Molecular characterization and resistance profile of nosocomial Acinetobacter baumannii in intensive care unit of tertiary care hospital in Bangladesh

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Abstract

This study was designed to investigate the resistance profile along with the genetic background of resistance to beta-lactam antibiotics among the nosocomial A. baumannii in Bangladesh. A. baumannii was confirmed by detecting blaOXA-51-like. Antibiotic susceptibility was determined by disk diffusion method. Agar dilution method was used to determine MIC of ceftazidime and imipenem. All A. baumannii were phenotypically screened for ampC, ESBL and MBL production. Genetic markers of antibiotic resistance such as blaampC, blaOXA-23, 40, 58 and 143, blaKPC, blaIMP, blavim and blaNDM-1, genetic environment around blaADC and ISAb1 upstream of blaOXA5 were evaluated by PCR. Twenty-four (96%) A. baumannii were considered as MDR. 96% A. baumannii were resistant to amoxiclav, ceftazidime, ciprofloxacin and cefoxitin, 92% to cefotaxime and piperacillin-tazobactam, 88% to cefepime, amikacin and imipenem, 52% to sulbactam-cefoperazone and 40% were resistant to aztreonam. All were sensitive to colistin. The distribution of several beta-lactamase genes such as blaOXA-51 (100%), blaADC-like (92%), blaNDM-1 (92%), EBC group (84%), blaOXA-23 (76%), blavim (72%), blakpc (44%), DHA group (24%), blaOXA-58 (16%), ACC group (8%) and CIT group (4%) were observed among the 25 A. baumannii. This is the first reported plasmid mediated ampC beta-lactamases in A. baumannii. blaOXA-51 was positive in 100%, blasdm-1 in 95.45%, blaOXA-23 in 77.27%, blavim in 72.73%, blakpc in 50% and blaOXA-58 in 18.18% of imipenem resistant isolates. MDR profile of nosocomial A. baumannii would highlight the importance of standard guideline of antimicrobials use and infection control policy in the hospitals of Bangladesh.

Key words: Acinetobacter baumannii, Antimicrobial resistance, Bangladesh, metallo-beta-lactamase, ampC beta-lactamase, New-Delhi metallo-beta-lactamase-1

Introduction

Multidrug resistant (MDR) Acinetobacter baumannii has emerged as an important cause of nosocomial infections with increased morbidity and mortality, evidently frequent in intensive care unit (ICU). The unique environment of ICU, artificial ventilation and other invasive procedures, exposure to antibiotics, colonization pressure, and underlying illness facilitate the spread of this species in ICU.¹,² A. baumannii has capacity to exchange genetic material which facilitates to acquire antimicrobial resistance determinants among the species³. The existence of 45 resistance genes on “resistance island” in MDR Acinetobacter strain indicates their frequency to acquisition of antimicrobial resistant genes.⁴ Overexpression of blaADC by insertion sequence (IS) at the promoter region poses resistance to cephalosporins is inextricably linked to A. baumannii.⁵,⁶ The dissemination of OXA, VIM, IMP and NDM-1 in this species also poses resistance to the reserve
antibiotic, carbapenem. Among these enzymes, oxacillinases (OXA-23-like; OXA-24-like; OXA-51-like OXA-58and OXA-143) have emerged globally as the major mechanism of carbapenem resistance in A. baumannii, of which OXA-51 is intrinsic to A. baumannii. ISAb1 serves as one of the strong promoters to overexpress the blaOXA. Recently, New-Delhi metallo-beta-lactamase-1 (NDM-1) among the species has created an additional public health risk, leaving few therapeutic option.7-9

Misuse and overuse of antibiotics is extremely common in Bangladesh due to lack of implication of proper guideline regarding the use of antibiotics. Selective pressure of antibiotics in Bangladeshi hospitals allows the preservation of MDR determinants not only in nosocomial pathogens but also in hospital environment.10-11 Bangladesh is the prevalent zone of antimicrobial resistance, which has been evidenced by previous studies. Previous reports suggest A. baumannii as one of the important nosocomial pathogens in Bangladesh and the resistance determinants are incredibly frequent among the species.3,12-14 To explore the present situation of nosocomial antimicrobial resistance in Bangladesh, this study investigated the resistance profile of nosocomial A. baumannii in Bangladesh. Present study also evaluated the genetic background of resistance to beta-lactam antibiotics among the nosocomial A. baumannii in the country.

Materials and Methods

This study was conducted in the Department of Microbiology of Dhaka Medical College (DMC) between July, 2013 and June, 2014 after getting approval from research review committee (RRC) and ethical review committee (ERC) of DMC according to the Declaration of Helsinki and national and institutional standards. Written consent was taken from all the participants for this study. Patients hospitalized more than 48 hours in ICU were included in this study to evaluate the hospital acquired infections in ICU.15 We collected 40 endotracheal aspirates from patients admitted in ICU of Dhaka medical college hospital (DMCH) and 12 A. baumannii strains from Microbiology laboratory of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic disorders (BIRDEM), Dhaka where the Acinetobacter were recovered from tracheal aspirates of ICU patients.

Isolation and Identification of A. baumannii: The microbial growth of endotracheal aspirate was classified as rare, light, moderate or heavy, based on semi quantitative culture on MacConkey agar media16 and moderate to heavy growth were considered as significant.17 The species of Acinetobacter were first isolated on the basis of gram staining, colony morphology on culture media and several biochemical tests. A. baumannii was identified by observing pale colony in MacConkey agar media, gram negative coccobacilli or cocci form in gram stained smear, alkaline slant and butt without H2S or gas production in triple sugar iron agar media, nonmotile, negative indole, urease and oxidase, positive citrate and catalase.18 A. baumannii was confirmed at the species level by detecting blaOXA-51-like intrinsic carbapenemase gene and fermentation/oxidation test on Hugh Leifon medium.18-19

Antimicrobial susceptibility and phenotypic screening of drug resistance among A. baumannii: Antibiotic resistance to commonly used antibiotics was determined by disk diffusion method.20 Isolates were considered as MDR, if these were resistant to 3 or more classes of antibiotics among penicillins, cephalosporins, carbapenems, monobactam, aminoglycosides, quinolones, polymyxin. Minimum inhibitory concentration (MIC) of ceftazidime and imipenem was determined by agar dilution method.7

Modified three dimensional (MTD) test was used for phenotypic detection of ampC beta-lactamase producers among the A. baumannii which were resistant to both second generation cephalosporin (cefotixin) and third generation cephalosporin (ceftazidime or cefotaxime).21 All the Acinetobacter were tested for extended spectrum beta-lactamase (ESBL) producers by double disc synergy (DDS) test.22 Modification of DDS test was done using a piperacillin-tazobactum (100/10μg) disc 15mm away from cefepime (30μg) disc to investigate the ESBL and ampC co-producers.23 Imipenem resistant isolates were screened for MBL producers by DDS test and combined disc (CD) assay.7
Molecular detection of antimicrobial resistant determinants of A. baumannii: The strains were screened for blaADC-like using ADC1 and ADC2 primers. The existence of ISAba1 and ISAba125 upstream of blaADC-like or presence of any novel IS upstream or downstream of the gene was evaluated by PCR using the primers ISAADC1/ISAADC2, 125F/125R, FU/RU and FD/RD. The expected products size 360bp and 267 bp by FU/RU and FD/RD primer sets were suggested as absence of any novel IS upstream and downstream of the gene, accordingly. PCR followed by sequencing was designed in this study to observe the presence of any novel IS upstream or downstream of blaADC-like. A multiplex PCR was performed to screen the presence of six families of plasmid mediatedampC β-lactamases (MOX, CIT, DHA, ACC, EBC and FOX group). To investigate the mechanism of carbapenem resistance, blaKPC, blampr, blavim, blamDR1 and blaOXA-51, 23, 40, 58 and 143 were examined among all the isolates.

To screen the presence of ISAba1 at the upstream of blaOXA-51, 23, 40, 58 and 143, PCR was designed using forward primer of ISAba1 and reverse primers of blaOXA-51, 23, 40, 58 and 143 among the blaOXA-51, 23, 40, 58 and 143 positive strains.

Table I: Distribution of beta-lactamase genes among the 25 A. baumannii resistant to different antibiotic agents

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<th>D (%)</th>
<th>AMC (%)</th>
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<th>CX (%)</th>
<th>CEP (%)</th>
<th>CEX (%)</th>
<th>AK (%)</th>
<th>CIP (%)</th>
<th>IM (%)</th>
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<td>(34.78)</td>
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*Abbreviations: RG, resistant gene; D, distribution of blasconcó, blad and blasml in 25 A. baumannii; AMC, Amoxiclav; CZ, Cefazidime; CX, Cefotaxime; CEP, Cefepime; CEX, Cefoxitin; AK, Amikacin; CIP, Ciprofloxacin; IM, Imipenem; S-C, Sulfactam-cefopeoran; CL, Colistin; P-T, Piperacillin-Tazobactam; AZ, Aztreonam.*

**Results**

Among the 40 samples collected from ICU of DMCH, 38 organisms were recovered of which 13 (32.5%) were Acinetobacter, 6 (15%) were Pseudomonas aeruginosa, 6 (15%) were Klebsiella pneumoniae, 3 (7.5%) were Klebsiella oxytox, 3 (7.5%) were Staphylococcus aureus.

A total of 25 Acinetobacter was included in this study. All the 25 isolated Acinetobacter were identified as A. baumannii by detecting blaOXA-51-like and several biochemical tests.

Twenty-four (96%) A. baumannii were considered as MDR. Ninety-six percent A. baumannii were resistant to amoxiclav, cefazidime, ciprofloxacin and cefotixin, 92% to cefotaxime and piperacillin-tazobactam, 88% to cefepine, amikacin and imipenem, 52% to sulfactam-cefopeoran and 40% were resistant to aztreonam. Among the MDR isolates, 20 (83.33%) and 4 (16.67%) were resistant to seven classes of antibiotics and 6 classes of antibiotics, respectively. However, all were sensitive to colistin.

No A. baumannii was detected as ESBL producer both by DDS test and modified DDS test. MTDT and PCR identified 9 (37.5%) and 23 (95.83%) of the cefoxitin and cefazidime and/or cefotaxime resistant isolates as ampC producers.
respectively. Twenty-three (95.83%) of the 24 cephalosporin resistant A. baumannii had the chromosomal blaADC, of which 10 (43.48%) showed positive result for the presence of ISAb1 upstream of the gene, while all (100%) the blaADC harboring strains were positive for ISAba125 upstream of the gene. ISAba125 is also present in the isolates having no blaADC. The primer sets FU/RU and FD/RD amplified specific region of 360 bp and 267 bp, respectively in all the isolates having blaADC. These results indicated the dearth of any novel IS upstream and downstream of the gene in our isolates. Simultaneous production of plasmid mediated ampC beta-lactamases was observed in all blaADC positive strains. In this study the predominant acquired ampC was the EBC group (84%), followed by DHA (24%), ACC (8%) and CIT (4%) among the 25 A. baumannii (Table II). The MIC of ceftazidime among the ampC producers ranged from ≥256µg/ml to 128µg/ml. One of the 24 cephalosporin resistant A. baumannii had neither blaADC nor any plasmid mediated blaampC, having 128µg/ml MIC of ceftazidime. Twenty-two (91.67%) of the 24 cephalosporin resistant isolates were concurrently resistant to imipenem and all had the blaampC. However, one cephalosporin sensitive A. baumannii was positive for EBC group.

The distribution of beta-lactamase genes and their relationship with antibiotic resistance in this study are depicted in Table I. Present study did not found any MOX and FOX family of beta-lactamase, blaOXA-24, blaOXA-143 and blaiMP. The presence of several resistance genes in single isolate was observed in this study. The association of blinDM-1 with other resistance genes is shown in Table II. Regardless of imipenem susceptibility, one of the 25 isolates had combination of blavIM, blaOXA-23 and blinDM-1, one carried the combination of blavIM and blaOXA-23 and one had blinDM-1.

**Discussion**

In recent time, MDR A. baumannii has appeared to be one of vital causes of nosocomial outbreaks in ICU throughout the world.1, 2 The propensity of multidrug resistance was also observed formerly among A. baumannii in Bangladeshi hospitals.13-14 In the present study, 96% of the A. baumannii were identified as MDR recovered from ICU patients. In this study, all the MDR isolates are shown to be resistant to ≥6 classes of antibiotics except colistin. A broad array of beta-lactamases has been reported in these organisms as the most prevalent mechanism of resistance to beta-lactams.3,5,6 Carbapenem resistance in Acinetobacter is in increasing trend worldwide.3,9 Though the most prevalent mechanism of carbapenem resistance in A. baumannii is the production of oxacillinas, they are weak carbapenem hydrolyser in absence of promoters.8 In this study, both chromosomal blaxoxA-51 (100%) and acquired oxacillinas such as blaxoxA-23 (77.27%) and blaxoxA-58 (18.18%) were found in imipenem.
resistant A. baumannii. However, only the \textit{bla}OXA-51 was associated with IS\textit{Aba1} in 22.72% imipenem resistant isolates.

Molecular assessment in this study explicating the major mechanism of carbapenem resistance was the presence of \textit{bla}NDM-1 (95.45%) in imipenem resistant \textit{A. baumannii}. NDM-1 producing \textit{A. baumannii} has been reported since 2010 with a high prevalence in Indian subcontinent\textsuperscript{2,9}. Our data suggest the increase in prevalence (from 22.86% to 95.45%) of \textit{bla}NDM-1 among the imipenem resistant isolates in Bangladesh.\textsuperscript{7} Though \textit{bla}NDM-1 was initially reported on plasmid of Enterobacteriaceae, later report of \textit{bla}NDM-1 in \textit{A. baumannii} on conjugative plasmid of varying size (30-50 kb) implies the inter species dissemination of this resistance determinant. The high level of inter lineage and inter species transfer of this gene are thought to be likelihood of global spread of this gene. The association of high number of resistance genes such as \textit{bla}OXA-48, \textit{blavim}, \textit{blakPC}, \textit{blaxa}-51, \textit{blaxa}-23, \textit{blaxa}-58, \textit{bladha} and \textit{bla}ADC and plasmid mediated ampC in NDM-1 positive strains (Table II) and their antimicrobial resistance profile (Table I) in this study confirms the association of \textit{bla}NDM-1 with several resistance genes, which coincides with previous observations. The level of resistance to carbapenem may vary ranging from 0.5 mg/l to >64 mg/l in spite of presence of carbapenemase including NDM-1.\textsuperscript{29} Present report is not an exception, which was revealed by presence of combination of \textit{blavim}, \textit{blaxa}-23 and \textit{blaxa}-23 in one and the combination of \textit{blavim} and \textit{blaxa}-23 in one and \textit{blaxa}-23 in one imipenem sensitive \textit{A. baumannii}. The insertional element \textit{IS\textit{Aba1}25} is widely distributed in \textit{A. baumannii} and poses carbapenem resistance by insertional inactivation of CarO outer membrane protein.\textsuperscript{30} In addition, the location of \textit{blaxa}-23 between two direct repeats of the \textit{IS\textit{Aba1}25} element is dependable for possible expression and dissemination of this gene.\textsuperscript{7} The concomitant presence of \textit{blaxa}-25 and \textit{IS\textit{Aba1}25} was also shown in this study (Table II). Hence the presence of \textit{IS\textit{Aba1}25} in all carbapenem resistant \textit{A. baumannii} in our study explains one of the possible mechanisms of reduced susceptibility to carbapenem.

The existence of \textit{blambls} poses resistance to carbapenem in addition to cephalosporin.\textsuperscript{3} However, we screened production of ampC beta-lactamases and ESBL among our strains as coexisting cause of cephalosporin resistance. Our study found high level of ceftazidime resistance among all the cephalosporin resistant isolates (MIC ranged from ≥256µg/ml to 128µg/ml). In this study, 95.83% of the cephalosporin resistant organisms had both ADC and at least one plasmid mediated ampC enzymes. Though plasmid mediated ampC beta-lactamases previously reported among the members of Enterobacteriaceae,\textsuperscript{31-34} this is the first report of plasmid mediated ampC enzymes in \textit{A. baumannii}. Most strains producing plasmid mediated ampC have been isolated from patients having history of prolong stay in ICU, invasive surgical procedures and underlying illness such as leukaemia or cancer.\textsuperscript{35} The presence of these enzymes in \textit{A. baumannii} indicates the dissemination of these genes in the hospital settings of Bangladesh and suggests a potential risk for hospital outbreaks in the country. The enzyme of EBC family was reported previously in Asia in \textit{K. pneumoniae}.\textsuperscript{32} This study detected a dominance of EBC group in \textit{A. baumannii} followed by DHA, ACC and CIT in Bangladesh, while the prevalent enzymes in the members of Enterobacteriaceae are the DHA and CMY groups.\textsuperscript{33-34} We also determined the overexpression of \textit{bladha} by screening \textit{IS\textit{Aba1}1} in 43.48% and \textit{IS\textit{Aba1}25} in 100% of ADC producing organisms which are the major machinery of cephalosporin resistance in \textit{A. baumannii}, as reported previously.\textsuperscript{3,6} \textit{IS\textit{Aba1}25} has greater ability to overproduce ADC than \textit{IS\textit{Aba1}1} suggest the possible overproduction of ADC due to \textit{IS\textit{Aba1}25} among our strains.\textsuperscript{24} As no ESBL producer was detected by phenotypic method, the genes for \textit{blambls} were not studied.

Antimicrobial resistance is thought to be a leading issue for the dissemination of nosocomial infections. Due to lack of proper policy, this issue has become more threatening in developing countries day by day.\textsuperscript{36} The worrying scenario was also observed in Bangladesh, which was reflected by our present data including our previous studies.\textsuperscript{7,12} The isolates showed resistance to most of the antimicrobials. The
most effective antimicrobial agent was colistin in our studied A. baumannii, irrespective of types of existing beta-lactamase genes. Aztreonam (60%) followed by sulbactam-cefoperazone (48%) sensitivity was observed to some extents in this study (Table II). This resistance profile of nosocomial Acinetobacter is very alarming, as there are a few reserve antimicrobials to manage the hospitalized patients in Bangladesh. MDR A. baumannii serves as reservoir of nosocomial infections due to its remarkable capability to achieve resistance determinants. Therefore, the multidrug resistance profile in our study demands urgent systemic surveillance of antimicrobial resistance in Bangladesh to know the exact epidemiology of resistant determinant in the country in order to develop standard infection control strategies in Bangladeshi hospitals.

Conclusion: Though antimicrobial resistance is now one of the important emerging public health problems in Bangladesh, there is no standard policy regarding use of antibiotics in health care settings in the country. We detected 96% A. baumannii as MDR. The distribution of antimicrobial resistance genes such as bla_\text{ampC} (both chromosomal and plasmid mediated) and carbapenemase genes (\text{bla}_{MBLs} and \text{bla}_{KPC}) were observed among 95.83% cephalosporin resistant A. baumannii and all (100%) imipenem resistant isolates, respectively. This is the first reported acquired ampC beta-lactamases in this organism. Results of this study indicate the occurrence of spreading resistant determinants in Bangladeshi hospitals. It is expected that these results will help to direct a standard guideline of rational antimicrobials use and infection control strategy in Bangladesh.

References


