

# The burden of antimicrobial resistance among cystic fibrosis patients: an emerging public health concern in tertiary care hospital

## Abstract

**Background:** Although Cystic fibrosis (CF), though rare in Bangladesh but it poses significant morbidity due to recurrent respiratory infections and progressive lung damage to the patients. Understanding the microbiological colonization patterns and antimicrobial resistance in Bangladeshi children with CF is important for optimizing the clinical management.

**Methods:** This cross-sectional study was conducted in a period of 12-months at a tertiary pediatric hospital in Bangladesh. Sputum or oropharyngeal swab samples were collected from clinically stable CF patients for microbiological culture and sensitivity testing. Isolates were identified using standard biochemical methods, and antibiotic susceptibility was assessed via the Kirby-Bauer disc diffusion method according to CLSI guidelines.

**Results:** A total of 65 CF patients were included, with a mean age  $76.63 \pm 41.08$  months. The most frequently isolated organisms were *Pseudomonas aeruginosa* (35.4%), *Staphylococcus aureus* (15.4%), and *Klebsiella pneumoniae* (23.1%). Multidrug-resistant (MDR) strains were observed in 10.4% isolates. Notably, sensitivity to ceftazidime, meropenem, and colistin remained relatively preserved in *P. aeruginosa*, while *S. aureus* showed high resistance to penicillin but retained sensitivity to vancomycin and linezolid.

**Conclusion:** In this study, children with cystic fibrosis in Bangladesh demonstrate a concerning prevalence of MDR respiratory pathogens, particularly *P. aeruginosa* and *S. aureus*. Periodic surveillance of microbial colonization and antimicrobial resistance patterns is essential to guide effective empirical therapy and limit resistance development.

**Keywords:** Cystic fibrosis, microbial colonization, antibiotic resistance, *Pseudomonas aeruginosa*, *Staphylococcus aureus*

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## Background

Cystic fibrosis (CF) is an inherited disease characterized by the accretion of thick, sticky mucus that can damage many of the body's organs. The disorder's most common features include progressive damage to the respiratory system and chronic digestive system problems. Cystic fibrosis (CF) is a life-limiting autosomal recessive disorder resulting from a genetic mutation targeting the cystic fibrosis trans-membrane conductance regulator (CFTR) gene.<sup>1</sup> The defect in the regulation of ion transport homeostasis in epithelial cells leads to a malfunction of many organs including the pancreas, the liver, the intestine, and mostly the lungs.<sup>2-5</sup>

CF has been reported in significant numbers in African Americans, and natives of Middle East countries, India and Pakistan. In the United States (US), approximately 30,000 individuals have CF; most are diagnosed by six months of age.<sup>6</sup> The incidence/prevalence of CF in the UK is 1 in 2500 live births and in India around 1 in 30000-40000 live birth.<sup>7</sup> Approximately 1 in 25 people of European descent, and 1 in 30 of Caucasian American, are a carrier of CF mutation. Although CF is less common in these groups, approximately 1 in 46 Hispanics, 1 in 65 Africans and 1 in 90 Asian carries at least one abnormal cystic fibrosis trans-membrane conductance regulator (CFTR) gene.<sup>6</sup>

In Asian populations, the existence of CF is now better established, but the incidence remains underestimated in most countries. The incidence of CF is 1/100,000 in the Indian population. The frequency of common mutation F508del in Indian children is between 19% and 34%.<sup>7</sup>

The burden of CF in Bangladesh is not well studied. A study conducted in Bangladesh has reported 9.06% of patients with respiratory problems have positive sweat chloride test.<sup>4</sup> Traditionally, *Pseudomonas aeruginosa* has been regarded as the main pathogen in CF and chronic infections have been linked to disease morbidity and mortality.<sup>8</sup> However, with intensified antibiotic therapy and prolonged patient survival, new 'emerging' pathogens, particularly fungi and rare bacteria, are increasingly found in adolescent and adult CF patients,<sup>9,10</sup> but their clinical impact on lung function remains poorly defined. Particularly, methicillin-resistant *Staphylococcus aureus* (MRSA),<sup>11-14</sup> non-tuberculous mycobacteria (NTM), *Stenotrophomonas maltophilia* and fungi are gaining increasing attention in CF lung disease.<sup>1</sup> Clinically, both MRSA infections and *Mycobacterium abscessus* complex were found to be associated with a worse course of CF lung disease.<sup>15</sup> Yet, the relative contribution of other emerging pathogens, such as *S. maltophilia*, *Aspergillus*, *Candida* and *Scedosporium*

species remains less precisely defined.<sup>9,15</sup> Overall, it remains poorly understood, whether colonization with these species merely reflects an advanced (more 'vulnerable') stage of CF lung disease or whether a specific microbial colonization pattern independently contributes to lung function decline; it remains further to be defined whether certain microbes attenuate or promote the colonization with other microbes (microbial interactions) within the course of CF lung disease progression<sup>14</sup>. With intensified antibiotic therapy and prolonged patient survival, new emerging pathogens particularly fungi and rare bacteria are increasingly found in adolescent and adult CF patients. CF lung disease is distinct from other organ system manifestations because (1) lung disease is the cause of premature death in about 95% of patients, and (2) only the lung develops a chronic infection phenotype with an associated intense inflammatory response.

Antibiotic resistance is a worldwide problem that can cross international boundaries and spread between continents with ease.<sup>16,17</sup> However, the subsequent and continuing intensive use of antibiotics since their introduction has helped to select a huge increase in the frequency of resistance among human pathogens.<sup>18</sup> The antibiotic resistance crisis has been attributed to the overuse and misuse of medications, as well as a lack of new drug development by the pharmaceutical industry due to reduced economic incentives and challenging regulatory requirements.<sup>19,20</sup> Therefore, the aim of this study was to determine the burden of antibiotic resistance patterns in cystic fibrosis patients by analyzing data collected in a tertiary hospital in Dhaka, Bangladesh.

## Materials and methods

This cross-sectional study was carried out in Bangladesh Shishu Hospital and Institute (BSH&I) in a period of 12 months among the patient visited to this tertiary care hospital. Ethical approval of this study was obtained from the Ethical Review Committee (ERC) before the start of the study. A written informed consent was obtained from a parent or legal guardian after explaining them about the study. Patients were included in the study at least one clinical presentation of the disease a. at least one clinical sign of cystic fibrosis b. A sibling carrying the diagnosis of cystic fibrosis. The evidence of CFTR was defined as an elevated chloride concentration in sweat ( $> 90\text{mmol/L}$ ) in at least two independent measurements. As the cut-off value of used pilocarpine iontophoresis device of our center was  $> 90\text{mmol/L}$ . Patients with history of antibiotic therapy in the last 90 days, Other respiratory conditions such as, pulmonary tuberculosis, asthma, pneumonia, interstitial lung disease, bronchiolitis obliterans etc., Cardiac disease, and liver disease were excluded from the study. Patients were interviewed with a structured questionnaire to fill out the required variables for all the cases. To examine the pattern of microorganisms isolated from posterior pharyngeal swab or sputum samples of cystic fibrosis patients' samples were collected according to age. Reviewing of other supporting medical documents were also examined.

## Specimen collection, culture and antimicrobial susceptibility test

Sputum samples were collected in sterile plastic disposable containers. Collected specimens were stored at ambient temperature and transferred to the microbiology laboratory of the study center. All specimens were inoculated and cultured in Blood agar, chocolate agar & Mac-Conkey's agar media.<sup>21</sup> Then streaking (spreading) was done to find out the isolated colony. Specimens were incubated overnight for 18-24 hr. at 37°C. After 24 hr. we observed for any colony growth & gram staining was done. On the 2<sup>nd</sup> day identification as well as antibiotic sensitivity were done in disk diffusion method according

to the institutional protocol.<sup>16</sup> Additional biochemical tests for bacterial identification were performed whenever necessary. Bacterial organisms were identified by using standard laboratory cultivation protocol, morpho type analysis, growth behavior on plates.<sup>22</sup>

## Statistical analysis

Statistical analyses were conducted using SPSS software version-24. Continuous variables were expressed as the mean and standard deviation. Categorical variables were expressed as counts (percentages). Nonparametric tests such as Fischer exact test were done as and when necessary. Statistical significance was determined at  $p \leq 0.05$ .

## Results

This observational cross-sectional study was conducted in the Department of Pediatric Respiratory Medicine, Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh. After careful history taking, examination and appropriate investigations, a total of 65 children visited the out-patient department, fulfilling inclusion and exclusion criteria, were included in this study. The mean age of all patients was  $76.63 \pm 41.08$  months (2-216 months) with majority belonged to 61-120 months of age (47.7%). About 45(69.2%) respondents were male and 20(30.8%) were female (Figure 1 & 2).

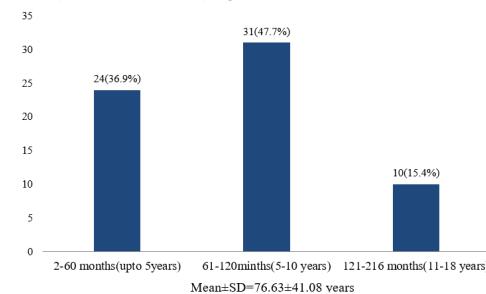


Figure 1 Distribution of age group of respondents (n=65).

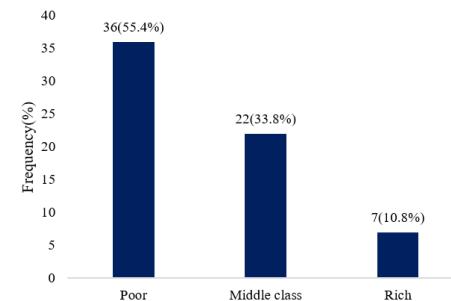


Figure 2 Distribution of socio-economic condition of respondents (n=65).

Socio-economic status more than half of the respondents was poor (55.4%) and others were middle class (33.8%) and rich (10.8%).

Clinical findings of the respondents were presented as cough (72.3%), shortness of breathing (67.7%), fever (33.8%) and wheezing (9.2%) (Table 1).

Table 1 Distribution of clinical findings of respondents (n=65)

Clinical findings	Frequency	Percentage
Fever	22	33.8
Cough	47	72.3
Shortness of breathing	44	67.7
Wheezing	6	9.2

BMI of the respondents showed majority were within normal growth percentile (50.8%), however about 38.5% were presented as underweight (below 5<sup>th</sup> percentile) (Table 2&3).

**Table 2** Distribution of BMI of respondents (n=65)

BMI	Frequency	Percentage
Underweight (<5th percentile)	25	38.5
Normal (6-85th percentile)	33	50.8
Overweight (86-95th percentile)	4	6.4
Obese (>95th percentile)	3	4.6

**Table 3** Distribution of bacterial and fungal microorganism in respondents with CF (n=65)

Microorganism	Frequency	Percentage
<b>Bacterial</b>	61	93.8
Pseudomonas aeruginosa	23	35.4
Klebsiella pneumoniae	15	23.1
Staphylococcus aureus	10	15.4
Escherichia coli	12	18.5
Acinetobacter spp	5	7.7
Streptococcus pneumoniae	3	4.6
<b>Fungal</b>		
Candida albicans	4	6.2

\*Multiple responses were considered

**Table 5** Distribution of antimicrobial sensitivity in gram negative bacteria in percentage

Antimicrobial agent	P. aeruginosa (%)	K. pneumoniae (%)	E. coli (%)	S. aureus (%)	S. pneumonia (%)	Acinetobacter spp (%)
Amikacin	52.2	40	100	Not done	Not done	40
Aztreonam	78.3	Not done	75	Not done	Not done	Not done
Amoxicillin clavulanate	Not done	Not done	not done	50	66.7	Not done
Ceftazidime	65	33.3	58.3	Not done	Not done	Not done
Ciprofloxacin	56.5	73.3	66.7	90	100	80
Ceftriaxone	43.5	46.7	not done	50	Not done	Not done
Cotrimoxazole	Not done	46.7	Not done	70	Not done	Not done
Erythromycin	Not done	33.3	Not done	Not done	33.3	Not done
Gentamycin	65.2	33.3	83.3	60	Not done	Not done
Imipenem	47.8	80	75	70	Not done	Not done
Meropenem	73.9	Not done	66.7	Not done	Not done	Not done
Piperacillin	65.2	46.7	75	Not done	Not done	40
Tobramycin	78.3	53.3	75	Not done	Not done	Not done
Vancomycin	Not done	46.7	Not done	70	Not done	Not done
Linezolid	Not done	Not done	Not done	90	66.7	Not done
Levofloxacin	78.3	80	91.7	90	66.7	80

## Discussion

Cystic fibrosis (CF), is a genetic disorder that affects mostly the lungs but also the pancreas, liver, kidney, intestines.<sup>23</sup> The main feature of cystic fibrosis (CF) is chronic respiratory infection, which may start very early in the life of these patients.<sup>24</sup> In infants, pulmonary infections with *Staphylococcus aureus* and *Haemophilus influenzae* are common and also later in childhood, infections with *Pseudomonas aeruginosa* (PA) become dominant.<sup>25</sup> Therefore, accurate identification of lower respiratory tract pathogens is crucial in the management of CF and is recommended to be performed at least every 3 months using bacterial culture sampling.<sup>26</sup> This observational

In this study, 4 types of gram-negative bacteria were found including *Pseudomonas aeruginosa* (35.4%), *Klebsiella pneumoniae* (23.1%), *Escherichia coli* (18.5%), *Staphylococcus aureus* (15.4%), *Acinetobacter spp.* (7.7%) and *Streptococcus pneumoniae* (4.6%). Besides, only one type of fungal microorganism, *Candida albicans* (6.2%), was also found in this study.

According to the pattern of microorganisms found in this study, multiple organisms were found in about 7 (10.8%) children. The rest of the children were infected with single organisms (89.2%) (Table 4).

**Table 4** Distribution of number of microorganisms in respondents with CF (n=65)

Number of organisms	Frequency	Percentage
Single	58	89.2
Multiple	7	10.8

Antimicrobial sensitivity of *P. aeruginosa* was found in Levofloxacin (78.3%), Aztreonam (78.3%), Tobramycin (78.3%), Meropenem (73.9%), gentamycin (65.2%), piperacillin (65.2%), Ceftazidime (65%), Amikacin (52.2%), Imipenem (47.8%), and Ceftriaxone (43.5%). *S. pneumoniae* presented antimicrobial sensitivity with Ciprofloxacin (100%), Levofloxacin (66.7%), Amoxicillin/clavulanate (66.7%), Linezolid (66.7%) and Erythromycin (33.3%). *K. pneumoniae* antimicrobial sensitivity was found in Imipenem (80%), Levofloxacin (80.0%), Ciprofloxacin (73.3%), Tobramycin (53.3%), Vancomycin, Ceftriaxone, Cotrimoxazole and Piperacilline (46.7%), Amikacin (40%) and Erythromycin (40%) (Table 5).

cross-sectional study was conducted with total 65 OPD patients with cystic fibrosis (CF). The main aim of the study was to find out the prevalence of microorganisms isolated from posterior pharyngeal swab or sputum samples of cystic fibrosis patients.

The mean age of this study of the patients was  $76.63 \pm 41.08$  months (2-216 months) with majority belonged to 61-120 months of age (47.7%). ARM Luthful Kabir et al.<sup>27</sup> showed that, age at diagnosis (mean:  $90.0 \pm 48.5$  months) revealed 24% (23/95) were under 5 years-old, 53% (50/95) were 5.1 to 10 years' age group and the rest 22 (23%) were older boys and girls belonging to 10.1 to 18 years old. About 45(69.2%) respondents were male and 20(30.8%) were

female present in this study. In Leila Azimi et al the mean age of the patients was  $6.7 \pm 5.2$  years and 28 (55%) were male patients in the sample.<sup>28</sup> The economic status of the respondents was poor (55.4%) in this study. Majority of the respondents were from rural areas (69.2%). ARM Luthful Kabir et al showed socio-economically, most children were poor (87.4%) belonging to "Lower to mid" income groups who maintained their livelihood with a very tight monthly average.<sup>27</sup> Age of onset of cystic fibrosis (CF) in respondents of this study were mostly (53.8%) within 2-6 months of age. The mean value of age of onset was  $9.83 \pm 8.99$  (SD) months. ARM Luthful Kabir et al.<sup>27</sup> showed, age of 95 children with CF at disease onset (mean:  $16.9 \pm 26.6$  months) was 74% (70 of 95 younger ones: 56% of 1-6 months-old toddlers and 18% of 7-12 months-old infants) and 26% (25/95) were  $>12$  months-old. Clinical findings of the respondents were presented as cough (72.3%), shortness of breathing (67.7%), fever (33.8%), wheezing (9.2%) of this study. Respiratory features were most common in our cohort similarly, chronic productive cough (90.71%), recurrent bronchopneumonia (72.09%) and asthma like presentation (44.19%) with wheezing and cough found in the study of Danish Abdul Aziz et al.<sup>29</sup> BMI of the respondents showed majority were within normal growth percentile (50.8%), however about 38.5% were presented as underweight (below 5<sup>th</sup> percentile) in this study. Body Mass Index (BMI) percentile in individuals 2 to 19 years (median) was 61.3 in 2020.<sup>30</sup>

In this study, 4-gram negative bacteria were found including *P. aeruginosa* (35.4%), *K. pneumoniae* (23.1%), *E. coli* (18.5%), *Acinetobacter* spp. (7.7%), and 2-gram positive microorganism including *S. aureus* (15.4%) and *S. pneumoniae* (4.6%). A total of 13 different organisms were isolated from the study population in Gulnaz Bashir et al, which included five gram-positive bacteria (38.4%), six gram-negative bacteria (46.1%), *Candida* spp. (7.6%) [*Candida albicans* (8) and *Candida tropicalis* (1)] and one filamentous fungus (7.6%) (*Aspergillus fumigatus*).<sup>31</sup>

Only one fungal microorganism found in this study was *Candida albicans* (6.2%). In the study of Leah Cuthbertson et al, showed the most common operational taxonomic unit (OTU) in patients with CF was *Candida parapsilosis* (20.4%), whereas in non-CF bronchiectasis sputum *Candida albicans* (21.8%) was most common; however, CF patients with overt fungal bronchitis were dominated by *Aspergillus* spp, *Exophiala* spp., *Candida parapsilosis* or *Scedosporium* spp.<sup>32</sup> Antimicrobial sensitivity of *P. aeruginosa* was found in Levofloxacin (78.3%), Aztreonam (78.3%), Tobramycin (78.3%), Meropenem (73.9%), Gentamycin (65.2%), Piperacillin (65.2%), Ceftazidime (65%), Amikacin (52.2%), Imipenem (47.8%), and Ceftriaxone (43.5%). The susceptibility rate of *P. aeruginosa* strains that were tested in this study of János Dégi et al, was in the following order: Ceftazidime (53.44%; 31/58), followed by Aztreonam (51.72%; 30/58), Amikacin (44.82%; 26/58), Azithromycin (41.37%; 24/58), Gentamicin (37.93%; 22/58), Cefepime (36.20%; 21/58), Meropenem (25.86%; 13/58), Piperacillin-Tazobactam (25.86%; 13/58), Imipenem (22.41%; 13/58), Ciprofloxacin (17.24%; 10/58), Tobramycin (8.62%; 5/58), and Polymyxin B (1.72; 1/58).<sup>33</sup> *S. pneumoniae* presented 100% antimicrobial sensitivity with Ciprofloxacin, and 66.7% with Levofloxacin, while *K. pneumoniae* had highest antimicrobial sensitivity both in Imipenem (80%) and Levofloxacin (80%). Antimicrobial susceptibility had been seen declining over years; however studies showed the most active agents for MDR/XDR isolates were ceftaroline (99.7%/99.1% susceptible), tigecycline (96.8%/95.9% susceptible), linezolid (100.0%/100.0% susceptible), and vancomycin (100.0%/100.0% susceptible).<sup>34</sup> *S. aureus* showed highest sensitivity with Levofloxacin (90%) and Ciprofloxacin

(90%) and *E. coli* showed highest sensitivity with Amikacin (100%) in this study. *S. aureus* revealed varying susceptibility to Imipenem (96.7%), Levofloxacin (86.7%), Chloramphenicol (83.3%), Cefoxitin (76.7%), Ciprofloxacin (66.7%), Gentamycin (63.3%), Tetracycline and Sulfa-methoxazole-trimethoprim (56.7%), and Vancomycin and Doxycycline (50%) in Olufemi Emmanuel Akanbi et al.<sup>35</sup> In our study there were no MDR MTB or MRSA isolated.

## Conclusion

This observational study tried to identify and reveal that nearly all the isolated bacteria developed substantial rates of resistance to most of the antibiotics that are used in the area. Therefore, in general, the antibiotic-resistant rate is high in the specified study hospital, the physician might prescribe antibiotics based on drug susceptibility reports available. In the case of the experimental treatment, it needs to be mandatory to prescribe antibiotics with less resistance that might be helpful to manage bacterial infections.

## Limitations

This was a single center study, and the sample size was smaller. Further, multicenter large study design is needed to draw conclusions better.

## Availability of data and materials

The dataset used in the current study is available from the corresponding author on reasonable request.

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The study is self-funded.

## Conflict of interest

There was no conflict of interest.

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