eastern Region of Kingdom of Saudi Arabia (KSA). All necessary techniques were used to culture and perform sensitivity of these isolates. There were 4532 isolates out of which 3018 (67%) were from patients. Out of *Acinetobacter baumanii* infected were 906 (20%) while other 3626 (80%) isolates were miscellaneous. Numbers of patients or cases were 480 (53%) out of 906 isolates and numbers of patients or cases in other organisms were 2538 (70%) out of 3626 isolates. *Acinetobacter baumanii* infected patients 221 (46%) were male and 259 (54%) were female and the male and female ratio of 1:1.2. In other organisms this male female ratio was almost same. There was steady rise in number of patients and the hence the isolates from 2004 to 2011. Majority of the bacterial strains were isolated as single organism but some were isolated as double or triple or quadruple or more organisms from different sites. Sensitive, Resistant and Multi-Drug Resistant *Acinetobacter baumanii* have been isolated from different sites. The other Gram negative isolates included *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Klebsiella* oxytoca, *Serratia marcescens* and *Stenotrophomonas maltophilia*. A significant rise in R and MDR but there is rise in R and MDR *Acinetobacter baumanii* Strains has been interceded other isolates. It is important to adopt proper and sustainable policies and guideline regarding antibiotics prescription and used. We should also check our infection control practices in our hospital or healthcare settings. We should start antibiotics stewardship in our hospital in order to reducing or overcoming antibiotics Resistant (R) and Multi-Drug Resistant (MDR) strains prevalence.

Keywords: *Acinetobacter baumanii*, Resistant (R), Multi-Drug Resistant (MDR).

INTRODUCTION

Acinetobacter baumanii the Gram-negative bacteria constitute the clinically significant pathogens for a number of reasons: *Acinetobacter baumanii* is often source of nosocomial infections, particularly in the intensive care units (10th most common etiological agents of nosocomial bloodstream infections, 1.3% of monobacterial and 2.1% of all ICU acquired skin/soft tissue infections) (Canton *et al.,* 2003, European Anti. Resist. Surveillance, Muray *et al.,* 2003, New Rev. CLSI 2011 and Sorberg *et al.,* 2003). This is also a pathogen that is noted for its ability to be multi drug resistant, making treatment problematic in many cases. *Acinetobacter baumanii* has emerged as an important nosocomial pathogen. Hospital outbreaks have also been described from various geographic areas and this organism has become endemic in some of them (Canton *et al.,* 2003, El Shafie *et al.,* 2004, Lizioli *et al.,* 2003, Meric *et al.,* 2005, Garcia-Rodriguez & Jones, 2002, Ayan *et al.,* 2003, Landman *et al.,* 2002 and Aygun *et al.,* 2002). The role environmental contamination in transmission of nosocomial infections in general and in *Acinetobacter baumanii* infection, in particular is well recognized (Canton *et al.,* 2003, Yuce *et al.,* 2004, Heider & Berhrns *et al.,* 2001, De-Waele *et al.,* 2004, NCCLS 2003, Rodriguez *et al.,* 2001 and Rodriguez *et al.,* 2005).

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Acinetobacter baumanii is not fastidious but is able to grow at various temperatures and pH conditions. This versatile organism exploits a variety of both carbon and energy sources. These properties elaborate the ability of *Acinetobacter spp. t*o survive either moist or dry condition within the hospital environment, thereby contributing to infection transmission. This hardship, combined to many antimicrobial agents, contributes to the organism's fitness and enables it to spread in the hospital settings. *Acinetobacter baumanii* strains have been associated with 5 to 10% of all ventilator associated pneumonia cases (Canton R *et al.,* 2003, Garcia-Rodriguez & Jones 2002, Ayan *et al.,* 2003, Landman *et al.,* 2002, Aygun *et al.,* 2002, Yuce *et al.,* 2004, Heider & Berhrns *et al.,* 2001, De-Waele *et al.,* 2004, NCCLS 2003, Rodriguez *et al.,* 2001, Rodriguez *et al.,* 2005 & 2000, Maragakis *et al.,* 2004, El-Shafie *et al.,*2004, del-Mar *et al.,* 2005, Heritier *et al.,* 2005, von-Dolinger *et al.,* 2005, Maslow *et al.,* 2005 and Hsueh *et al.,* 2005). Sensitive (S) antibiotic are those show acceptable range of zone of inhibition or MIC against different bacteria of different groups against antibiotics. Resistant is natural ability of an organism to show or elicit Resistance (R) to one or two groups of antibiotics and Multi-Drug Resistant (MDR) are bacteria showing resistant to more than two groups of antibiotics (Garcia-Rodriguez & Jones 2002, NCCLS 2003, Lee *et al.,* 2006, Clisneros *et al.,* 2005, Hawkey & Finch 2007, Fraise 2006, CLSI 2006 and Insa *et al.,* 2007).

Thus it is difficult to determine its attribute mortality. Though MDR *Acinetobacter baumanii* is considered to be a hospital acquired infectious agent, patients occasionally present with community acquired colonization of chronic wounds. In order to provide timely and proper antibiotic therapy it is important to know the characteristics of those patients with colonization and invasive infection with MDR *Acinetobacter baumannii* (Pachon-Ibanez *et al.,* 2004, Henwood *et al.,* 2002, Van Looveren & Goossen 2004, Sader *et al.,* 2005 and Akinci *et al.,* 2005). The purpose of this study is to determine the resistance patterns of *Acinetobacter baumanii* in different patients. The source of infection and the prevalence of co-infecting pathogens will also be investigated. Rapid global emergence of carbapenem resistance through upregulation of innate resistance mechanisms and acquisition of foreign determinants. The most prevalent mechanism of Beta-lactam resistance is enzymatic degradation, but multiple mechanisms often work to concert: *Amp C* cephalosporinases, ESBLS (Extended Spectrum Beta Lactamase) carbapenemases. Nonenzymatic β-lactam resistance due to changes in out outer membrane proteins, multi drug efflux pumps and affinity or expression of PBPS (Penicillin Binding Proteins). Aminoglycocoside modifying enzymes tend to be co-located within class 1 integrons. Resistance to quinolones is mediated by mutations in the *gyr A* and *par C* genes and efflux pump(s). There is a wide array of multidrug efflux systems: for example the AdeABC pump has a vast substrate profile that includes b-lactam, aminoglycosides, macrolides, fluoroquinolones, trimethoprim, tetracyclines (Canton *et al.,* 2003, European Anti. Resist. Surveillance, Muray *et al.,* 2003, New Rev. CLSI 2011, Sorberg *et al.,* 2003, Baran *et al.,* 2007, Hoban *et al.,* 2005, Tognim *et al.,* 2004, Kuo *et al.,* 2004 and Falagas *et al.,* 2005).

Acinetobacter baumanii is typically less common prevalent on general medical floors, but is seen frequently (In intensive care units, and the incidence is seen to be on the rise *Acinetobacter baumanii* is similar to pseudomonas in the sense that it is uncommon for "healthy" people to be infected. What makes *A. baumannii* an important and difficult? Pathogen is that it is seen in patients with less ability to fight infection and is often resistant to treatment with antibiotic because resistance can be acquired in many forms, including over-expression of antibiotic efflux pumps or expression of beta-lactamases, including ESBLs and metallo-ß-lactamases, which can cause carbapenem resistance. MDR genes can be found on the same segment portion of the bacteria genome that can lead to co-expression when that portion of genome is activated. Due to high levels of resistance it is be necessary to use antibiotics with higher levels of toxicity, which clearly is problematic in critically ill patients who are often less able to tolerate the negative effects of these medications such as polymyxins. The IDSA (Infectious Disease of South America) has placed *Acinetobacter baumanii* on its "hit list" of dangerous microbes due to its combination of antibiotic resistance and predilection for seriously ill patients. Cases of colistin resistance were reported in other study, and *Acinetobacter baumanii* was noted as more likely to be resistant than *Pseudomonas aeruginosa*. Tigecycline is a newer antibiotic that also has bioactivity against *Acinetobacter baumanii*, but in cases of MDR *Acinetobacter baumanii* only few options are left (Canton *et al.,* 2003, Posteir *et al.,* 2004, Oliva *et al.,* 2005, Taccome *et al.,* 2005, Brodie *et al.,* 2000, Orsi *et al.,* 2002, Lahir *et al.,* 2004, Landman *et al.,* 2002, Viiegas MV & Harstein 2003, Grady *et al.,* 2002, Karlowsky *et al.,* 2003 and Melamed *et al.,* 2003).

MATERIALS AND METHODS

This study was designed to collect data of different stains of *Acinetobacter baumanii* Whether Sensitive (S), Resistant (R), Multi-Drug Resistant (MDR) strains along with other Gram negative organisms isolated from different sites from 1st January 2004 to 31st December 2011 at King Abdulaziz Hospital (NGHA) Al-Ahsa, Eastern Region of Kingdom of Saudi Arabia (KSA). All necessary techniques were used to culture and determine sensitivity pattern of these organisms. Different media used for isolation of bacteria according to site, growth Gram staining was done and 20E and 20NE API kits were

Table 1: Acinetobacter baumanii and other bacterial strains isolates during 2004 to 2011

Group	No. of Isolates	No. of Caes/Patients
Acinetobacter baumanii	906 (20)	480 (53)
Other isolates	3626 (80)	2538 (70)
Total	4532 (100)	3018 (67)

Table 2: Number of Isolates, Cases (Male, Female) cases with reference against Acinetobacter baumanii and other bacterial strains

Group	Acinetobacter baumanii	Other isolates	Total
Male	221 (46)	1360 (45)	1581 (45.2)
Female	259 (54)	1658 (55)	1917 (54.8)
Total	480 (100)	3018 (100)	3498 (100)

Table 3: Sensitivity Pattern of Acinetobacter baumanii strains and other isolates

Year	No. of Isolates	*Acinetobacter baumanii*	Other isolates
2004	44 (1.0)	03 (0.3)	41 (1.1)
2005	158 (3.5)	12 (1.3)	146 (4.0)
2006	335 (7.4)	15 (1.7)	320 (8.8)
2007	454 (10.0)	28 (3.1)	426 (11.8)
2008	603 (13.3)	49 (5.4)	554 (15.3)
2009	707 (15.6)	81 (8.9)	626 (17.3)
2010	1106 (24.4)	362 (40.0)	744 (20.5)
2011	1125 (24.8)	356 (39.3)	769 (21.2)
Total	4532 (100)	906 (100)	3626 (100)

Table 4: Number of organisms isolated from each cases

Organism(s)	*Acinetobacter baumanii*	Percentages
Single	842	93
Two	47	5.2
Three	12	1.3
Four or >	5	0.5
Total	906	100

Results in parenthesis are percentages

Table 5: Antibiotics Sensitivity Pattern of Acinetbacter baumanii

Antibiotics	*Acinetobacter baumanii* Sensitive	Sensitive Percentages	*Acinetobacter baumanii* Resistant	Resistant Percentages
Amikacin	435	48.0	471	52
Ciprofloxacin	426	47.0	480	53
Cefepime	426	47.0	480	53
Ceftoxime	118	13.0	788	87
Ceftazidime	462	51.0	444	49
Gentamycin	553	61.0	353	39
Imipenem	725	80.0	181	20
Meropenem	507	56.0	399	44
Trimethoprim-Sulfamethaxazole	634	70.0	272	30
Pipercillin-Tazocin	426	47.0	480	53

(Note Tigecycline over all sensitivity was 60% and 40% resistant but we started it from 2008 that's why not included in list)

Table 6: Acinetobacter baumannii Resistant (R) and Multi-Drug Resistant (MDR)

Antibiotics	*Acinetobacter baumanii* (Total number of Resistant)	Number of *Acinetobacter baumanii* (Resistance to 2 or < antibiotic)	Percentage of *Acinetobacter baumanii* (Resistance to 2 or < antibiotic)	Number of *Acinetobacter baumanii* (MDR)	Percentage of *Acinetobacter baumanii* (MDR)
Amikacin	471	38	8.0	433	92.0
Ciprofloxacin	480	29	6.0	451	94.0
Cefepime	480	34	7.0	446	93.0
Ceftoxime	788	39	5.0	749	95.0
Ceftazidime	444	22	5.0	422	95.0
Gentamycin	353	25	7.0	328	93.0
Imipenem	181	27	15.0	154	85.0
Meropenem	399	68	17.0	331	83.0
Trimethoprim-Sulfamethaxazole	272	8	3.0	264	97.0
Pipercillin-Tazocin	480	48	10.0	432	90.0

Note Tigecycline over all sensitivity was 60% and 40% resistant but we started it from 2008 that's why not included in list

Table 7: Miscellaneous (Non-Acinetobacter baumanii)

Group	Other isolates	Percentages of other isolates
Escherichia coli	1350	37.2
Klebsiella pneumoniae	876	24.2
Proteus vulgaris.	714	19.7
Klebsiella oxytoca	408	11.2
Serratia marcescens.	170	4.7
Stenotrophomonas maltophilia	108	3.0
Total	3626	100

Table 8: MDR *Acinetobacter baumanii* and Pseudomonas aeruginosa isolated from different sites

Sites of isolates	*Acinetobacter baumanii*	Other isolates
Sputum	215(23.7)	925 (25.5)
Tracheal Aspirates	195(21.5)	872 (24.0)
Urine	144(15.9)	865 (23.9)
Wound Swab	120(13.2)	680 (18.7)
Rectal Swab	110(12.1)	42 (1.2)
Blood	31 (3.4)	36 (1.0)
Throat Swab	28 (3.1)	00 (0.0)
Endo	17 (1.9)	25 (0.7)
BAL	12 (1.3)	62 (1.7)
Eye	11 (1.2)	46 (1.3)
Ear	09 (1.0)	56 (1.52)
Tissue	06 (0.7)	08 (0.24)
Abscess	04 (0.5)	06 (0.16)
Fluid	04 (0.5)	03 (008)
Total	906(100.0)	3626 (100)

Results in parenthesis are percentages

used for identification of bacteria. Sensitivity discs (Kirby-Bauer) and MIC (Minimum Inhibitory Concentration) by E-test were used to look for sensitivity and resistant pattern against different groups of antibiotics.

RESULTS

A total number of 4532 isolates were involved in this study. *Acinetobacter baumanii* were 906 (20%) while other isolates were 3626 (80%) out of total. Number of

patients/cases were 480 (53%) with the reference to *Acinetobacter baumanii* and in other 2538 (70%) were relevant for the bacterial isolates (table 1).

Male patients constitutes 221 (46%) while Female were 259 (54%) who suffered *Acinetobacter baumanii* infections with male and female ratio of 1:1.2 and male were 1360 (45%) and female were 1658 (55%) in other isolates cases/patients with similar ratio as seen in *Acinetobacter baumanii*. Same male and female percentage and ratio in total patients/cases (table 2) was noticed. Numbers of total isolates were increase from 1.0% to 24.8% during last 8 years. In *Acinetobacter baumanii* a steady rise was seen from 0.3% to 40% till 2010 but in 2011 there is slight decrease in number and percentage, which was 356 (39.3%). In other isolates, a steady rise was observed from 1.1% to 21.2% during 2004 to 2011 (table No.3). Majority of *Acinetobacter baumanii* it were the single isolates 842 (93%), double isolates included 47 (5.2%), triple isolates were 12 (1.3%) while quadruple or more were 05 (0.5%) as can be seen in table 4. Out of a total 471 resistant *Acintobacter baumanii* to amkicin were 38 (8.0%) and 433 (92%) were found MDR. Out of 480 ciprofloxacin resistant were 29 (6.0%) belong to category and 451 (94%) were found MDR. Cefepime resistant 34 (7%) and 446 (93%) were MDR out of 480. Cefotoxime out of 788, there were 39 (5.0%) resistant and 749 (95.0%) were MDR. Ceftazidine from 444 there were 22 (5.0%) resistant and 422 (95.0%) were MDR. Gentamicin have 25 (7.0%) resistant and 328 (93.0%) MDR out of 353. Imipenem have 27 (15.0%) resistant and 154 (85.0%) MDR out of 181. There were 68 (17.0%) resistant and 331 (83.0%) were MDR out of 399 for meropenem. Trimethoprim/sulfamethaxole 8 (3.0%) were resistant and 264 (97.0%) MDR out of 272 and Pipercillin-Tazobactam from 480 there were 48 (10.0%) resistant and 432 (90.0%) MDR (table 6).

Maximum resistance was offered against to ceftoxime i.e. 87% followed by 53% against ciprofloxacin, cefepime and Piperecillin-Tazocin, 49% against ceftazidime, 44% against meropenem, 39% against gentamycin, 30% against septran while 20% isolates resistant to imipenem. Tigecycline resistance is on increasing trend every year since 2008 upto 2011 however this time period was not included in this study as it had not started in 2004 (table 5).

If we look in to resistant and multi-drug resistant of *Acinetobacter baumaniii* averge resistance (R) was 100 (23.0%) and Multi-Drug Resistance (MDR) or Pan-Drug resistance (PDR) was 335 (77.0%) out of 435. Some were MDR were resistant to almost all antibiotics (table 6) except Polymyxcin B and Colistin (table 6).

Other isolates belong to Gram negative group included: *Escherichia coli* 1350 (37.2%), *Klebsiella pneumoniae* 876 (24.2%), *Proteus vulgaris* 714 (19.7%), *Klebsiella oxytoca* 408 (11.2%), *Serratia marcescens* 170 (4.7%), and *Stenotrophomonas maltophilia* 108 (3.0%) as seen in table 7. Majority of the bacterial strains were isolated from respiratory system followed by urinary tract, wounds and colo-rectal area table 8.

DISCUSSION

The present includes 20% isolates of *Acinetobacter baumanii* and 80% belonging to the bacterial group from 4532. Other is isolates are significantly more than *Acinetobacter baumanii*. Number of patients/cases were 53% positive for *Acinetobacter baumanii* as compared to other isolates which were 70% table 1, These data are different in different studies. Much difference in male and female population was witnessed Sorberg M., et al; 2003 and El-Shafie SS, Alishaq M, Leni Garcia M; 2004. Females patients were recorded slightly more than the male (table 2). There was not much difference in male and female populations in miscellaneous other studies. There has been steady rise in total number of organisms, *Acinetobacter baumanii* and other isolates during 2004 to 2011 (table 3). Majority of studies were not extended time increased was bar check for that was steady rise. *Acinetobacter baumanii* was isolated as single site in 93% time (table 4). This was also noted in other studies Ayan M, Durmaz R, Aktas and Durmaz B; 2003.. General resistance pattern to different antibiotics was found variable from 20%-87% (table 5). General resistance to antibiotics was offered by 3.0% to 17.0% isolates and MDR of was much higher which ranged from 83.0% to 97.0% throughout studies. MDR inclusive antibiotics except only Polymyxin B and Colistin (Sorberg M., et al; 2003 and El-Shafie SS, Alishaq M, Leni Garcia M; 2004, El-Shafie SS, Alishaq M, Leni Garcia M; 2004. Del Mar TM, et al.;2005, Heritier C. et al; 2005, von Dolinger DB, et al; 2005, Maslow JN, elal; 2005, Hsueh PR,Chen WH, Luh KT; 2005, Lee JC, et al; and Clisneros et al; 2005). The average resistance rate for Resistant (R) 23% and Multi-Drug Resistant (MDR) or Pan-Drug Resistance (PDR) were 77% table No.6). MDR or PDR was usually very high in majority of studies and majority were resistance to all antibiotics except Polymyxin B and Colistin. Other bacterial isolated were six (table No.7). Other Gram negative organisms were isolated in some studies numbering more than our isolates. Maximum *Acinetobacter baumanii* isolates belonging to respiratory tract (Approximately 50%) followed by UTIs (15.9%), wound swabs (13.2%) and rectal swabs (12.1%). The rest were considerable low in number (table 8). Sites distribution was variable in different studies. In net shell *Acinetobacter baumanii* is one of the leading nosocomial pathogens worldwide[29-32]. Nosocomial infections caused by this organism are often difficult to manage as it have both intrinsic resistance of the species (constitutive expression of Amp C Beta-lactamase and efflux pumps,

combined with low permeability of the outer membrane) and its remarkable capability to acquire more resistance mechanisms against to many groups of antimicrobial agents including Beta-lactams, aminoglycosides and fluoroquinolones. This organism represents a phenomenon of microbial resistance, since practically all known mechanisms of antibacterial resistance can be seen: derepression of chromosomal Amp C cephalosporinase; amplication of production of resistance plasmids or integron-mediated beta-lactamases from different molecular classes (carbenicillinases and ESBLs belonging to class A, class D oxacillinases and class B carbapenem-hydrolyzing enzymes); diminished outer membrane permeability (loss of Opr D proteins); overexpression of active efflux systems with wide substrate profile; synthesis of aminoglycoside-modifying enzymes (phosphoryltransferases, acetyltransferases and adenyltransferases) and structural alterations of topoisomerases II and IV determining quinolone resistance. Worryingly, these mechanisms are often present simultaneously, thereby conferring multiresistant phenotypes. These are the known mechanisms for Pseudomonas aeruginosa and *Acinetobacter baumanii* which made this organism difficult to treat (Pachon-Ibanez *et al.,* 2004, Henwood *et al.,* 2002, Van Looveren & Goossen 2004, Sader *et al.,* 2005 and Akinci *et al.,* 2005, Posteir *et al.,* 2004, Oliva *et al.,* 2005, Taccome *et al.,* 2005, Brodie *et al.,* 2000, Orsi *et al.,* 2002, Lahir *et al.,* 2004, Landman *et al.,* 2002, Viiegas & Harstein 2003, Grady *et al.,* 2002, Karlowsky *et al.,* 2003, Melamed *et al.,* 2003, Baran *et al.,* 2007, Hoban *et al.,* 2005, Tognim *et al.,* 2004, Kuo *et al.,* 2004, Falagas *et al.,* 2005 Posteir *et al.,* 2004, Oliva *et al.,* 2005, Taccome *et al.,* 2005, Brodie *et al.,* 2000, Orsi *et al.,* 2002, Lahir *et al.,* 2004, Landman *et al.,* 2002, Viiegas & Harstein 2003, Grady *et al.,* 2002, Karlowsky *et al.,* 2003 and Melamed *et al.,* 2003).

CONCLUSION

There has been steady rise in *Acinetobacter baumanii* resistance and multi-drug Resistance against drugs and rapidly increasing in the isolates from young adults and stabilizing in the elderly. Most common anatomical site of isolation is respiratory tract. The R and MDR *Acinetbacter baumanii* show need interest by antibiotics and infection prevention policies and procedures including antibiotics stewardship programs and surveillance studies. It should be kept in mind that eight top Pharmaceutical (Avantis, Abbot, Bristal-Mayers Squibb, Eli Lilly, Procter & Gamble, Roche and Wyeth) companies has stop antibiotics research work due to very high research and development cost from US$800 million to 1.7 billion and it requires 10 or more years to reach out one antibiotic (Karlowsky *et al.,* 2003, Melamed *et al.,* 2003, Projan 2003 and Wenzel 2004).

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