academicJournals

Vol. 9(2), pp. 78-82, 14 January, 2015
DOI: 10.5897/AJMR2014.6840
Article Number: 99518C850123
ISSN 1996-0808

http://www.academicjournals.org/AJMR

African Journal of Microbiology Research

Full Length Research Paper

β-Lactam - β-lactamase inhibitor combinations as the choice therapy for multidrug resistant Acinetobacter

Farhan Rasheed*, Raja Kamran Afzal and Muhammad Jan Leghari

Microbiology Department, Combined Military Hospital, Lahore, Pakistan.

Received 19 April, 2014; Accepted 22 December, 2014

Acinetobacter, an important nosocomial pathogen, is capable of causing infectious outbreaks in critically ill patients which results into high morbidity and mortality worldwide. It is rated among top seven pathogens that disturb the health care delivery system. The situation has become complicated due to the organism's capability to acquire diverse resistance mechanisms. This has resulted in the emergence of multidrug resistant and pan-drug resistant strains. A total of 100 clinical isolates of *Acinetobacter* spp. were evaluated against five β-lactam – β-lactamase inhibitor combinations by modified Kirby Bauer disc diffusion method using Mueller-Hinton agar. Zone sizes were interpreted according to CLSI 2012 guidelines. Out of 100 isolates, 85 were *Acinetobacter baumannii*, 9 were *Acinetobacter johnsonii* and 6 were *Acinetobacter lwoffii.* Eighty four isolates of *A. baumannii,* 8 isolates of *A. johnsonii* and all 6 isolates of *A. lwoffii* were multidrug resistant. One isolate from each of *A. baumanni* and *A. johnsonii,* and no isolate of *A. lwoffii* were susceptible to co-amoxiclav. Twenty eight isolates of *A. baumanni,* one isolate of *A. johnsonii* and no isolate of *A. lwoffii* were susceptible to ampicillin-sulbactam. Forty one (41) isolates of *A. baumanni,* one isolate of *A. johnsonii* and no isolate of *A. lwoffii* were susceptible to piperacillin-sulbactam. Eight isolates of *A. baumanni,* one isolate of *A. johnsonii* and no isolate of *A. lwoffii* were susceptible to piperacillin-tazobactam. Forty eight isolates of *A. baumannii,* one isolate of *A. johnsonii*, and no isolate of *A. lwoffii* were susceptible to cefoperazone-sulbactam. Cefoperazone-sulbactam was the most effective combination against 49% isolates of Acinetobacter. Ninety one percent isolates were resistant to piperacillin-tazobactam. Combinations having sulbactam were more effective as compared to others. This work also support the postulate that sulbactam, though not an antimicrobial, but does possess antibacterial activity against Acinetobacter species.

Key words: Acinetobacter, β-lactam – β-lactamase inhibitor combinations, cefoperazone-sulbactam.

INTRODUCTION

Acinetobacter is a Gram negative cocco-bacillus, aerobic, pleomorphic, non-fermenting, non-fastidious, non-motile, catalase-positive and oxidase-negative opportunistic pathogen. This genus consists of 35 species (Turton et al., 2005). Out of these, *Acinetobacter baumannii* is responsible for about 80% of clinical conditions (Sebeny et al., 2008). Acinetobacter has a high incidence among immunocompromised individuals, particularly those who

*Corresponding author. E-mail: dr.farhanrasheed@gmail.com.

have experienced a prolonged hospital stay (Montefour et al., 2008). It has been observed to colonize the skin as well as the respiratory and oropharyngeal secretions of hospitalized patients (Sebeny et al., 2008). Propensity to tolerate drying and resistance to multiple classes of antibiotics are the other key factors that enable this organism to survive and spread in the hospital environment. Bacteremia, urinary tract infections, pneumonia, and meningitis, are the main complications resulting from *Acinetobacter* spp. induced nosocomial infections (Ionescu and Constantiniu, 2004). A*. baumannii* earlier became one of the most common hospital acquired pneumonia causing pathogen (Glew et al., 1977). There are some reports documenting *A. baumannii* the cause of community-acquired pneumonia also (Leung et al., 2006). A study in USA showed that, almost 4% of combat wound infections in battle field soldiers were due to *Acinetobacter* spp. (CDC, 2002). The ability of *A. baumannii* to form biofilms allows it to grow in unfavorable conditions and environments also. *A. baumannii* has been shown to form biofilms on inanimate surfaces, which can include glass and equipment used in intensive care units, and on biotic surfaces such as epithelial cells (Gaddy and Actis, 2009).

The increasing bacterial resistance to carbapenems or even to colistin or tigecycline is of great concern because these antibiotics are the last therapeutic regimen for many bacterial infections (Hoffmann et al., 2010; Peleg et al., 2008; Dijkshoorn et al., 2007; Bergogne-Berezin and Towner, 1996). Bacterial strains are referred to as multi-drug resistant, when resistance to three or more classes of antibiotics is demonstrated (Peleg et al., 2008). The emergence of resistance to all β-lactams especially the broad spectrum carbapenems depicts the capability of *A. baumannii* strains to change their response rapidly to environmental changes by selective pressure. Acquiring resistance mechanism due to chromosomal reassortment and through plasmids have made *A. baumannii* a pathogen of emerging threat. Although, we have limited data of genetic reassortment of *A. baumannii* and other species of Acinetobacter, especially *A. baylyi*, these pathogens are highly competent in acquiring resistance (Bacher et al., 2006; Vaneechoutte et al., 2006).

Acinetobacter can acquire resistance either by enzymatic method or non-enzymatic methods. Mostly, *A. baumannii* acquire resistance to β-lactams by producing β-lactamases, in particular to β-lactams during enzymatic degradation by β-lactamases (Bou et al., 2000; Tsakris et al., 2006). The enzymatic modification is another tool for resistance that is genes coding for aminoglycoside modifying enzymes are present in multidrug-resistant *A. baumannii* strains (Lee et al., 2005; Zarrilli et al., 2004).

In resistance mechanisms of Acinetobacter, all of the major enzyme classes have been found, including acetyltransferases, nucleotidyltransferases, and phosphotransferases (Hujer et al., 2006; Nemec et al., 2004). The resistance to β-lactams, including carbapenem, has also been associated with non-enzymatic resistance mechanisms, including changes in outer membrane proteins (OMPs) (Gribun et al., 2003; Mussi et al., 2005), multidrug efflux pumps (Heritier et al., 2005; Higgins et al., 2004), and alterations in the affinity of penicillin-binding proteins (Siroy et al., 2006). The resistance to tetracycline group may be mediated by efflux or ribosomal protection (Fluit et al., 2005). The term “pan-resistance” has been used to describe strains of Acinetobacter species that are resistant to all standard antimicrobial agents tested except colistin (Paterson, 2006).

The broad spectrum of activity of β-lactamase inhibitors in combination with β-lactam antibiotics originates from the ability of respective inhibitors to inactivate a wide range of β-lactamases produced by Gram positive, Gram negative and even acid-fast pathogens. Clinical experience confirms their effectiveness in the empirical treatment of respiratory, intra-abdominal, skin, and soft tissue infections. Their role in treating various multidrug resistant pathogens is gaining importance (Perez-Llarena and Bou, 2009). The aim of the present study was to test the effectiveness of 5 different combinations of β-lactam- β-lactamase inhibitors against multi drug resistant clinical isolate of *Acinetobacter* spp.

MATERIALS AND METHODS

This descriptive, cross-sectional study was carried out in the Department of Microbiology, Combined Military Hospital, Lahore, from January to October 2012. Clinical specimens like blood, pus, double lumen tip, ascitic fluid, tracheal aspirate, naso-bronchial lavage (NBL), cerebrospinal fluid (CSF), high vaginal swab (HVS) were cultured on blood and MacConkey agar, while the urine samples on were cultured on cysteine lactose electrolyte deficient (CLED) agar. Later the isolates were identified by Gram staining, a positive catalase test and negative cytochrome oxidase test. Species level identification was done by API-20NE (biomerieux, France). Duplicate samples of the same patient during the same episode of illness were excluded. A total of 100 clinical isolates of *Acinetobacter* spp. were included in this study. Antimicrobial susceptibility testing of the isolates was carried out using the modified Kirby-Bauer disc diffusion method. Bacterial suspensions equivalent to 0.5 McFarland turbidity standard were prepared and inoculated on Mueller Hinton agar plates. Isolates resistant to three or more classes of antibiotics (aminoglycoside, quinolones and third generation cephalosporin) were labelled as multidrug resistant. Antibiotic discs of co-amoxiclav 30 µg (amoxicillin 20 µg + clavulanate 10 µg), ampicillin-sulbactam 20 µg (ampicillin 10 µg + sulbactam 10µg), piperacillin-tazobactam 110 µg (piperacillin 100 µg + tazobactam 10 µg), piperacillin-sulbactam 130 µg (piperacillin 100 µg + sulbactam 30 µg), cefoperazone-sulbactam 105 µg (cefoperazone 70 µg + sulbactam 35 µg), (Oxoid, UK) were applied followed by incubation at 35°C for 18 - 24 h. The results were interpreted following the Clinical and Laboratory Standards Institute guidelines 2012 (CLSI, 2012) as shown in Table 1.

American Type Culture Collection (ATCC) *Escherichia coli* 35218 was used as the quality control strain. Data was analyzed using Statistical Package for Social Sciences (SPSS) version 19. Qualitative variables for example clinical specimens and antimicrobial susceptibility were expressed as frequency and percentages.

Table 1. Clinical and Laboratory Standards Institute guidelines 2012.

β-Lactam-B-lactamase Inhibitor combinations drugs	Sensitive (zone size in mm)	Intermediate (zone size in mm)	Resistant (zone size in mm)
Amoxicillin-clavulanate (30 µg)	≥ 18	14-17	≤ 13
Ampicillin-sulbactam (20 µg)	≥ 15	12-14	≤ 11
Piperacillin-tazobactam (110 µg)	≥ 21	18-20	≤ 17
Piperacillin-sulbactam (130 µg)	≥ 21	18-20	≤ 17
Cefaperazone-sulbactam (105 µg)	≥ 21	18-20	≤ 17

Table 2. Percentage of MDR Acinetobacter.

Isolates	MDR Acinetobacter
Acinetobacter baumannii	84 (98.8%)
Acinetobacter johnsonii	8 (88.8%)
Acinetobacter lwoffii	6 (100%)
Total	98 (98%)

Figure 1. Susceptibility of Acinetobacter against β-lactam - β-lactamase Inhibitors.

RESULTS

Out of 100 isolates, 85 were *A. baumannii*, 9 were *A. johnsonii* and 6 were A*. lwoffii.* Out of 85 isolates of *A. baumannii,* 84 (98.8%) were multidrug resistant, out of 9 isolates of *A. johnsonii*, 8 (88.8%) were multidrug resistant and all 6 (100%) isolates of *A. lwoffii* were multidrug resistant (Table 2). One from each *A. baumannii* and *A. johnsonii* isolates was susceptible to co-amoxiclav; all 6 isolates of *A. lwoffii* were resistant to it. Overall, only 2% of isolates were susceptible to co-amoxiclav. Twenty eight (32.94%) isolates of *A. baumannii* and one (11.11%) of *A. johnsonii* were susceptible to ampicillin-sulbactam, all 6 (100%) isolates of *A. lwoffii* were resistant to it. Overall, 29% isolates were susceptible to ampicillin-sulbactam. Forty one (48.23%) isolates of *A. baumannii* and one (11.11%) isolate of *A. johnsonii*, were susceptible to piperacillin-sulbactam, all 6 (100%) isolates of *A. lwoffii* were resistant to it. Overall, 42% isolates were susceptible to piperacillin-sulbactam. Eight (9.41%) isolates of *A. baumannii* and one (11.11%) isolate of *A. johnsonii*, were susceptible to piperacillin-tazobactam, all 6 (100%) isolates of *A. lwoffii* were resistant to it (Figure 1). Overall, 9% isolates were susceptible to piperacillin-tazobactam. Forty eight (56.47%) isolates of *A. baumannii* and one (11.11%) isolate of *A. johnsonii*, were susceptible to cefoperazone-sulbactam, all 6 (100%) isolates of *A. lwoffii* were resistant to it. Overall, 49% isolates were susceptible to cefoperazone-sulbactam (Figure 2).

DISCUSSION

In this study, cefoperazone-sulbactam among β-lactam - β-lactamase inhibitors was the most effective combination against 49% of Acinetobacter isolates. Nighty eight percent of total isolates were resistant to co-amoxiclav, 71% isolates were resistant to ampicillin-sulbactam, 58% isolates were resistant to piperacillin-sulbactam and 91% isolates were resistant to piperacillin-tazobactam. Combinations having sulbactam were more effective as compared to others. These results also supports the postulate that sulbactam, though not antimicrobial but does possess antibacterial activity against Acinetobacter species (Visalli et al., 1997).

A local study in 2012 showed that antimicrobial resistance in *Acinetobacter ssp*. is on rise. 46 isolates of *Acinetobacter spp.* were included in that study. 30.4% isolates were susceptible to ceftriaxone, 67.4% isolates were susceptible to cefepime, 56.5% isolates were susceptible to ciprofloxacin, 82.6% isolates were susceptible to both imipenem and meropenem. 23.9% of isolates were susceptible to co-amoxiclav as compared to 2% isolates of our study, 78.0% of isolates were susceptible to piperacillin-tazobactam as compared to 9% isolates of our study, 93% of isolates were susceptible to cefoperazone-sulbactam as compared to 49% of our study.

In that study all isolates were from blood culture specimens while in our study all kinds of clinical specimens

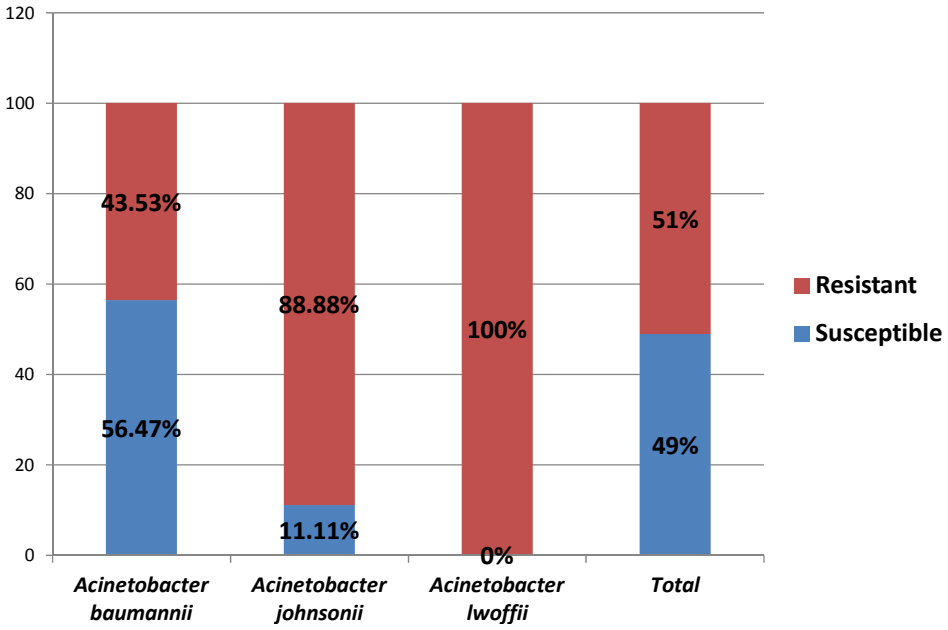

Figure 2. Susceptibility of Acinetobacter isolates to cefoperazone-sulbactam

were included (Javed et al., 2012).

In a study from USA in 1997, 3 combinations of β-lactam-β-lactamase inhibitors were tested against Acinetobacter species. In that study, 86.9% isolates of *Acinetobacter* spp. were susceptible to ampicillin-sulbactam, while in our study only 29% of isolates were susceptible to this combination. Their 84.8% isolates of *Acinetobacter* spp. were susceptible to piperacillin-tazobactam, while in our study only 9% of isolates were susceptible to it. Their 54.4% isolates were susceptible to co-amoxiclav, whereas only 2% of our isolates were susceptible to it. The other two combinations were not tested in that study. As compared to previous study our study has decreased susceptibility pattern; possible reason for that previous study is that it was conducted almost 16 years ago and *Acinetobacter* spp. has acquired resistance over time (Seward et al., 1998).

In a study from Germany in 2004, 115 isolates of *A. baumannii* were tested against different combinations of β-lactam - β-lactamase inhibitors. In that study, 35.6% isolates of *A. baumannii* were susceptible to co-amoxiclav as compared to 2% isolates of our study, 87.2% isolates of *A. baumannii* were susceptible to ampicillin-sulbactam as compared to 29% isolates of our study, 70.1% isolates of *A. baumannii* were susceptible to piperacillin-tazobactam as compared to 9% isolates of our study, 91.8% isolates of *A. baumannii* were susceptible to cefoperazone-sulbactam as compared to 49% of our study (Higgins et al., 2004). A common finding in our study with that of Higgins et al. (2004) that cefoperazone-sulbactam was the most effective drug against Acinetobacter, although time difference between 2 studies is almost 10 years. One difference between the two studies is that in German study 100% isolates were of *A. baumannii,* while in our study 85% isolates were of *A. baumannii* (Higgins et al., 2004).

In a study from Germany in 2005, 469 isolates of *Acinetobacter* spp. were tested against 6 different β-lactam - β-lactamase inhibitors combinations. In that study, 33.9% isolates of *A. baumannii* were susceptible to co-amoxiclav as compared to 2% isolates of our study, 90.9% isolates of *A. baumannii* were susceptible to ampicillin-sulbactam as compared to 29% isolates of our study, 79.7% isolates of *A. baumannii* were susceptible to piperacillin-tazobactam as compared to 9% isolates of our study, 91.4% isolates of *A. baumannii* were susceptible to piperacillin-sulbactam as compared to 42% of our study. Piperacillin-sulbactam was most effective combination susceptible to 91.4% of isolates as compared to our cefoperazone-sulbactam susceptible to 49% of isolates (Brauers et al., 2005).

In 2013, a study was conducted in Malaysia on 141 isolates of *Acinetobacter spp*. They tested different combinations of β-lactam - β-lactamase combinations but not all combinations which are included in our study. 14.2% isolates of *Acinetobacter* spp. were susceptible to co-amoxiclav as compared to 2% isolates of our study, in both studies 29% isolates of *Acinetobacter* spp. were susceptible to ampicillin-sulbactam, 23% isolates of *Acinetobacter* spp. were susceptible to piperacillin-tazobactam as compared to 9% isolates of our study, 29.1% isolates of *Acinetobacter* spp. were susceptible to cefoperazone-sulbactam as compared to 49% of our study. Results of both studies are comparable and it may

be because of the same time period (Biglari et al., 2013).

Although resistance is emerging against β-lactam - β-lactamase combinations in *Acinetobacter* spp. but combinations containing sulbactam are still more effective as compared to other combinations and may represent an effective therapeutic option.

Conflict of interests

The authors have not declared any conflict of interest.

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