

An Emergence of a MRAB: With Growing Necessity of Antibiotic Pharmacist in Infectious Era

Maria A*, Somia G, Hina L, Ishrat I and Munawerah F

Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan

*Corresponding author: Maria A, Lecturer, Faculty of Pharmacy, Jinnah University for Women, Karachi 74600, Pakistan, Tel: +92331-3119160; E-mail: maria.ayub2000@gmail.com

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Abstract

Multi-drug Resistant pathogens pose a serious challenge against lifesaving antimicrobials globally. MRAB (multi drug resistant *Acinetobacter baumannii*) has a capability for extensive adaptation of multi-drug resistance pattern particularly in immune compromised patients which became resistant to carbapenems beta lactamase antimicrobials. The objective of the study is to evaluate multidrug resistance pattern of *A. baumannii* among broad spectrum antimicrobials with intention to highlight the growing need of antibiotic pharmacist in south Asia to encounter such life threatening multidrug resistance pattern. For the purpose of this study MRAB isolates with sensitivity and resistance pattern carefully evaluated by hospital pharmacist to determine such pattern with rationale utilization of therapy. Resulting data of about 146 isolates of MRAB interpreted by pharmacist which shows about 78% isolates were resistant to more than four broad spectrum antimicrobials. Amoxicillin has been resistant to 90%, Piperacillin 67%, third generation cephalosporin 92% with 75% of fourth generation cefepime, carbapenems 67%, aminoglycosides 75%, quinolones 54% and Polymyxin B 47% resistance respectively. This retrospective studies drawn conclusion that the effective utilization with evaluation of adaptive drug resistance can encounter threats associated with multidrug resistance pathogens and pharmacist can imparts key role in rationale utilization of antimicrobials with growing concern of implementation of specialty role in healthcare sector of south Asia.

Keywords: MRAB; Evaluation; Pathogenesis; Drug resistance; Sensitivity

Introduction

Multi-drug Resistant pathogens create an emergence against life threatening antimicrobials is a major growing concern and challenging task Globally and in the USA [1-2]. Regardless of this serious issue with increase in threshold of antimicrobials resistance, termination of development of new antimicrobials by pharmaceutical industries create an emergence to treat multidrug resistant pathogens [3-6]. However the adaptation of pathogens resistance against wide range of antimicrobials among gram positive and gram negative microbes *Acinetobacter baumannii*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, MRSA, VRSA and *E. coli* emerge a serious concern to encounter infectious disease [7].

A. baumannii, a superbug with gram negative staining aerobe is versatile pathogen having high threshold among immunodeficient patients predominantly exposed to prolong hospital admissions [8]. *Acinetobacter* accounts for significant taxonomic variation globally resistant to variety of antimicrobial is a major growing concern for Health sector and create emergence against broad spectrum antimicrobials. This pathogen have prolong survival threshold especially measure leading cause of hospital acquired nosocomial infections. It targets the open skin wounds and respiratory tract infection and mucosal secretions, pneumonia in hospital setting mostly caused by this pathogen additionally it affects bone, nervous system and infection involving soft tissues is major growing concern in hospital settings [8-10].

This pathogen presented as high alert with red alarming situation due to multidrug resistant antimicrobial spectrum [8,11]. *Acinetobacter*, has taken importance globally in term of current and scientific modified era day by day and reviewed previously in 19th century [12] incidence of multidrug resistance microbes presently is serious threat for both community and hospital acquired nosocomial infection the prevalence of antimicrobial resistance accounts for the 3rd major leading concern in health sector by world Health organization (WHO). *Klebsiella pneumoniae*, *A. baumannii*, *Staphylococcus aureus*, *Enterococcus faecium*, *Pseudomonas aeruginosa* classified as multidrug resistant pathogens [8,13].

A. baumannii accounts for meningitis, soft skin sepsis, urinary tract infections, bronchitis and endocarditis presenting a challenging concern primarily in the intensive care units [14]. Infection resulting from this pathogen often hard due to highly acquired resistance mechanism by this bad bug especially beta-lactamase inducing resistance mechanism of in gram negative aerobe [14,15]. Although *A. baumannii* reported in past 1970s possess sensitivity against variety of antimicrobials but now in current era of infectious disease *A. baumannii* have adapted a resistance mechanism against first line antimicrobials [16,17]. Pathogenicity caused by this pathogens specially targets soft tissue open wounds exposed as a result of accidental injury and burns and mucosal lining of respiratory tract [8,10,17,18]. Although, *A. baumannii* accounts rarely found as normal flora of skin approximately just 3% according to one study in spite of the this fact its responsible for skin infection [19]. *A. baumannii* is isolated mostly from people about 22% in homeless serve as host for this pathogen [20]. *A. baumannii* threshold is high among soldier infected with open wounds infections [21].

A. baumannii creates an emergence once it has been isolated in any healthcare setting due to high risk pathogenicity especially in the intensive care units patient with severe illness [22]. People with immunodeficiency with prolonged stay at hospital are highly at risk infected with this pathogens. People exposed to ventilating devices and other disposable devices present high risk group susceptible to the infection associated with *baumannii* due to its ability to make biofilm which colonize mucosal lining of respiratory tract [23-25]. Ability of *A. baumannii* to adapt extensive and multi-drug resistance according to environmental factor imparts a contributing factor for emergence of resistance with acquisition of Innate adaptive resistance mechanism by up regulation considerably taken into account as multidrug resistance *A. baumannii* MRAB with rapid emergent resistant species of *A. baumannii* resistant with beta-lactams drugs even with carbapenems [26-28].

For the improvement of rationale utilization of drug therapy role of pharmacist must be evident to utilize properly of available drugs and the growing need for pharmacists does exist in the clinical area proved by the study conducted at California San Francisco medical center proven the role of pharmacist additionally to the medical staff and nursing staff. New drug formulary system to elaborate the role of pharmacist in patient care and the clinical pharmacist can play key role for drug information resurgence and propagate role in healthcare setting effectively [29]. Extensive irrational prescribing threshold of antimicrobials in hospital settings at UK, the role of introduction of antibiotic pharmacist specialty with proper monitoring of antibiotic utilization, its indication by clinicians, and provide sound knowledge of antimicrobials to all healthcare co-providers. Pharmacist should need to prove their role in drug intervention may imparts their beneficial role in many situations to expand their role by taking effective decision such as antimicrobial stop and shifting towards intravenous route to oral safe route and other important interventions as necessary to augment patient care [30].

The objective of this study was to identify the multidrug resistance pattern against lifesaving antimicrobials by their sensitivity and resistance pattern against *A. baumannii* with growing concern that the need of antibiotic pharmacist in Pakistan healthcare sectors and to find out the target rational therapy to encounter the multidrug resistance threaten associated with irrational practice in healthcare sector and clinical pharmacist may play a key role in appropriate utilization of this antimicrobials against bad bug pathogens. Multidrug resistance is a major growing concern in hospital setting especially in the intensive care units of public and private health care sector primarily in immune compromised patients.

Methodology

Collection of bacterial strains

About 146 clinical isolates of *Acinetobacter baumannii* resistant to multiple drugs (90% to penicillin & 75% to cefepime) were obtained from different secondary and tertiary care center of Karachi of public and private sector. Isolates obtained from in and out patients were mostly from chronically ill and immune compromised system and those admitted at intensive care units. Specimen collection from these source specifically designed in this study to evaluate multidrug resistance *A. baumannii*.

Isolates were tested in the laboratories on the basis of their biochemical testing and colony growth characteristics and finally

preserved on slant at controlled temperature of 4°C. Antimicrobial susceptibility and resistance evaluated by according to CLSI Reference standard of Clinical and laboratory standard institute.

Preparation of medium & its inoculation

Antibiograms obtained from all participant healthcare centers were based on Kirby-Bauer Disk diffusion method and inoculums of micro broth dilutions prepared by Muller-Hinton broth (MHB) with suspended colonies were equivalent to 0.5 McFarland Standard. All results interpreted on sheets complied according to CLSI (NCCLS) [31]. Incubation period for this method is 35 ± 2°C with supportive ambient air for 20-24 hours.

Susceptibility testing

More than 35 antibiotics were selected against 75% cefepime and 90% resistant isolates of *A. baumannii* with Disc content of antimicrobial piperacillin 100 µg, Cefepime & Ceftazidime 30 µg, Monobactams (Aztreonam) 30 µg, meropenem & imipenem 10 µg, Aminoglycosides (Amikacin) 30 µg, (tobramycin and gentamycin) 10 µg and quinolones (ciprofloxacin) 5 µg correspondingly according to CLSI directed zone of resistance and susceptibility size with exclusion of intermediate size zone.

Incorporation of pharmacist

After the collection of testing report of 4th Generation resistant isolate *A. baumannii* Pharmacist paid their attention and presented detailed report on rationale utilization of antibiotics upon invitation by healthcare authorities and they introduced key points regarding proper utilization of antimicrobials and to encounter resistance associated with Multi drug resistant pathogens.

They can designed and improve their hospital formulary according to patient susceptibility response in view of the fact to make sure rational utilization of antimicrobials can prevent this major issue against Bad bugs after reported linezolid and glycopeptides resistance in tertiary care centers. Resulting outcome analyzed statistically by applying IBM SPSS Statistics 21 version software and p-value less than 0.05 considered significant statistically.

Results

After careful evaluation with hospitals Antibiograms of MRAB All resulting data interpreted by hospital pharmacist with the help of statistical analysis and spss software to provide key pattern of drug resistance adaptive mechanism in MRAB isolates.

For the measurement of resulting outcomes of antimicrobials sensitivity pattern more than 146 isolates were evaluated from January 2013-august 2015 from different tertiary healthcare center of patient with chronic illness.

Samples collection source were mostly from blood, urine, pus and sputum with highest percentage of blood sample shown in Figure 1.

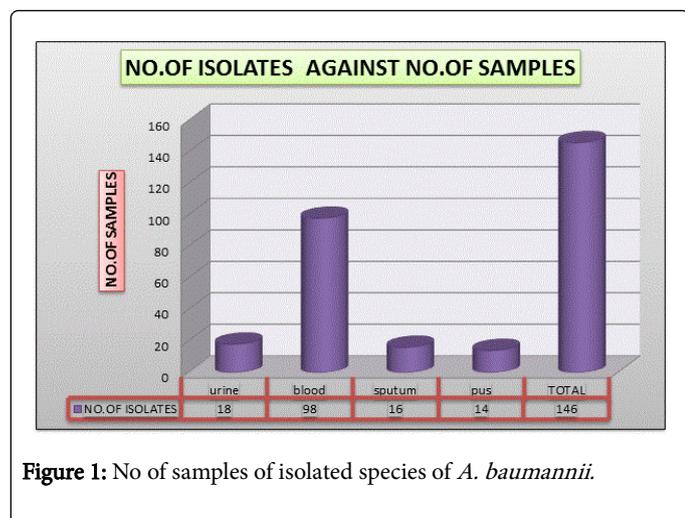


Figure 1: No of samples of isolated species of *A. baumannii*.

All the isolates were tested against more than 20 antimicrobials and the resulting Antibiograms clearly shows that about 78% isolates were resistant to more than four broad spectrum antimicrobials shown in Figure 2.

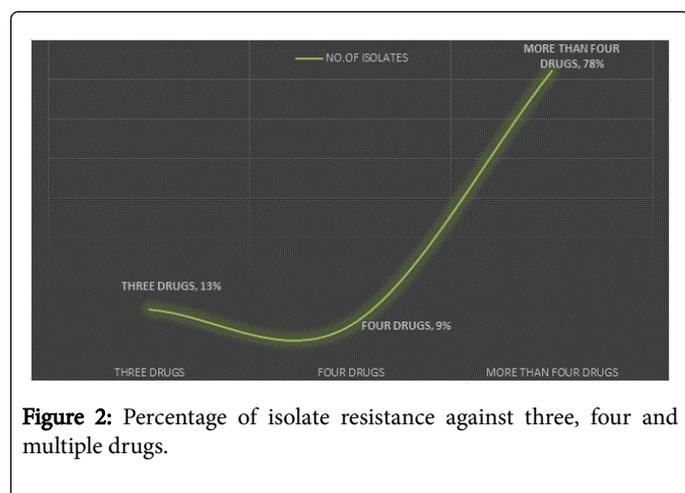


Figure 2: Percentage of isolate resistance against three, four and multiple drugs.

Resulting Antibigrams of MRAB from different tertiary care center were 75% resistant to 4th generation cephalosporins which clearly reflects less efficacy of beta lactam antibiotics Figure 3 clearly demonstrate 86% resistance against piperacillin, 82% cefepime,

carbapenems 79%, aminoglycosides 88%, quinolones 95% and Polymyxin-B 94% respectively in isolates of MRAB resistant to three broad spectrum antimicrobials.

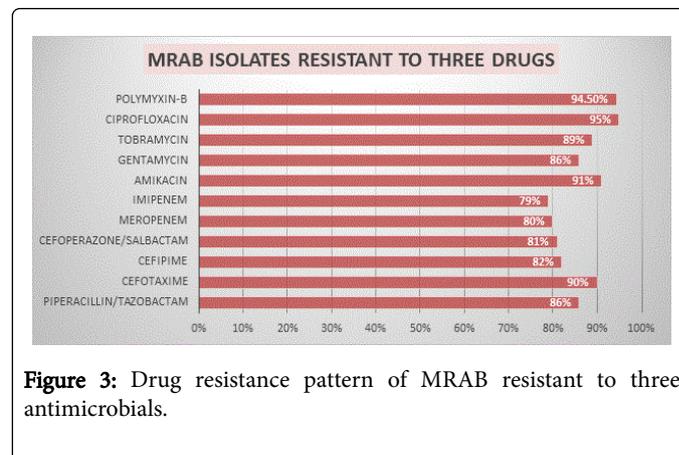


Figure 3: Drug resistance pattern of MRAB resistant to three antimicrobials.

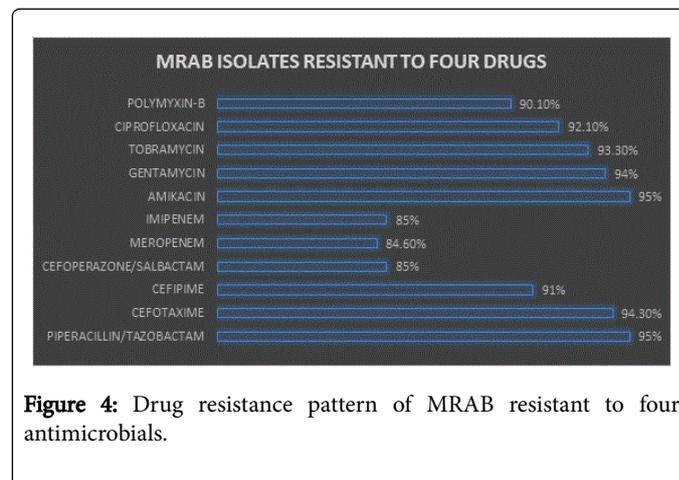


Figure 4: Drug resistance pattern of MRAB resistant to four antimicrobials.

Figure 4 and Table 1 shows isolates which were resistant to four drugs involving loss of sensitivity in amikacin & piperacillin 95%, quinolones 92%, cefepime 91% with highest sensitivity shown in carbapenems of 15% respectively. From T-test the resulting outcome is significant which clearly reveals the fact that there is significant change in sensitivity and resistance pattern among different class of antimicrobials ($p < 0.05$).

Parameter	Chloroform Extract	Acetogenin fraction
Total soluble polyphenols (mg/g DW)	0.72 ± 0.02	0.032 ± 0.001
ABTS assay (mmol TE/g DW)	22.19 ± 0.15	4.91 ± 0.23
DPPH assay (mmol TE/g DW)	1.02 ± 0.14	0.58 ± 0.07
Reducing power (µM AA equivalent)	23.85 ± 0.07	21.77 ± 0.39
Total antioxidant activity (µg α-tocopherol equivalent)	33.76 ± 2.91	4.85 ± 2.10

Table 1: Total soluble polyphenols and antioxidant activity of chloroform extract and acetogenin fraction obtained from *Annona muricata* fruit pulp.

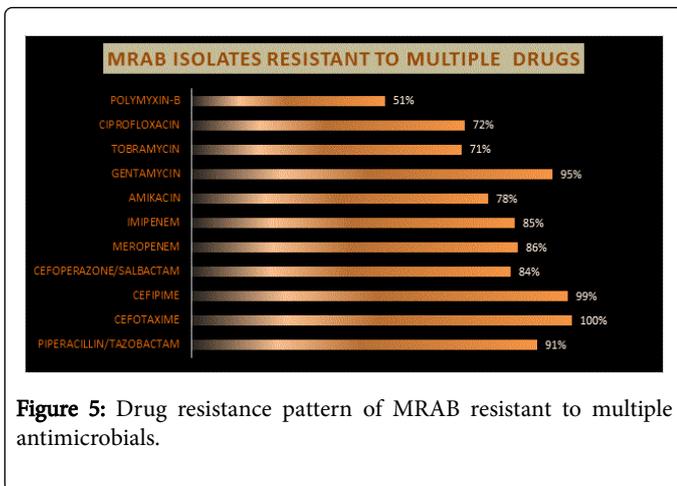


Figure 5: Drug resistance pattern of MRAB resistant to multiple antimicrobials.

Multiple drug resistant isolates shows highest sensitivity against Polymyxin-B 49%, ciprofloxacin 30%, aminoglycosides 27%, carbapenems 15%, with highest percentage of resistance against cephalosporins about 99% respectively shown in Figures 5 and 6.

Table 1 and Figure 6 demonstrate comparative efficacy with less sensitivity of antimicrobials against MRAB and pharmacist evaluated these all MRAB evolution of resistance against broad spectrum antimicrobials which provide best treatment option with less chance of resistance particularly in immune compromised patients.

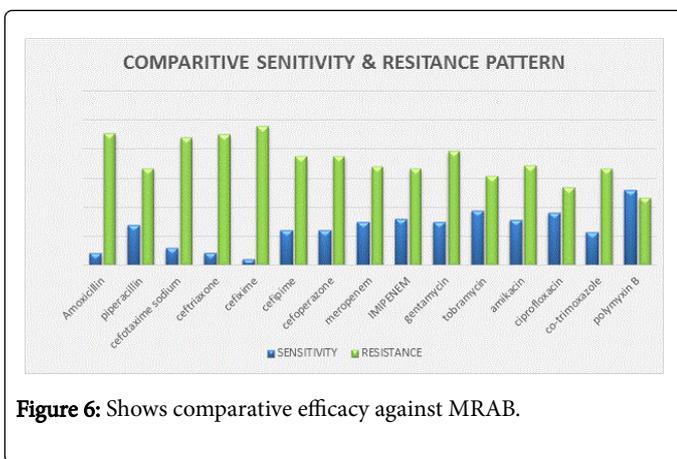


Figure 6: Shows comparative efficacy against MRAB.

Discussion

Contingency of strains that are resistant to nearly all available drugs and receivable to increase in antimicrobial resistance, *Acinetobacter baumannii* is attracting much recognition. All of the considerable resistance mechanisms that are known to fall in bacteria, the resistance of *A. baumannii* to antimicrobial agents is mediated also through this mechanism involving target sites adaptation, enzymes inactivation, drugs ornament of decreased influx as well as increased ornament of active efflux. Associated with the resistance beta lactamases is the most sundry group of enzyme and have been distinguished so far in *A. baumannii* of type of this enzyme is about more than 50 enzymes. At least nine definite modifying enzymes by the acknowledgment in some strains of the Aminoglycosides resistance [32]. Resistant to the agents implicated Aminoglycosides, beta lactamase as well as fluoroquinolones in strains of *A. baumannii* an upward mode have

proposed by several studies. Among clinicians, the resistance amidst *A. baumannii* strains to β -lactam agents is of great interest. This study clearly illustrates and identified the sources of MRAB in terms of isolation which about 98% from the blood. In this study, spectrum of antibiotic is assessed with especial attention of pharmacist and shows multiple drug resistance species of species against more than four antimicrobials up to 78% resulting an emergence condition.

This study also demonstrated the pattern of multi drug resistance against the broad spectrum antimicrobials like carbapenems class from which MRAB resist up to 80% from imipenem, a novel drug in this modern era so creating a difficult situation for health care partitions as highlighted by involvement of pharmacist. Well addition to this resistance which is very important concern in healthcare settings, treatment of this multidrug resistance pathogen cannot also be avoided. Treatment against this pathogen is a key point in this study effectively evaluated by the involvement of the pharmacist as MRAB resistance most commonly found in immune compromised patients, critically ill patients such as who admitted in ICU, so in these conditions choice of antibiotic should be rationale to provide maximum therapeutic effect as the necessity of these type of patients. Antimicrobials sensitivity against MRAB, from which higher percentage from Polymyxin B obtained up to 49% later this 27% sensitivity obtained from aminoglycosides and the hallmark of the antibiotic era is that MRAB is sensitive to carbapenems is only about 15% which is the novel drug in clinical setting now a days. In this study pharmacist also highlighted the main concern of antimicrobials relative to clinical point of view that now a days cephalosporins are commonly use against many infections in terms of drug of choice in irrational therapy but MRAB resistance is found up to 99% against cephalosporins. In *A. baumannii* resistance to extended-spectrum cephalosporins the main mechanism involved are the plasmid-encoded Ambler class A, B, and D β -lactamases and cephalosporins chromosomal over-expression [33].

From various geographic areas hospitals epidemics have been outlined about MRAB [34-37]. *A. baumannii* is able to grow at numerous temperature conditions and PH as well as it does not have any fastidious growth requirements [38]. To persist in either moist or dry conditions in the hospital environment contributing transmission The all-around organism exploits a variety of both carbon and energy sources and this characteristics explains the ability of *Acinetobacter* species [39,40]. Although it is prevalent in hospitals and rare isolates have been found in community suggested by literature review but recently some community cases of this pathogen has also reported. In northern Australia and southern Asia an occurrence of community-acquired was recently described associated with high mortality in patients. In that study were bacteremia (31.6%) and had acute respiratory distress syndrome and disseminated intravascular coagulation with a significant percentage of the patients [41-43]. We will not be able to use anymore antimicrobial agents against this opportunistic pathogen among beta lactams antibiotics as well as we need to used tool having ability to sort out the resistance mechanism and there is need of discovery of antimicrobials which could treat effectively this isolate. Infection control is also can be used to control resistance by imparting various health workers like pharmacists.

Pharmacist are integral part of healthcare team their specialty role i.e., antibiotic Pharmacist concept is still controversial in south Asia as patients need no suggestion for safe utilization of antimicrobials other than physician. Pharmacist can utilize their knowledge regarding rational utilization of drug to prevent this life threatening resistance

against infectious disease. In this study Pharmacist from different hospital setting make their effort to designed strategy to combat antimicrobial resistance. Pharmacist better suggestion make their necessity in incorporation of major health issues which is accepted by healthcare practitioner and high authorities as they suggested incorporation of antibiotic pharmacist in south Asia is now obligatory. It is not an effortless assignment in *A. baumannii* with a fulfillment of multidrug resistance. By the consequences, new antimicrobial which regulate this pathogen there is also a decided downturn in the advancement.

The end of the “antibiotic era” may be faced soon by us. The fruit of human infinite, has been responded by an escalation of resistance mechanisms in bacteria because the initial and seemingly unstoppable success of antibiotics.

Conclusion

An emergence of Multidrug resistant *Acinetobacter baumannii* create an emergence against lifesaving antimicrobials because of loss of sensitivity in infectious era. Patient with chronic illness need rational utilization of antimicrobials to combat resistance against superbug. Inclusion of antibiotic pharmacist can encounter this problem in south Asia as essential lacking of evident role of pharmacist in specialty care in immune deficient patients. Pharmacist have useful knowledge regarding drug selection, utilization, monitoring of adverse drug reaction and drug effectiveness against infectious disease. Their inclusion in health care team against infectious disease can minimize resistance and loss of antimicrobial efficacy by finding bacterial evolution mechanism.

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