ORIGINAL ARTICLE

SPECTRUM OF PULMONARY EXACERBATION IN CHILDREN AND ADOLESCENT WITH CYSTIC FIBROSIS AND PHYSICIANS' PRACTICES: EXPERIENCE FROM TERTIARY CARE CENTER FROM LOWER-MIDDLE INCOME COUNTRY

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Background: Pulmonary exacerbations (PEx) are major contributor of significant morbidity and mortality in CF patients. Managing PEx needs standardization and without standard local practice guidelines there will be significant variation in practice in managing these children. The aim of this study is to analyse the clinical management of PEx in our setup and to document variation in practices among physicians. **Methods:** Children and adolescents ≤18 years with CF pulmonary exacerbations admitted at high dependency unit (HDU) or wards were included in the study. Frequencies of different intravenous antibiotic combinations were documented along with use of different inhaled antibiotics and inhalation therapy. Practices of different physician were further studied with regards to use of systemic steroids, oral azithromycin and inhaled antibiotics. One way ANOVA was used to assess differences between physicians' practices. **Results**: Fifty-seven patients were selected according to the inclusion criteria for 114 different exacerbations. Mean pulmonary exacerbation (PEx) for a patient (events/person-year) over five years was 3.16±1.41 per year and average length of stay was 5.7±4.4 days. Combination of intravenous ceftazidime and amikacin was the most frequently used regimen (28.07%). Five different physicians dealing with majority of the exacerbations (n=74) were studied further. Variability among consultants was significant in using systemic steroids (21.42–92.30%), use of maintenance oral azithromycin (0–80%) and inhaled antibiotics (0-86.6%). **Conclusion**: Significant variation exists in practices of physicians dealing with CF PEx. Variability observed in our study will definitely provide openings for local CF experts to come up with standardized inpatient exacerbation guidelines.

Keywords: Cystic Fibrosis; Exacerbation; Management guidelines; Practice Variability

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INTRODUCTION

Cystic fibrosis (CF) is a life limiting disorder featured mainly with respiratory and gastrointestinal clinical manifestations. Pulmonary exacerbations (PEx) are a major contributor of morbidity and mortality in CF patients.[1–3] There is no established consensus on clinical definition for pulmonary exacerbation in CF population, but clinical features of exacerbations are well known which include worsening cough with increased sputum amount, shortness of breath, chest pain, lethargy, loss in weight and appetite, and declining pulmonary function measurements.[4–6] Pulmonary exacerbations have been associated with poor quality of life and survival.[7] There are multiple international guidelines on the management of pulmonary exacerbation including recent European Cystic Fibrosis Society (ECSF) guidelines[8], NICE guidelines[9] and Cystic Fibrosis Foundation (CFF) expert guidelines[10]. Managing pulmonary exacerbations is a multidimensional process with different strategies including inhaled antibiotics, oral antibiotics, and mucolytic agents. Previous studies have also advocated the need for standardized practices in managing CF exacerbation.[11]

In Pakistan, multiple centers are dealing with pulmonary exacerbations in cystic fibrosis patients without proper guidelines and practices may vary from physician to physician. We hypothesize that significant variation exists in inpatient PEx treatment and this study documents such differences in our setup. The aim of this study is to analyze the clinical management of PEx in our setup and to document variation in practice.

MATERIAL AND METHODS

This was five-year retrospective observational study on inpatient admissions for CF-related pulmonary exacerbations from 1st January 2015 through December 31st, 2019 conducted at the Aga Khan University Hospital Karachi, Pakistan. Data was collected and documented from individual patient's

chart and online patient care software. Laboratory and medication data coinciding with the dates of exacerbation and hospital stay of individual patient was retrieved.

Children and adolescents with sweat chloride values more than 60mmol/L were marked as positive and consistent with the diagnosis of CF. Sweat was produced by means of pilocarpine iontophoresis and Wescor Macro-duct sweat collection system was used to collect it.

Case definition of CF Pulmonary Exacerbation was taken from clinical evidence stating CF patients who were admitted in the ward or receiving intravenous antibiotics, presented with respiratory distress, increase frequency of cough, increased sputum production, increase work of breathing, and/or new crackles on auscultation or new radiological finding on chest x-rays as new consolidations ± collapse or infiltrates.[5]

Children and adolescents ≤18 years with CF Pulmonary exacerbations admitted at high dependency units (HDU) or ward through emergency services or clinics were included in the study.

Referred patients with pulmonary exacerbations who remained admitted in other hospital were excluded from the study. Patients with acute pancreatitis were excluded from the study.

Mean characteristics of the cohort with respect to number of exacerbations, average length of hospital stay, age at presentation and diagnosis were noted along with pertinent laboratory investigations including mean sweat chloride levels. Frequency of different intravenous combination antibiotics were documented along with use of different inhaled antibiotics and inhalation therapy. Mode of respiratory support was noted, and patient outcome was categorized into patient discharged home, shifted to PICU, and expired at HDU with DNV (Do Not Resuscitate) status. Practices of different physicians were further studied in regards to use of systemic steroids, oral azithromycin and inhaled antibiotics.

Characteristics for the cohort were presented as descriptive statistics. Mean and standard deviation were described for continuous variables. Frequencies and percentages were reported for different variables. One-way ANOVA was used to assess significant differences in treatments between the five physicians. *p*-value <0.05 was considered as significant. SPSS version 23 was used to analyse the data.

RESULTS

Fifty-seven patients were enrolled according to inclusion criteria and all 114 individual pulmonary exacerbations were examined. Average age at diagnosis was 3.12±2.52 years and mean age at first exacerbation was 3.8±2.21 years. Over five years, average recorded exacerbations per year were 22.80±3.56. Mean pulmonary exacerbations for a patient (events/person-year) during five years were 3.16±1.41 per year and average length of stay was 5.7±4.4 days (Table-1).

December was the peak month with maximum number of exacerbations in all five years (Figure I). Combination of IV ceftazidime and amikacin was the most frequently used regimen (28.07%) followed by IV piperacillin-tazobactam plus amikacin combination (24.5%). Gentamycin was the most frequently used inhaled antibiotic in the exacerbation regimen. Systemic corticosteroids were used in 54.38% of the exacerbations. Oral azithromycin as maintenance therapy was continued in 54 (47.36%) different exacerbations. (Table-2)

In 78 (68.42%) different exacerbations, Inhaled antibiotics were used. Hypertonic saline was the most frequently used mucolytic agent as a continuation of maintenance inhalation therapy. Use of inhaled corticosteroids was found to be 67.54%. In 68.4% of the exacerbations, CF patients were started on supplemental oxygen with nasal prongs or facemask. Nasal CPAP was started in 31.57% exacerbations as the first line respiratory support. Average days on respiratory support were 5.3±1.31 days. In 79.8% incidences patients were shifted to ward in stable condition and discharged home. Fifteen percent of the patients were shifted to PICU due to increased work of breathing or deterioration of their condition. Six expiries were noted during their stay in the HDU as DNV code was opted by the patients' attendant with no ventilator support. (Table-2)

Five different physicians dealing with majority of exacerbations (74) were studied further on their practices on using systemic steroids and inhaled antibiotics and on continuing maintenance oral azithromycin therapy in managing CF related pulmonary exacerbations. Variability among consultants was significant in using systemic steroids (21.42–92.30%), use of maintenance oral azithromycin (0–80%) and inhaled antibiotics (0–86.6%) (Table-3 and Figure-2)

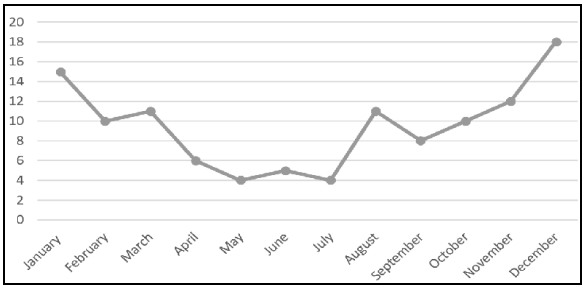

Figure-1: Month-wise cumulative frequencies of exacerbations over five years

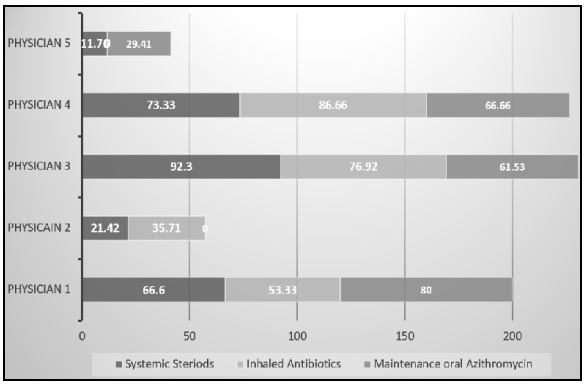

Figure-2: Physician Practices on systemic steroids, oral azithromycin and inhaled Antibiotics

Table-1: Demographic details

Number of CF patients (n)	**57**
Male: Female	1.7: 1
Mean age of cohort (Years)	8.43±5.81
Mean age at diagnosis (Years)	3.12±2.52
Mean age at first Exacerbation (Years)	3.8±2.21
Mean sweat chloride level (mmol/L)	75.51±8.89
Total number of exacerbations (n)	114
Mean exacerbations per year (inpatient)	22.80±3.56
Mean exacerbation events per patient per year	3.16±1.41
Average length of hospital stays (days)	6.7±4.4

Table-2: Management and outcome

	Number of exacerbations n=114
Intravenous Antibiotic Combinations	**n (%)**
Ceftazidime and amikacin	32 (28.07)
Piperacillin-tazobactam plus amikacin	28 (24.56)
Meropenem and vancomycin	21 (18.42)
Azithromycin and ceftazidime	17 (14.91)
Ciprofloxacin and azithromycin	11 (9.64)
Ceftriaxone and clindamycin	5 (4.38)
Inhaled Antibiotics	
Amikacin	17 (14.91)
Gentamicin	42 (36.84)
Colomycin	14 (12.28)
Tobramycin	5 (4.38)
Inhalation therapy	
Hypertonic saline	65 (57.01)
Salbutamol	81 (71.05)
Ipratropium bromide	29 (25.43)
Beclomethasone	77 (67.54)
N-acetyl cysteine	27 (23.68)
Respiratory Support	
Supplemental oxygen	78 (68.42)
Nasal CPAP	36 (31.57)
Outcome	
Discharged home	91 (79.82)
Shifted to PICU	17 (14.91)
Expired at HDU (DNV status)	6 (5.26)

(HDU=High Dependency Unit, CPAP=Continuous Positive Airway Pressure, PICU=Paediatric Intensive Care Unit, DNV=Do Not ventilate)

Table-3: Physician's data (n=74)

	Physician 1	**Physician 2**	**Physician 3**	**Physician 4**	**Physician 5**	***p*-value**
Number of Exacerbations	15	14	13	15	17	
Systemic steroids	10 (66.66%)	3 (21.42%)	12 (92.30%)	11 (73.33%)	2 (11.76%)	0.023
Inhaled Antibiotics	8 (53.33%)	5 (35.71%)	10 (76.92%)	13 (86.66%)	0	0.032
Maintenance Oral Azithromycin	12 (80%)	0	8 (61.53%)	10 (66.66%)	5 (29.41%)	0.029

DISCUSSION

In this study 57 CF patients were studied for their 114 different exacerbations. It was quite evident that the current inpatient CF exacerbation management in our setup showed significant variability in the usage of systemic antibiotics, systemic corticosteroids, inhaled antibiotics, and maintenance oral azithromycin therapy.

Average age at diagnosis in our patient cohort was 3.12±2.52 years which shows an obvious lack of screening programs in our population. This delay in diagnosing CF patients has a direct impact on the quality of life and results in increased morbidity and mortality in this population.[12,13] Mean pulmonary exacerbation rate (exacerbations/person-year) among all enrolled patients was 3.16±1.41 which is quite similar to the findings of Brumback *et al.*[14] Median Length of stay (LOS) was 6.7±4.4 which is quite low as compared to other international registries. Due to a heavy cost of inpatient services most of these patients preferred to complete IV antibiotics at home. Three most frequently used intravenous antibiotic combinations were ceftazidime with amikacin, piperacillin-tazobactam with amikacin, and meropenem with vancomycin which make up 70% of all intravenous admission antibiotic regimens. The combination regimens are ideally preferred due to "dual cover" of *Pseudomonas aeruginosa*, recognized as the major cause of morbidity and mortality in CF patients.[15] Choice of antibiotic regimens at admission was fairly variable, as six diverse antibiotic regimens were initially used during these exacerbations. The choice of these antibiotics was determined according to the prevalent antibiotic resistance pattern.[16] Our local data suggests that ceftazidime resistance is emerging with time and physicians are more comfortable with piperacillin-tazobactum plus amikacin or meropenem and vancomycin regimen as empiric antibiotics in first 24–48 hours. For about 68% different exacerbations, inhaled antibiotics were used, and gentamicin was the most frequently utilized (36.84%) inhaled antibiotic. Combination strategy of using inhaled and IV antibiotics at the same time in treating pulmonary exacerbations is debatable, and guidelines suggest inadequate evidence to endorse in favour or against

this regimen.[17] Further studies are required to document effectiveness of combined inhaled and intravenous antibiotic in managing pulmonary exacerbations.[18]

Evidence in most CF guidelines is inadequate and neither of them clearly point in favour or against the use of systemic corticosteroids during pulmonary exacerbations.[8,10] Our data showed significant variability in systemic corticosteroid use among physicians for pulmonary exacerbations. There is strong physician recommendation in certain studies to use systemic steroids during pulmonary exacerbations.[19] A randomized, controlled trial in children showed the role of Intravenous hydrocortisone in improving lung function following hospitalization.[20] Another study revealed no significant difference in lung function or markers of sputum inflammation between the groups.[6, 21] Median hypertonic saline use was 57% which was quite low than most of the reported studies.[22] Decreased use of hypertonic saline in our study could be due to a variety of factors, including lack of knowledge about hypertonic saline, discontinuation of hypertonic saline due to bronchospasm or haemoptysis, and physician preferences. Previous studies suggested that using hypertonic saline for CF exacerbations did not reduce the length of hospital stay but helped in quick resolution of symptoms.[23]

Maintenance oral azithromycin therapy is recommended by CF guidelines, as long-term strategy for the maintenance of pulmonary health in CF patients. Median maintenance azithromycin use in the inpatient setting was 47%, with significant variation between different physicians. Evidence suggests that regular and intermittent (3 days/week) oral azithromycin regimen is effective in controlling symptoms in patients with *Pseudomonas aeruginosa* colonization.[24]

Limitations of our study include lack of data on CF genotypes and lung function tests at the time of exacerbations. In addition, complete information on home Intravenous or oral antibiotics were not available for further analysis.

CONCLUSION

The variability of practices seen in our study can definitely provide openings for local physician CF groups to come up with standardized inpatient exacerbation guidelines and practices to improve CF-related outcomes. We hope our results will incentivize future prospective studies from this region regarding standardization of PEx practices and management strategies. This will definitely benefit our CF patients towards better quality of life and pulmonary health.

AUTHORS' CONTRIBUTION

DA, SS, HI and FM contributed to the conception and design of the study. AA and NA contributed to data collection. HI and FM contributed to the analysis and interpretation of the data and the drafting and critical revision of the manuscript. All the authors have read and approved the final version of the manuscript.

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