Archives of Pediatrics and Neonatology
ISSN: 2638-5155
Volume 3, Issue 2, 2020, PP: 01-05

Management of a Child with Cystic Fibrosis Pulmonary Exacerbation Secondary to Covid-19 Infection admitted to Pediatric Intensive Care - A Case Report

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Introduction

COVID-19 infection causes mild disease in children generally. However, severe respiratory disease requiring respiratory support is reported, most commonly in children with chronic pulmonary disease which accounted for 30% of Pediatric Intensive Case Unit (PICU) admission in a multicenter cohort study[1]. Early data suggested that the course of disease in CF may not be as severe as expected when compared with patients with other underlying lung diseases.[2] We present a child with CF who required PICU admission due to COVID-19 infection.

Case Presentation

A 12 year old boy with pancreatic insufficient CF, genotype heterozygous C.1647T>G (p.Ser549Arg) and C.1175T>G (p.Val392Gly) presented to our emergency room (ER) with fever, worsening productive cough, chest pain and fatigue for 2 days. He had no runny nose, hemoptysis, diarrhea or other significant symptoms. No reported sick contact at home but he had been recently hospitalized for CF exacerbation and was discharged 2 weeks prior to this presentation during which he was tested negative for SARS-CoV-2 RNA Polymerase chain reaction (PCR). His background history is significant for severe lung disease (baseline FEV1 around 50%), poor nutritional status (BMI < 3rd percentile), allergic bronchopulmonary aspergillosis (ABPA), chronic pseudomonas aeruginosa and methicillin resistant Staphylococcus aureus (MRSA) airway infection. His home medications include: ivacaftor, dornase alpha nebulization, alternate months tobramycin nebulization, pancreatic enzymes, multivitamins supplementation and salbutamol inhalers as needed. In addition, he has been on daily oral prednisolone (1 mg/kg) and itraconazole for ABPA over the last 6 weeks.

At presentation, he looked sick but not toxic, was afebrile (36.7C), tachypneic (37/min), tachycardic 139 /min, normo-tensive 116/76 mmHg with low oxygen saturation at 89% in room air. His examination was significant for nasal flaring, intercostal retractions, bilateral reduced breathing sounds and diffuse coarse crackles worse than his known baseline. Other systemic examinations were unremarkable. He tested positive on nasopharyngeal aspirate for SARS-CoV-2 RNA PCRby GeneXpert System.

His investigations showed high total WBC with neutrophilia, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum ferritin, Interleukin-6(IL-6) and D-dimer (Table1). His venous blood gas showed a pH of 7.50, pCO2 of 40 mmHg and a bicarbonate of 30 mmol/L. His chest radiograph on day 1 of admission is shown on Figure 1.

He was admitted to the PICU with a clinical diagnosis of CF pulmonary exacerbation secondary to COVID-19 infection. Due to persistent respiratory distress and hypoxemia despite airway clearance, after he was started on non-invasive ventilation (NIV) 12 hours of admission under airborne precautions. He was commenced on piperacillin/tazobactam, gentamicin and co-trimoxazole based on his previous sputum bacterial cultures. For COVID-19 infection, he was started on favipiravir, hydroxychloroquine and received convalescent plasma on days 2 and 5 of PICU stay. Prednisolone and itraconazole were continued as part of his ABPA treatment. Low molecular heparin was discussed but was not added early in the course

because of a recent history of hemoptysis prior to this admission.

Performing chest physiotherapy while under isolation was challenging due to high risk of exposure to health care workers. To optimize airway clearance, his home VEST machine was used 2-3 times per day and dornase alpha dose was increased to twice a day. He was closely monitored for hemoptysis which occurred on day 8 of admission after which it was reduced to a once daily dosing. He was not given hypertonic saline due to a past history of severe bronchospasm.

He showed clinical deterioration on day 5 of admission with worsening hypoxemia reaching 77% in room air. His saturation to FiO_2(S-F) ratio was 174 on 7L/min of oxygen indicating a significant acute lung injury. It was notable that his hypoxemia was out of proportion when compared to his respiratory effort. This clinical deterioration was concerning for an early cytokine release syndromeso he was given a dose of Tocilizumab. Pronation was considered but it was challenging to get him to cooperate with that. Low molecular weight heparin was started on day 7 of PICU stay after careful consideration with close monitoring for hemoptysis.

The child recovered slowly and was transferred from PICU on day 9 of admission. He completed 14 days of intravenous antibiotic treatment and was discharged home in stable condition with an oxygen saturation of 95-96% in room air on oral ciprofloxacin. Pulmonary function test was not performed before discharge due to the current hospital infection control policy.

Table1. *Relevant lab investigations during hospitalization.*

	Day1	Day2	Day5	Day7	Day11
Haemoglobin (g/dl)	12.7			13.1	
White Blood Cells (10^9/L)	18.1		5.4	7	
Absolute Neutrophils Count (10^9/L)	11.9		4.1	5.6	
Absolute Lymphocytes Count (10^9/L)	3.4		0.8	1	
Platelet count (10^9/L)	313		123	418	
C-Reactive Protein (mg/l)		166		5.9	<0.4
Serum Ferritin (ug/L)		91		36	
Interleukin-6 (pg/ml)		594		269	
D-dimer (mg/l)		0.43	1.12	0.68	

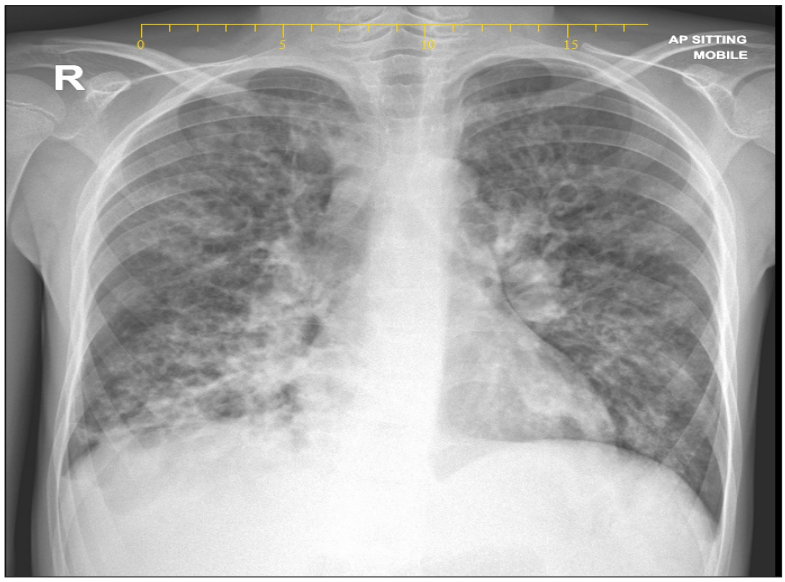

Fig1. *Chest radiograph performed on day 1 of admission showing extensive bronchiectatic changes (as before), increased peri-bronchial wall thickening and patchy opacification.*

Discussion

As of July 12th, the European Cystic Fibrosis Society registry documented that out of 126 patients with CF and confirmed COVID-19 infection, only 9 needed intensive care and three died.[3] The United Kingdom (UK) registry reported a death of one adult with CF out of a total 26 affected due to complications related to COVID-19 infection.[4] Common symptoms seen in patients with CF and COVID-19 infection were fever, increased cough, fatigue, increased sputum, headache and increased dyspnea respectively.[3]The exact reason behind a milder disease in CF is not fully understood.

COVID-19 pneumonia is associated with hypoxemia which is disproportionate to pulmonary mechanics which was noted in our patient. Both NIV and invasive ventilation are used for respiratory support during the current pandamic.[5] NIV is an aerosol generating procedure and therefore, there was a preference of early invasive ventilation in patients with COVID-19 presenting with respiratory distress. However, the process of tracheal intubation is not free from this risk.[6]From past experience, there was no increased risk of transmission to health care workers with NIV treatment during SARS pandemic when it was carried in negative pressure rooms with the use of full personal protection equipment.[7]NIV was found to produce the same improvement in gas exchange among responders while reducing nosocomial infections associated with invasive ventilation.[8]Aerosol generation was found to increase with the use of a single limb circuit with exhalation valves compared to dual limb circuit with no exhalation valves.[9]Therefore, it is advised to use dual limb circuit NIV with filters close to exhalation port and minimize leakage around interface.[10] The European Society for Paediatric and Neonatal Intensive Care recommends the use of NIV as the first respiratory support in COVID-19 pneumonia with consideration of invasive ventilation if no improvement is seen in oxygen saturation or respiratory distress 60 to 90 minutes post treatment.[11]

All therapeutic options for COVID-19 respiratory disease are still in the context of clinical trials.[12–15]For children and adults with CF who required hospital admission, different modalities of treatments based on the severity of their illness were used. The European Cystic Fibrosis Society project documented that 20 patients received Azithromycin, 13 received Hydroxychloroquine, 8 systemic steroids, 5 anti-viral and 3 Tocilizumab.[3]

The Infectious Diseases Society of America (IDSA) has a conditional recommendation to use remdesivir for severe COVID-19 disease but this medication is not yet available in our country. It decreases the viral load, improve progression of clinical disease and shortens recovery time.[13,16] Based on the limited available data, Faviripavir has significantly improved SARS-CoV-2 clearance time for mild or moderate disease with low adverse event rate.[15] Hydroxychloroquine has received worldwide attention initially as a potential treatment based on positive results from small studies which was not supported later.[17] The use of convalescent plasma from patients with past SARS-CoV-2 infection is reported to reduce the hospital stay and mortality rate.[18] Therapeutic plasma exchange is another described modality of treatment. Our local experience in Oman showed higher extubation rate and lower 28 day mortality among 31 adults admitted to intensive care unit with acute respiratory distress syndrome(ARDS) or severe pneumonia when compared to controls.[19]

Several studies showed that cytokine release syndrome (CRS) can lead to a rapid deterioration of COVID-19 patients.[20] Therefore, all patients with severe disease should be screened for CRS as early intervention can reduce mortality. Tocilizumab is an IL-6 receptor antagonist, which has been approved by the FDA for the treatment of COVID-19 related CRS should be considered early in severe disease for a better effect.[20,21]

In addition, studies showed that severe COVID-19 disease is associated with increased risk of coagulopathy, disseminated intravascular coagulation and venous thromboembolism. Increased D-dimer and prothrombin time are associated with poor prognosis and higher mortality rate in this population.[22]Therefor, early introduction of anticoagulant therapy in severe COVID-19 infection is recommended to improve outcome.[22,23]

Providing airway clearance can significantly reduce the need for ventilatory support, days of mechanical ventilation and hospitalization in patients with moderate to severe respiratory symptoms. However, due to the global shortage of personal protective equipment and high risk of nosocomial spread during

these techniques, it has been recommended that during COVID-19 pandemic, airway clearance should be performed through minimal contact.[24]It should be emphasized that airway clearance remains a corner stone in the management of CF exacerbation which should not change when managing CF exacerbation secondary to COVID-19 after taking the needed precautions. Utilization of parental experience and home equipment (VEST, PEP device, etc) may help to overcome this obstacle as we have experienced with our patient.

Conclusion

Our limited experience with this single pediatric patient highlights that SARS-CoV-2 can trigger CF pulmonary exacerbation which is characterized by fever and hypoxemia that is more pronounced when compared to typical CF pulmonary exacerbation. With appropriate management the outcome was positive which is an important message to the CF community worldwide.

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Citation: **Hussain Mohsin, Sumaya Al Oraimi, Nawal Al Maskari, et. al.** *Management of a Child with Cystic Fibrosis Pulmonary Exacerbation Secondary to Covid-19 Infection Admitted to Pediatric Intensive Care - A Case Report. Archives of Pediatrics and Neonatology. 2020; 3(2): 01-05.*