International Journal of Research in Medical Sciences
Afroz J et al. Int J Res Med Sci. 2020 Mar;8(3):1094-1102
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20200787

Original Research Article

Multidrug resistant clinical strains isolated from tracheal aspirates of patients in Dhaka, Bangladesh

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Received: 11 January 2020
Revised: 31 January 2020
Accepted: 05 February 2020

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ABSTRACT

Background: Antimicrobial resistance poses a major threat in the treatment of respiratory disease especially in developing countries like Bangladesh. Multidrug-resistant (MDR) bacteria along with extremely drug resistant (XDR) bacteria have emerged as major clinical and therapeutic dilemma in the treatment of tracheal infections here. Thus, the aim of this study is to assess multidrug resistance among clinical strains isolated from tracheal aspirates of patients in Dhaka, Bangladesh.
Methods: Total 200 clinical isolates from tracheal aspirates were identified and their antibiotic susceptibility profiles were evaluated by using the VITEK 2 system following the Clinical and Laboratory Standards Institute guidelines. Patient information on diagnosis, sex, age was obtained from hospital data.
Results: Of 200 clinical isolates obtained, *Pseudomonas aeruginosa* was the most frequent pathogens (30.5%) followed by *Acinetobacter baumannii* (29%), *Klebsiella pneumoniae* (22.5%), *Streptococcus pneumoniae* (7.5%), *Escherichia coli* (5%), *Staphylococcus aureus* (2%), *Proteus spp* (1.5%), *Enterobacter spp* (1%), *Citrobacter spp* (0.5%), *Providencia spp* (0.5%). Of 20 different antibiotics tested, highest number of isolates (86%) showed resistance to third generation cephalosporin cefixime, however least number of isolates showed resistance to polymixin antibiotics- colistin (12.5%) and polymixin B (6%). Tracheal infection was found to be more prevalent in males rather than in females although this difference was not statistically significant. The prevalence of infections was highest among the patients of age-group (old adults) ≥60 years (61.5%). Of 200 clinical isolates, 43 (21.5%) were XDR and 125 (62.5%) were MDR bacteria. Of 200 clinical isolates, the synthesis of extended spectrum β-lactamases (ESBL) and carbepenemase were detected in 59 (29.5%) and 98 (49%) strains respectively.
Conclusions: Tracheal infections caused by β-lactamase producing MDR and XDR pathogens among patients are high in Dhaka, Bangladesh. Therefore, there is an urgent need for constant surveillance and interventions in Bangladesh in order to prevent further spreading of those resistant organisms.

Keywords: Tracheal infection, MDR, XDR, β-lactamases

INTRODUCTION

Lower respiratory infections are one of the leading causes of global morbidity and mortality from infectious diseases worldwide.[1] Community acquired pneumonia

(CAP), nosocomial pneumonia and acute and chronic bronchial infections in patients with chronic obstructive pulmonary disease (COPD) and bronchiectasis are known as the most common respiratory diseases those are responsible for elevated morbidity and mortality rate.[2] Lower respiratory tract infections like tracheal infections are caused by both of Gram-positive and Gram-negative bacteria. The emergence of multidrug-resistant (MDR) bacteria poses a major threat in hospital settings.[3] The most frequent multidrug-resistant bacteria associated with tracheal infections are *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Acinetobacter baumannii,* and other Enterobacteriaceae.[4]

Antibiotic resistance is an increasingly serious threat to global public health that threatens our ability to treat common infectious diseases, resulting in prolonged illness, disability and death.[5] In recent years, several studies have reported an increased number of bacteria causing both hospital-acquired and community-acquired infections.[3,6] Enterobacteriaceae including *K. pneumoniae, E. coli* as well as *Enterobacter spp.* along with other bacteria such as *P. aeruginosa* and *A. baumannii* have been identified as major cause of multi-drug resistant (MDR) and extremely drug resistant (XDR) bacterial infections in respiratory tract.[6-9]

However, Gram-positive organisms such as *Staphylococcus aureus* which is a common causative agent of severe infections in health facilities and in the community become resistant to first-line drugs.[5] Patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA) are estimated to be 64% more likely to die than people with a non-resistant form of the infection whereas MRSA are also reported to cause tracheal infections.[5,10] For the treatment of life-threatening infections caused by Enterobacteriaceae which are resistant to carbapenems, colistin is used as the last resort of treatment.[11]

However, resistance to colistin has been detected recently in several countries, making infections untreatable those are caused by such bacteria.[5, 11]

Resistance to broad spectrum β-lactams mediated by extended spectrum β-lactamases (ESBL) is a global threat.[12] The emergence of ESBL along with carbapenemases is caused by using β-lactam antibiotics extensively over the last several decades in the clinical practice.[13] New variants of β-lactamases have emerged due to the selective pressure imposed by the use and overuse of new antibiotics in the treatment of patients.[14]

Most ESBL producing organisms are also resistant to aminogylcosides, fluoroquinolones, tetracyclines, chloramphenicol and sulfonamides as they have large plasmids where ESBL genes along with other antimicrobial resistant genes are present.[13]

This study aimed to assess multidrug-resistance among bacteria those are responsible to cause lower respiratory tract infections in Dhaka, Bangladesh to guide treatment protocols along with to determine the existence of ESBL, carbapenemase production in multi-drug and extensively-drug resistant bacterial strains isolated from tracheal aspirates. The data further provides a baseline for future comparative studies.

METHODS

The study was conducted between January 2018 and June 2019, in Dhaka Central International Medical College and Hospital in Dhaka, Bangladesh. Of 850 patients attended, 200 patients were suffering from productive coughing, pain below the sternum, short and rapid breathing or chest pain along with fever and headache. Tracheal aspirates specimens (N=200) were aseptically collected from the patients (N=200; Male=133, Female=67) belonging to all age group and both sexes diagnosed with productive coughing, pain below the sternum, short and rapid breathing or chest pain along with fever and headache. Patients who were confirmed to be cases of having asthma and sinusitis were excluded from the study. Tracheal aspirates specimens were subsequently transported to microbiology laboratory of Primasia University for bacterial isolation and identification, phenotypic determination of antibiotic susceptibility, identification of multidrug resistant (MDR), extremely drug resistant (XDR), pan-drug resistant (PDR) organisms along with detection of ESBL and carbapenemase production. Information on diagnosis, sex, age was obtained from patients' records.

Bacterial strains

Of 200 tracheal aspirates, 149 samples showed bacterial growth whereas 51 were sterile. Of 149 samples, total of 200 clinical, non-duplicate bacteria were isolated those were maintained on nutrient agar slants, frozen in lyophilizing medium at -70°C. The identification of bacterial isolates and the evaluation of their antibiotic susceptibility profiles were performed using the VITEK 2 system (bioMérieux, Inc., Hazelwood, MO, United States) following the Clinical and Laboratory Standards Institute guidelines.[15]

Antimicrobial drug susceptibility testing was conducted by Kirby-Bauer method in accordance with the Clinical and Laboratory Standards Institute against penicillins with β-lactamase inhibitors[amoxicillin-clavulanic acid (10 µg), piperacillin-tazobactam (100/10 µg)], cephalosporin [cefuroxime (10 µg), cefixime (5 µg), cefotaxime (30 µg), ceftazidime(30 µg), ceftriaxone (30 µg), cefepime (30 µg)], monobactam [aztreonam(30 µg)], carbapenems [imipenem (10 µg), meropenem(10 µg)], aminoglycosides [gentamicin (10 µg), amikacin(30 µg), netilmicin(10 µg)], fluoroquinolones [ciprofloxacin (5 µg), levofloxacin (5 µg)], folate pathway inhibitor [co trimoxazole (25 µg)], polymyxin [colistin (10 µg), polymyxin B (300U)], glycylcyclines [tigecyclin, (15 µg)]. Methicillin (5 µg) is used only against *S. aureus.*

Susceptibility to tigecyclin was interpreted using breakpoints proposed by the European Committee on Antimicrobial Susceptibilities Testing (EUCAST).[15,16] The combination disk test using cefotaxime and ceftazidime, alone and in combination with clavulanic acid was performed in accordance with Clinical and Laboratory Standards Institute guidelines for detection of ESBL (1). Determination of the production of carbapenemase was carried out by modified Hodge test and imipenem-EDTA disk synergy test as described.[15,17] MDR, XDR and PDR isolates were identified according to the guidelines recommended by joint initiative of the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC).[18]

Statistical analysis

Data were compiled, tabulated and analyzed in accordance with the objectives of the research. Microsoft Excel spread sheets was used for analyzing the experimental data. Descriptive statistics were reported as frequency along with percentage. The antimicrobial susceptibility of test bacteria was evaluated by a 2-type categorical rating scale as susceptible (antibiotic indicated as fully effective), and resistant (indicated as non-effective). For the testing association between categorical data, Pearson's chi-square test was used. A two tailed p-value p <0.05 was considered statistically significant.

RESULTS

Of 200 clinical, non-duplicate bacterial isolates obtained, *P. aeruginosa* was the most frequent pathogens (N=61/200, 30.5%) followed by *A. baumannii* (N=58/200, 29%), *K. pneumoniae* (N=45/200, 22.5%), *S. pneumoniae* (N=15/200, 7.5%), *E. coli* (N=10/200, 5%), *S. aureus* (N=4/200, 2%), *Proteus spp.* (N=3/200, 1.5%), *Enterobacter spp.* (N=2/100, 1%), *Citrobacter spp.* (1/200, 0.5%), *Providencia spp.* (N=1/200, 0.5%) (Table 1 and Figure 1).

Table 1: Bacterial isolates from tracheal aspirates specimen.

Bacterial isolates	Total number of isolates(N)	Number of isolated organisms N (%)
Pseudomnas aeruginosa	200	61 (30.5)
Acinetobacter baumannii		58 (29)
K. pneumoniae		45 (22.5)
Streptococcus spp.		15 (7.5)
E. coli		10 (5)
Staphylococcus spp.		4 (2)
Proteus spp.		3 (1.5)
Enterobacter spp.		2 (1)
Citrobacter spp.		1 (0.5)
Providencia spp.		1(0.5)

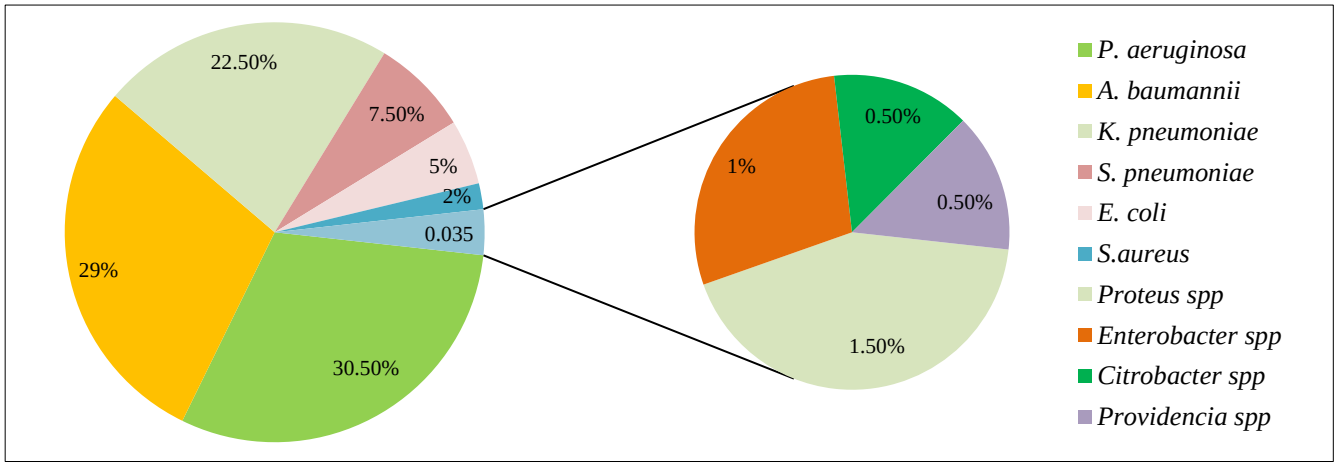

Figure 1: All species causing tracheal infections were showed in the pie chart. The left pie showed six major abundant species, the right pie showed other genera which were not classified to species.

Of 20 different antibiotics tested, highest number of isolates (N=172/200, 86%) showed resistance to third generation cephalosporin cefixime, however least number of isolates showed resistance to polymixin antibiotics-colistin (N=25/200, 12.5%) and polymixin B (N=12/200, 6%) (Table 2).

Demographic characteristics of patients with bacterial infections

The patients' ages ranged between 1 month to 95 years with the gender distribution of 133 (66.5%) males and 67 (33.5%) females. The prevalence of infections was

highest among the patients of age-group (old adults) ≥60 years (N=123/200, 61.5%) followed by middle aged adults (50-59 years) 12% (N=24/200), young adults (30-39 years) 6% (N=12/200), baby (0-2 years) 5.5% (N=11/200), in 3-12 years 5% (N=10/200), in 20-29 years 3.5% (N=7/200). The least prevalence rate (N=2/200, 1%) was found in young adults of age group 13-19 years (Table 3). Tracheal infection was found to be more prevalent in males rather than in females although this difference was not statistically significant (p-value p <0.40). The highest prevalence of infections caused by *A. baumannii* was in males (N=42/58, 72.4%) than in females (N=16/58, 27.58%). The prevalence of both *P. aeruginosa* and *K. pneumoniae* were higher in males (N=38/61, 62.3%; N=30/45, 66.67%) than in females (N=23/61, 37.7%; N=15/45, 33.33%) (Table 4).

XDR and MDR strains

Of 200 bacterial isolates obtained from tracheal aspirates, 68% (N=136/200) isolates were MDR whereas 22% (N=43/200) were XDR (Figure 2). Of 61 *P. aeruginosa* strains tested, 14 (23%) were XDR and 43 (70.4%) were MDR organisms whereas of 58 strains of *A. baumannii*, 33 (57%) were MDR and 17 (29%) were XDR. Of 45 *K. pneumoniae*, 32 (71.1%) were MDR and 9 (20%) were XDR (Table 5). For *S. pneumoniae*, all strains (N=12/15, 80%) were MDR among which 1 strain (7%) was XDR though 1 strain was found to be sensitive to all drugs. Of 10 strains *E. coli*, 5 strains (50%) were MDR and 2 were XDR (20%). For *S. aureus*, *Proteus spp.*, *Enterobacter spp.*, *Citrobacter spp.* and *Providencia spp.*, all strains were found to be MDR (Table 5).

Table 2: Resistance rate of isolates to different antibiotics.

Antibiotics	Total number of isolates (N)	Susceptible N (%)	Intermediate N (%)	Resistant N (%)
Penicillins	200			
Penicillin with β-lactamase Inhibitors				
Amox/Clav		38 (19)	3 (1.5)	159 (79.5)
Piperacillin/Tazobactam		102 (51)	12 (6)	86 (43)
Cephalosporins				
Second Generation				
Cefuroxime		32 (32)	6 (3)	162 (81)
Third Generation				
Cefixime		28 (14)	0 (0.0)	172 (86)
Cefotaxime		36 (18)	5 (2.5)	159 (79.5)
Ceftazidime		73 (36.5)	10 (5)	117 (58.5)
Ceftriaxone		40(20)	7 (3.5)	153 (76.5)
Fourth Generation				
Cefepime		83 (41.5)	8 (4)	109 (54.5)
Aminoglycosides				
Amikacin		80 (40)	5 (2.5)	115 (57.5)
Gentamicin		91 (45.5)	0	109 (54.5)
Netilmicin		92 (46)	1 (0.5)	101 (50.5)
Carbapenems				
Imipenem		85 (42.5)	3 (1.5)	112 (56)
Meropenem		92 (46)	1 (0.5)	107 (53.5)
Monobactams				
Aztreonam		49 (24.5)	11 (5.5)	140 (70)
Fluoroquinolones				
Ciprofloxacin		68 (34)	12 (6)	120 (60)
Levofloxacin		80 (40)	5 (2.5)	115 (57.5)
Folate Pathway Inhibitors				
Co-trimoxazole		77 (38.5)	4 (2)	119 (59.5)
Polymixins				
Colistin		173 (86.5)	2 (1)	25 (12.5)
Polymixin B		188 (94)	0 (0.0)	12 (6)
Glycylcyclines				
Tigecyclin		136 (68)	24 (12)	40 (20)

Table 3: Distribution of different isolates among different age group of patients.

			No. of Isolated organisms N (%)									
Age group	Age Inter-vals	No. of patients (N=200) (%)	*A. bau-mannii* (N=58)	*E. coli* (N=10)	*K. pneu-moniae* (N=45)	*P. aeru-ginosa* (N=61)	*S. pneu-moniae* (N=15)	*S. aureus* (N=4)	*Citrobacter spp.* (N=1)	*Enterobacter spp.* (N=2)	*Proteus spp.* (N=3)	*Providencia spp.* (N=1)
Baby	0-2	11 (5.5)	1(1.7)	2 (20)	2 (4.5)	5 (8.2)	1 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Young Adults	3-12	10 (5)	10 (17.3)	2 (20)	3 (6.7)	8 (13.1)	4 (26.7)	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)
	13-19	2 (1)										
	20-29	7 (3.5)										
	30-39	12 (6)										
Mid Aged Adults	40-49	11 (5.5)	9 (15.5)	1 (10)	6 (13.3)	11 (18)	5 (33.3)	1 (25)	0 (0)	1 (50)	0 (0)	1 (100)
	50-59	24 (12)										
Old Adults	60-69	44 (22)	38 (65.5)	5 (50)	34 (75.5)	37 (60.7)	5 (33.3)	2 (50)	1 (100)	1 (50)	3 (100)	0 (0)
	70-79	42 (21)										
	80-89	25 (12.5)										
	90-99	12 (6)										
	100-Above	0 (0)										

Table 4: Distribution of isolates according to the patients' gender.

		Gender	
Bacterial isolates (N)	**Number of isolated organisms N**	**Male**	**Female**
Pseudomonas aeruginosa	61	38 (62)	23 (38)
Acinetobacter baumannii	58	42 (72)	16 (28)
K. pneumoniae	45	30 (67)	15 (33)
Streptococcus spp.	15	7 (47)	8 (53)
E. coli	10	9 (90)	1 (10)
Staphylococcus spp.	4	3 (75)	1 (25)
Proteus spp.	3	1 (33)	2 (67)
Enterobacter spp.	2	1 (50)	1 (50)
Citrobacter spp.	1	1 (100)	0 (0)
Providencia spp.	1	1 (100)	0 (0)
Frequency	200	133 (66.5)	67 (33.5)

Table 5: Prevalence of MDR and XDR isolates causing tracheal infections.

Bacterial Isolates (N)	Number of isolated organisms N	No. of MDR organisms N (%)	No. of XDR organisms N (%)
Pseudomonas aeruginosa	61	43 (70.49)	14 (23)
Acinetobacter baumannii	58	33 (56.89)	17 (29)
K. pneumoniae	45	32 (71.1)	9 (20)
Streptococcus spp.	15	12 (80)	1 (7)
E. coli	10	5 (50)	2 (20)
Staphylococcus spp.	4	4 (100)	0 (0)
Proteus spp	3	3 (100)	0 (0)
Enterobacter spp.	2	2 (100)	0 (0)
Citrobacter spp.	1	1 (100)	0 (0)
Providencia spp.	1	1 (100)	0 (0)
Frequency	200	136 (68)	43 (22)

Extended spectrum β-Lactamase (ESBL) and carbapenemase producing strains

Of 200 clinical isolates, the synthesis of ESBL and carbepenemase were detected in 59 (29.5%) and 98 (49%) strains respectively. Of 58 strains of *A. baumannii*, 28 (48%) and 18 (31%) strains produced carbapenemase and ESBL respectively (Table 6). Of 45 strains of *K. pneumonia*, carbepenemase and ESBL were detected in 22 (49%) and 16 (36%) strains respectively. Of 10 *E. coli* strains, 5 (50%) and 3 (30%) strains produced carbapenemase and ESBL respectively. Carbapenemase production was found in *S. pneumoniae* (N=4/15, 27%), *Proteus spp.* (N=2/3, 67%), *Citrobacter spp.* (N=1/1, 100%) and in *Providencia spp.* (N=1/1, 100%) though no ESBL production was found (Table 6). Most of the

antibiotics tested were non-effective against ESBL and carbapenemase producer whereas polymixin B, colistin, tigecyclin were found to be effective regimens against ESBL and carbepemase producers.

Table 6: Distribution of ESBL and carbapenemase production in different isolates.

		Types of β-lactamase production	
Bacterial isolates (N)	**Number of isolated organisms N**	**Carbapenemase**	**ESBL**
Pseudomonas aeruginosa	61	35 (57)	22 (36)
Acinetobacter baumannii	58	28 (48)	18 (31)
K. pneumoniae	45	22 (49)	16 (36)
Streptococcus spp.	15	4 (27)	0 (0)
E. coli	10	5 (50)	3 (30)
Staphylococcus spp.	4	0 (0)	0 (0)
Proteus spp.	3	2 (67)	0 (0)
Enterobacter spp.	2	0 (0)	0 (0)
Citrobacter spp.	1	1 (100)	0 (0)
Providencia spp.	1	1 (100)	1 (100)
Frequency	200	98 (49)	59 (29.5)

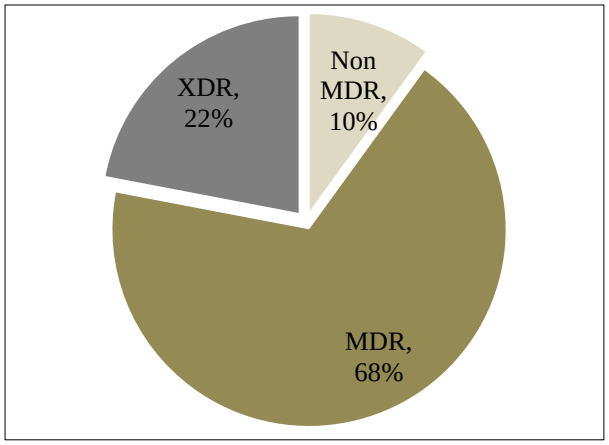

Figure 2: Prevalence of MDR and XDR isolates causing tracheal infections was showed in the pie chart. MDR bacterial isolates comprised the major portion of total number of bacterial isolates.

DISCUSSION

Antimicrobial resistance (AMR) is a major problem to global public health that requires action across all government sectors and society.[5] Infections caused by resistant bacteria responsible for longer duration of illness, additional tests and use of more expensive drugs rather than those infections which are caused by nonresistant bacterial species.[5] Epidemiological surveillance of resistance to antibiotics is essential in developing countries like Bangladesh where infections caused by multi-drug resistant bacteria which have resulted in increased morbidity and mortality.[19-20] Antibiotic resistance is an increasingly serious threat in Bangladesh which is most likely a result of unrestricted use of antimicrobial drugs.[21]

Study observed the prevalence of tracheal infections was highest among the patients of old adults whose age was ≥60 years; however least susceptibility to these infections was noticed in young adults of age group 13-19 years. The annual incidence of pneumonia in the elderly people is four-times higher than that of younger populations reported elsewhere.[22] Tracheal infection was found to be more prevalent in males rather than in females.

Tracheal infection in patients was caused mainly by *P. aeruginosa* (30.5%) followed by *A. baumannii* (29%). Since *P. aeruginosa* is an opportunist, it can colonize the respiratory tracts after endotracheal intubation or in critically ill and immunocompromised patients, especially in cystic fibrosis patients where it can be aspirated into the lungs.[23-25] Tracheal intubation and use of carbapenems are considered as risk factors for patients with *P. aeruginosa* infection.[23] A report published in 2016 showed that 33.9% of *P. aeruginosa* were resistant to at least one of the antimicrobial groups under surveillance in Europe.[26] Study found 23% strains of *P. aeruginosa* were XDR and 70.4% were MDR organisms.

A. baumannii is an important nosocomial pathogen in healthcare facilities and has become one of the most significant microorganisms causing infections in hospitalized patients in last few decades.[27] A study conducted at the Dhaka Medical College Hospital (DMCH) showed 96% strains of *A. baumannii* isolated from endotracheal aspirates collected from patients, were multidrug resistant.[28] Another study carried in Square Hospitals Ltd. showed 90 % of the *A. baumannii* strains isolated from the patients with lower respiratory tract infections, were multidrug resistant.[29] In this study, 57% *A. baumannii* were MDR and 29% were XDR indicating an alarming situation.

The highest incidence rate of respiratory tract infection was caused by *A. baumannii* (25%) followed by *Pseudomonas spp.* (15%) and *Klebsiella spp.* (10%).[30] Our findings correlate with these reports though *P. aeruginosa* was to be found as a predominate organisms causing respiratory tract infections. It was observed that among 45 strains of *K. pneumoniae*, 71% were MDR and 20% were XDR. *K. pneumoniae* was the most common causative agent of nosocomial pneumonia where the presence of MDR *K. pneumoniae* strains was prevalent.[31] However, other studies showed the most prevalent organism causing tracheal infections was *Enterobacter spp.* followed by *P. aeruginosa*.[32] Though only 1% strains causing tracheal infection were *Enterobacter spp.* in our study, those were multidrug resistant. Moreover, it was observed methicillin resistant *S. aureus* (MRSA) was found to be responsible for tracheal infections**.** A report stated elsewhere that MRSA is a cause of lung infection including airway infection, community-acquired pneumonia and hospital-acquired pneumonia.[33]

Among the Gram-negative bacteria causing chronic respiratory disease, *E. coli* is considered one of the major respiratory threats.[34] Our study showed 20% *E. coli* strains were XDR and 50% were MDR. *S. pneumoniae* is an important causative agent of chronic respiratory disease including tracheal infections that result in higher rate of morbidity and mortality due to MDR *S. pneumoniae*.[35] It was observed 80% strains of *S. pneumoniae* causing tracheal infection were MDR.

The present study observed highest number of strains of both Gram-positive and Gram-negative bacteria showed resistance to third generation cephalosporins, however the most effective antibiotics were polymixin antibiotics especially colistin and polymixin B along with tigecyclin. These findings correlate with other reports where colistin was reported as an effective drug in the treatment of infections caused by MDR bacteria.[36-37]

In the recent years, antimicrobial resistance mediated by ESBL- and carbapenemase has been found to be ubiquitous and the current dissemination of these enzymes makes it mandatory to understand this phenomenon especially because of the higher mortality, morbidity, and increased health treatment costs associated with resistance to β-lactams.[38,39] The increasing rate of dissemination of carbapenemase in Bangladesh has been documented with the isolation of clinical *A. baumannii*, *P. aeruginosa* and *K. pneumoniae*.[40]

The present study showed the synthesis of ESBL and carbepenemase were detected in 29.5% and 49% strains respectively where it was noticed most of the antibiotics tested were non-effective against ESBL and carbapenemase producer, however, polymixin B, colistin, tigecyclin were found as effective antibiotics against ESBL and carbepemase producers.

CONCLUSION

The study demonstrated high prevalence of β-lactamase producing multidrug resistant bacteria implicated in the tracheal infections diagnosed among patients. Infections were common among the elderly people and predominantly caused by *P. aeruginosa* followed by *A. baumannii, K. pneumonia, Streptococcus spp* during the period of our study. Appropriate and justified use of antimicrobial agents should be ensured in controlling the growing danger of antimicrobial drug resistance. Therefore, there is an urgent need for constant surveillance and interventions in Bangladesh in order to prevent further spreading of those resistant organisms. Further studies at molecular level will be required to determine the mechanism(s) of resistance by genotypic methods.

ACKNOWLEDGEMENTS

Authors would like to thank all the patients of Dhaka Central International Medical College and Hospital from whom the clinical strains were isolated. Authors would like to thank Bangladesh Council of Scientific and Industrial Research (BCSIR) for the generous support.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee from Bangladesh Council of Scientific and Industrial Research (BCSIR), Rajshahi

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Cite this article as: Afroz J, Jubyda FT, Sharmin S, Faruq J, Dey AK, Ibrahim M, et al. Multidrug resistant clinical strains isolated from tracheal aspirates of patients in Dhaka, Bangladesh. Int J Res Med Sci 2020;8:1094-102.