Original Article

Role of inhaled antibiotics in children and adolescents with cystic fibrosis: Experience from the tertiary care center

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ABSTRACT

Introduction: Cystic fibrosis (CF) remains under-diagnosed in Pakistan. CF population has increased tendency for *Pseudomonas aeruginosa* (Pa) infection and it is one of the leading causes of mortality. Utilizing inhaled antibiotics (IAs) for the treatment of Pa infection has been well established in the literature. There is limited data available on CF in Pakistan, especially regarding the efficacy of IAs. The aim of this study is to investigate the role of IAs on Pa infection in children and adolescents with CF. **Methodology:** CF patients enrolled between January 2012 and December 2019 were selected as part of this retrospective cohort study. CF patients from 2 to 18 years of age who cultured Pa on any respiratory sample and who had never been Pa-free in at least two sputum cultures in the previous 12 months were included. Patients were divided into an IA group and a noninhaled antibiotic (NIA) group based on the treatment they received. Follow-up was done between 3 and 6 months posttherapy on Pseudomonas growth in the sputum. The number of pulmonary exacerbations were documented for 6 months follow-up. **Results:** Eighty-one children with CF were enrolled during the study period, of which 39 were in the IA group and 42 were in the NIA group. There was no significant difference in their demographics and initial clinical characteristics. The mean pulmonary exacerbations after 6 months were lower in the IA group as compared to the NIA group (1.102 ± 0.50 vs. 2.45 ± 0.89: $P = 0.001$). Follow-up between 3 and 6 months showed greater Pseudomonas colonization in the IA group versus the NIA group (53.84% vs. 92.85%: $P = 0.001$). **Conclusion:** IAs in combination with airway clearance therapy and oral or IV antibiotics are an effective regimen for children with CF.

KEY WORDS: Cystic fibrosis, inhaled antibiotics, *Pseudomonas aeruginosa,* pulmonary exacerbations

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Submitted: 23-Jun-2021 **Accepted:** 25-Nov-2021 **Published:** 20-Apr-2022

INTRODUCTION

Cystic fibrosis (CF) is a common life-limiting, autosomal recessive genetic disorder, occurring in 1 in 3500 live births among caucasians.[1-3] While the prevalence of CF in Pakistan is unknown, it often remains underdiagnosed and easily missed in Pakistan, due to lack of awareness and effective diagnostic tools.[4,5]

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_370_21

CF is the result of a mutation in the CF transmembrane conductance regulator (CFTR), causing a buildup of thick, abnormal mucus that often obstructs airways.[6,7] As a multisystem disease, CF presents with respiratory insufficiency, chronic respiratory cough, and diarrhea, and can also involve the pancreas and reproductive tracts.

How to cite this article: Aziz DA, Abbas A, Alam A, Aziz N. Role of inhaled antibiotics in children and adolescents with cystic fibrosis: Experience from the tertiary care center. Lung India 2022;39:274-8.

Pulmonary exacerbation occurs when there is worsening of respiratory symptoms including cough with increased sputum and shortness of breath.[8] Repeated accumulation of mucus in the airways can result in the progression of respiratory symptoms and cause chronic lung infection, a major contributor of increased morbidity and mortality due to a gradual decline in lung function.[9] Pulmonary disease from chronic lung infection can ultimately lead to respiratory failure, and currently remains a primary cause of death in CF patients. Infection in CF predominantly involves *Pseudomonas aeruginosa* (Pa), as also seen in a retrospective study conducted in Pakistan on children with CF, in which more than a quarter of patients presented with Pa colonization at the time of diagnosis.[10] Pa infection in pediatric CF patients is found to be a predictor of morbidity and mortality and is associated with a 2.6-fold increase in the 8-year risk of death.[11]

To combat Pa infections in children, various regimens have been described, typically antipseudomonal antibiotics including aminoglycosides, aztreonam, ciprofloxacin, and colistin. These can be inhaled, intravenous (IV), or oral.[12] The CF Foundation recommends that children with CF between the ages of 2 and 5 years utilize alternate-month inhaled antipseudomonal antibiotics for Pa infections.[13] However, treatment of CF infections is becoming increasingly difficult due to multiple mechanisms of antimicrobial resistance, and the rise in multidrug-resistant Pa.[14]

Inhaled antibiotic (IA) therapy has significantly contributed to improved survival in CF patients through improvement in lung function, delay in lung function decline, improved quality of life, and reduced frequency of exacerbation, and efficacy has been observed in previous studies.[15,16] As compared to systemic antibiotics, IAs in CF allow for high concentration at the site of infection, and have a reduced risk of systemic toxicity.[17] Multiple studies have shown improvement in lung function after utilizing nebulized gentamycin or aerosolized tobramycin in conjunction with IV or oral antibiotics for CF infections in children.[18,19]

Limited studies are present in the literature on CF in the Pakistani population, especially with regards to management and drug therapy. Current studies in this setting explore genetic mutations of CF in the Pakistani population, as well as the role of oral azithromycin on pulmonary exacerbations in children with CF.[4,5] There has yet to be a study that compares an IA regimen with a noninhaled antibiotic regimen in combating Pa infections in the Pakistani population. Therefore, the aim of this study was to investigate the role of IAs in children and adolescents with CF and Pa infection, at the Aga Khan University Hospital in Karachi, Pakistan.

METHODOLOGY

This was a retrospective cohort study conducted from January 2012 to December 2019 at a tertiary care hospital, Aga Khan University Hospital, Karachi. Ethical approval was obtained from the Ethical review committee of the university. Children and adolescents from 2 years to 18 years of age were included in the study having cultured Pa on any respiratory sample, who had never been Pa-free in at least two sputum cultures in the previous 12 months. The enrolled CF patients were then categorized into two groups namely IA group (IA) exposed and noninhaled antibiotics (NIAs) group unexposed based on their antibiotic use. Children with chronic allergic bronchopulmonary aspergillosis and patients with more than one organism in sputum culture during the study period were excluded from the study. Similarly, patients who were lost to follow-up or had a indeterminate use of IAs were excluded from the study.

IA group has received 3 months IAs twice daily after airway clearance therapy combined with 3 months oral ciprofloxacin (20 mg/kg twice daily) or other antipseudomonal antibiotic including IV antibiotics 2 to 3 weeks in between oral antibiotics for breakthrough exacerbations. The IV treatment was initiated in the hospital in continuation with IAs, followed by oral ciprofloxacin and IAs for up to 3 months. NIA group received oral ciprofloxacin and other IV antipseudomonal therapy without IAs. Follow-up between 3 to 6 months posttherapy was documented for sputum pseudomonas growth and the number of pulmonary exacerbations in these patients [Figure 1].

Different IAs were used with IV gentamicin being the most frequently consumed IA [Figure 2]. Standard doses for IAs were used according to the evidence-based literature. Tobramycin is recommended for children 6 years and older, and given as a nebulizer solution 300 mg/5 mL twice daily in a 28 day on- and off-cycle.[20-22] Colistin or Colomycin has been administered previously in children with CF 0 – 18 years of age at 2 million units twice daily.[23] Amikacin can be used off-label to treat lower airway infections, in a dosage of 250 mg nebulized daily, and up to 500 mg twice a day if tolerated.[17] Gentamicin was prescribed for children over the age of 1 twice daily at 120 mg.[24]

Online pharmacy data and individual patients' charts were reviewed to ensure compliance in grouping patients. CF pulmonary exacerbations were defined as patients who were admitted to the hospital or started on IV antibiotics and presented with respiratory distress, increased frequency of cough, increased sputum production, increase work of breathing, and/or new crackles on auscultation

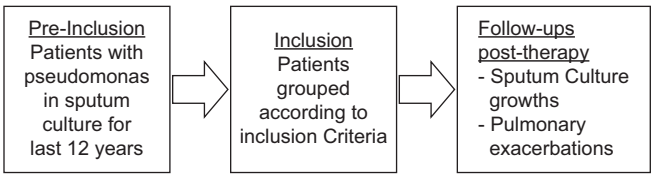

Figure 1: Study design

or new radiological finding on chest X-rays as new consolidations ± collapse or infiltrates.[25]

Independent variables included age, age at diagnosis and gender, height and weight on admission, sputum culture results, and exacerbations were documented. The data were analyzed using IBM Corp. released 2013, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Continuous variables were expressed as mean and standard deviation, while categorical variables were described as frequency and percentages. The Independent sample *t*-test was used for means and the Chi-square test was used for categorical data to assess significant differences between IA and NIA groups. $P \leq 0.05$ was considered significant, with a type I error of 5%.

RESULTS

A total of 260 patients' charts and laboratory data were reviewed f which 81 patients were included in the study. Thirty-nine children were classified into the IA group, and 42 were classified into the NIAs group. Patient demographics and clinical characteristics of both groups are presented in Table 1. No significant difference was observed between the two groups with regards to each factor including age, pulmonary exacerbations per year, sweat chloride levels, and regular use of intermittent azithromycin.

The number of pulmonary exacerbations reported during 6 months follow-up was less in the IA group as compared to NIA [1.102 ± 0.50 vs. 2.45 ± 0.89: $P = 0.001$; Table 2].

There was also a significant difference in Pseudomonas colonization in the IA group and the NIA group after 6 months follow up [53.84% vs. 92.85%: $P = 0.001$; Table 2].

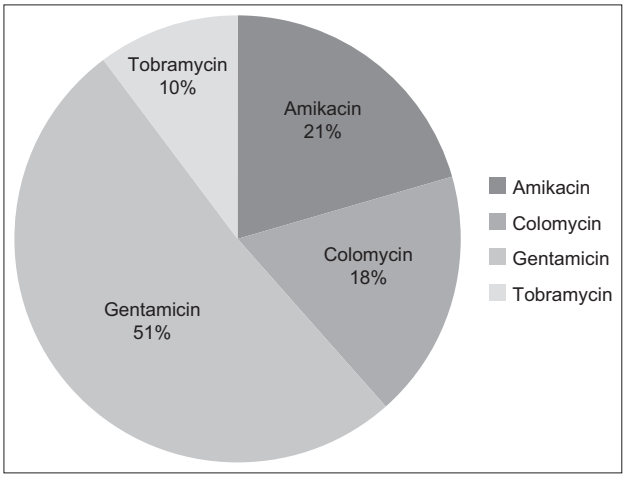

Figure 2: Percentages of different inhaled antibiotics

DISCUSSION

This retrospective cohort study in a Pakistani setting sought to describe the eradication of Pa infection in children with CF, through a regimen that includes IAs in combination with oral or IV antibiotics and airway clearance therapy, as compared to the regimen with only NIAs.

In our study, children that utilized IAs experienced less pulmonary exacerbations and showed less growth of Pseudomonas in 3 and 6 months follow-up, as compared to children that utilized NIAs. These results suggest that incorporating IAs can contribute to better outcomes in children with CF infections, contrary to previous studies that state there is no significant difference, or that systemic antibiotics result in greater reduction in lower airway inflammation in CF as opposed to inhaled.[10,26] Although IV antibiotics are fundamental in decreasing bacterial load for Pa infection treatment, they do not penetrate into the sputum or yield high sputum concentrations in the manner IAs do.[27] Because IAs are also able to achieve higher drug concentrations at the target site, a lower dose is required as compared to systemic antibiotics to achieve maximum bacterial killing, allowing it to eradicate even resistant strains.[6,28] While there are no clinical care guidelines present for the management of CF in Pakistan or South Asia, our results suggest that IAs can be recommended in future curated guidelines, similar to the recommendations of the CF Foundation in the United States.[22]

The findings in our study are consistent with previous studies in the literature, including in a South African setting where nebulized gentamicin in conjunction with systemic antibiotics was found to be effective for eradication of early Pa infections in children with CF.[9] The results are also consistent with a randomized controlled placebo trial conducted at 15 centers across 9 countries including Canada, Egypt, and Switzerland, which concluded that the use of inhaled tobramycin is

Table I: Demographic and clinical characteristics of cystic fibrosis children in two groups

	AI Group (39)	NIA Group (42)	*P*
Age (years)	6.457±3.15	7.36±2.34	0.45
Age at diagnosis (years)	4.01±2.78	3.87±2.15	0.56
Male: female	2.3:1	2.1:1	
Weight (kg)	12.30±3.61	13.42±4.29	0.31
Mean height (cm)	129.49±19.59	138.74±17.92	0.49
Sweat chloride levels (ug/l)	87.56±3.83	79.41±4.23	0.17
Regular use of intermittent azithromycin (%)	28 (71.79)	35 (83.34)	0.25
Pulmonary exacerbations/years, mean±SD	3.33±0.46	3.48±0.51	0.64

AI: Inhaled antibiotic, NIA: Noninhaled antibiotics, SD: Standard deviation

Table 2: Follow-up outcomes between two groups

	AI Group (39)	NIA Group (42)	*P*
Number of exacerbations (6 months follow-up)	1.102±0.50	2.45±0.89	0.001
Patients with sputum pseudomonas aeruginosa Growth (Between 3-6 months posttherapy) (%)	21 (53.84)	39 (92.85)	0.001

AI: Inhaled antibiotic, NIA: Noninhaled antibiotics

effective in eradicating Pa infection in pediatric CF patients younger than 7 years of age.[28] While this study did not utilize aztreonam as an option for IAs, recent studies have shown its efficacy for Pa infections in patients with CF aged 6 years and older.[12,21,22]

Although this study explored Pa infections, *Staphylococcus aureus*-especially methicillin-resistant *S. aureus*-is also a common pathogen affecting CF patients.[14] In a previous Pakistani study, *S. aureus* was the second most common infectious agent found at the time of diagnosis in children with CF, after Pa.[3] Future studies can explore the optimal treatment option and regimen for other pathogens causing infection in pediatric CF patients, such as *S. aureus*.

While it was once thought that CF was a disorder limited to Caucasians, the rise in studies from this region concludes otherwise. Similar to Pakistan, India, Bangladesh, and Sri Lanka experience the problem of nonavailability of sweat testing facilities, lack of neonatal screening, and have different genetic patterns than Caucasian CF patients, overall leading to the under-diagnosis of CF.[29-32] To our knowledge, no study such as ours has been previously done in the Indian subcontinent. Furthermore, a previous comparative study from the UK found that Asian CF patients – including Pakistani, Indian, and Bangladeshi – had significantly worse lung function, and may suffer worse outcomes.[33] This emphasizes the need for further studies on effective treatment and guidelines for a disease that was once thought rare in this region.[5]

There are a number of limitations to this study. First, the number of study participants was small. Despite this limitation, the findings reported in this study remain relevant to guiding the management of Pa infections in CF, especially in this region. Second, while the efficacy of an IA regimen as compared to a noninhaled antibiotic regimen in children was demonstrated, this study did not evaluate which specific IA brought about the most superior effects, and only explored IAs as a whole. Additional studies would be needed to compare different IAs for effectiveness, and to determine the optimal therapy for Pa eradication.

CONCLUSION

IAs in combination with airway clearance therapy and oral or IV antibiotics appear to be more effective than a regimen with NIAs for eradication of Pa infection in children with CF. Further studies are needed from Pakistan and the region on CF management and treatment, and guidelines must be created to ensure optimal outcomes and reduced morbidity.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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