1. Epidemiology, clinical presentation and respiratory sequelae of severe Adenoviral Pneumonia (ADVP) in children admitted in a tertiary care Pediatric Intensive Care Unit (PICU) in Kolkata, India.

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None

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1. ABSTRACT

i. Objective- To describe epidemiological, clinical, biochemical, and radiological profile of children admitted in PICU of a tertiary care hospital with severe Adenoviral Pneumonia (ADVP) and respiratory sequelae among them.

ii. Design-This is a single-center, prospective observational study conducted at the Institute of Child Health

iii. Settings-The study had been done in PICU and General Pediatric ward of Institute of Child Health a 200 bedded tertiary level 3 Pediatric Hospital of Kolkata, India.

iv. Patient-Children less than 10 years of age admitted with features of Lower Respiratory Tract Infection(LRTI)/Pneumonia and became positive for adenovirus by respiratory sample PCR and needed intensive care at any point of the disease course during the period of -1st December 2018 to 1st May 2019 and then followed up.

v. Interventions-This is a non interventional study. Standard protocolized treatment of patients with severe adenoviral pneumonia needing PICU care had been done.

vi. Main outcome measures- Survival , poor prognostic factors and development of respiratory sequalae.

vii. Results-96 cases in total and 33 among them needed PICU care and had been considered as severe ADVP. Males were in higher proportion than female and almost all had fever, cough, and respiratory distress at the time of admission. 67% of patients presented after one week of appearance of symptoms.24 patients had SPO2 <90% in room air at the time of hospital admission. 29 kids needed respiratory support beyond simple oxygen therapy. HRCT, done in most of the kids with recurrent symptoms mostly showed features of Post Infective Bronchiolitis Obliterans.

2. INTRODUCTION

Human adenovirus is an important cause of febrile illness affecting mainly the respiratory system ranging from pharyngitis, coryza to fatal pneumonia also affecting other systems causing gastrointestinal, hepatological, ophthalmic diseases. Though most of the infections result in complete recovery it may results in considerable morbidities and mortalities in selected patients who developed adenoviral Pneumonia(ADVP)/Lower respiratory tract infection(LRTI)[1,2,3,4].

Adenovirus LRTI may present as bronchiolitis with predominantly wheezy symptoms or may present like bronchopneumonia or lobar consolidation and progress to develop Acute Respiratory Distress Syndrome(ARDS)[5,6]. Life-threatening severity is mainly noted in children with impaired T cell immunity like AIDS, neoplasm, or post-transplantation. But recently many reports had been published all over the world where apparently immunocompetent kids had been affected by severe ADVP[4,5]. Another unique feature of ADVP is that even after resolution of the acute phase, a significant number of severe cases go into a chronic form with persistent wheezing with waxing and waning symptoms needing continuous or intermittent respiratory support and oxygen supplementation and developed PIBO or bronchiectasis[1,4].

In this study, we concentrated mainly on the sickest cohort of ADVP who needed PICU care but were apparently immunocompetent.

3. MATERIALS AND METHODS

This is a single-center, prospective study conducted at the Institute of Child Health, Kolkata, and included all children aged less than 10 years, admitted to PICU of the hospital with laboratory-confirmed Adenoviral LRTI/ADVP between 1st December 2018 and 1st May 2019.

Among all the admitted patients (N=96) with microbiologically confirmed Adenoviral Infection those needing PICU care had been defined as Severe ADVP(N=33). Nasopharyngeal swab in non-intubated patients and Bronchoalveolar lavage (BAL) fluid from intubated patients had been collected by the standard operating procedure. Real-time multiplex PCR. SpinStarTM Pathogen Nucleic Acid Kit 1.0 is used for nucleic acid extraction and RespiFinder® 2SMART is used to perform multiplex RT-PCR in Rotor-Gene Q of Qiagen following manufacturer's guidelines.

Data collection was done from PICU during patient admission, stay, and during follow-up in the study period which was of history, findings during admission including vitals and the need for respiratory support, laboratory findings, and conditions during follow-up.

For statistical analysis, proportions, and means (SD) were calculated for categorical and continuous variables by the vital status of the children. Univariable regression analyses were done to measure the association between demographic, clinical, laboratory, and radiological variables with mortality. For binary outcomes, generalized linear models (GLMs) of the binomial family with a log-link function will be used to calculate the effect size (relative risk and 95% confidence interval (CI)]. For continuous outcomes, GLMs of the Gaussian family with an identity-link function will be used to calculate the effect size (difference in means and 95% CIs). We used STATA version 16(Stata Corporation, College Station, TX) for most statistical analyses.

Ethical clearance and consent.

Ethical approval for this study was obtained from the institutional ethics committee. Verbal consents were taken from the patient's parents. Questionnaires were given to the parents whose children were followed up.

4. RESULTS

During the study period, 96 children admitted to the hospital with adenoviral infection as confirmed by PCR. 33 children were admitted to PICU and included in this study. Proportionately male(n=26) children were admitted more as compared to female(n=7) counterpart with male-female ratio(3.7:1).Most of the children were aged between 6 months to 1 year, with a mean age of 9.7 months and SD of 5.13.

Table 1: clinical symptoms and examination findings in children with adenoviral infection on admission

None of the children had any premorbid condition and only1 had low birth weight. All the kids were apparently immunocompetent, though no specific immunological testing had been done except in 3, where the immunoglobulin profile and flow-cytometry for CD4 and CD8 were normal. The duration between onset of symptoms to presentation to our PICU varied widely. 45.5% presented within 7 days of onset of symptoms, 51.5% presented within 1 week to 1 month of onset of symptoms and 3% presented very late, after 1 month of onset of symptoms. (Table 1)All children had a fever, cough, and respiratory distress of different severity. There was a history of convulsion or convulsion after admission in 5 cases (15.15%). But altered sensorium was there in 9 children during disease(27.27%). Also, diarrhea was seen in5 cases (15.15%).

19(57.6%) kids had SPO2 below 90% on admission. 32(96.96%) children had some sort of chest retractions on admission. 11 children had hepatomegaly and 3 of them had Splenomegaly and hepatomegaly.

Table 2- Laboratory Features at the time of PICU admission

(table 2) Hemoglobin was <10 gm% in significant numbers of children (~50%). Total leucocyte count was high in 21 children (63.6%).C Reactive Protein(CRP) was raised in 66.7% of children(22). The serum sodium level was deranged in 13 children(37.5%). Liver enzymes were deranged in a significant proportion of patients(46%). Blood cultures were negative during the course in PICU in 26 children(78.78%).7 kids(21.21%) developed nosocomial sepsis during the PICU stay. A total of 6 kids among these 33 developed features suggestive of hyperferritinemic sepsis with MODS in the course of the

illness. Chest x-ray revealed bilateral patchy opacities in 14 children (42.4%), lobar consolidation in 3 children(9.1%) hyperaerated lungs in 14 children (42.4%), and normal in1 child.

Table 3: Treatment and Outcome

Figure 1

(table 3) 29(86.2%) children required some sort of respiratory support of which 25 children required invasive ventilation, 2 children were managed only with non-invasive ventilation, and 2 children improved with only HHFNC.

Corticosteroid was used in 24 children(72%). No antiviral drugs were used in our cohort. All of our children received antibiotics.

Among these 22 survivors, 2 lost to follow up, and the rest 20 kids followed up for at least 15 months, the median duration for follow up being 13 months.

Among these 20 kids, 2 did well in the follow up without any recurrence or persistent significant chest symptoms.

Rest 18 developed either recurrent or persistent chest symptoms.10 of them needed a total of 32 hospital admissions for exacerbation of symptoms. Two are at present in home oxygen and one is with home HHFNC.

The exacerbations had been managed on an OPD basis in the rest of 8 patients with an average of 3.2 exacerbations/patient/year. 6 patients did not have an exacerbation in the last 4 months and on tapering doses of inhaled corticosteroid.

15 among those with recurrent symptoms underwent HRCT of the chest during the disease. 12(80%) showed features of post-infectious bronchiolitis obliterans, 2(13.3%) had bronchiectasis and one showed persistent Pneumonia. 5 kids underwent fibreoptic bronchoscopy but didn't reveal any significant pathology of the tracheobronchial tree except a mild degree of airway-malacia in 2(10%).

Table 4: Association between demographic, clinical, laboratory and radiological parameters with mortality

Statistical analysis (Table 4) shows the association between demographic, clinical, laboratory, and radiological parameters with mortality. Duration of illness (β coefficient: 0.02; 95% CI: 0.003 to 0.03) and chest x-ray with patchy opacities (RR: 9.6; 95% CI: 1.2 to 76.7) were associated with increased risk of mortality.

5. DISCUSSION

The family of adenovirus comprises more than 60 serotypes divided into subgroups or subspecies (AtoG) which can affect many systems of the body namely the respiratory tract. Adenoviral epidemics are seen many times [4,7]. The traditional belief is that adenoviral diseases specially ADVP or Adenoviral LRTI are mostly self-limiting in immunocompetent kids and can cause life-threatening infection only in immunocompromised children. But there are lots of case reports and series where we have seen fatal and life-threatening ADVP in otherwise immunocompetent kids[1,4,7].

This study of us on severe ADVP in PICU among immunocompetent kids summarizes their epidemiology, clinical presentation, biochemical parameters, risk factors associated with high mortality, and respiratory sequelae.

Out of 96 diagnosed cases of adenoviral infection, 33 children (34.4%) were severe cases and required PICU care and included in the study. Severity in our study is higher than studies by Jose A et.al.[1] and LiMin Lim et.al.[4]. Male children were admitted more as compared to female children, this finding is similar to earlier studies from Malaysia by LI Min Lim et.al.[4], Brazil by Elenice et.al.[8], and Taiwan by Hsiu-lin Chena et.al.[9]. Most of the children in our study were between age 6 months to 1 year followed by the age group of 1-2 years and <6 months, this data is consistent with the study by Elenice et.al.[8] and by Rajkumar et.al.[10].

All kids in our study presented with different severity of fever with cough and respiratory distress followed by altered sensorium (27.3%), diarrhea, and convulsions (15%). Severe ADVP is usually associated with a high-grade fever unlike other viral pneumonia or bronchiolitis illness.

Significant numbers of severe ADVP presents with leucocytosis with a raised CRP, unlike other viral pneumonia. In our cohort, CRP was raised in almost 67% cases and was extremely high(>100mg/L) in 2 children. Hsiu-Lin Chen et.al. showed leucocytosis in 23% of children and raised CRP in 35.8% of children[9]. Another initial diagnostic point of severe ADVP is the presence of transaminitis. SGPT and SGOT were deranged in 46% of cases in our cohort, wherein Taiwanese study[9] almost all cases had normal liver enzymes.

Severe ADVP can have different appearances radiologically. It may present with bilateral hyperinflated lung fields suggestive of air trapping or bilateral patchy opacities suggestive of bronchopneumonia or even can present with typical lobar consolidation mimicking bacterial pneumonia. We found bronchopneumonic presentations had the most severe disease and increased mortality.

Treatment of adenoviral infection in immunocompetent kids is mainly supportive as it is self-limiting infection[1,11,12] but, we have encountered severe ADVP needed PICU care in one-third of the admitted adenoviral infections. Almost all children received antibiotics treatment before adenoviral etiology had been confirmed and was continued as many of the children had a secondary bacterial infection. [13,14].Most of the severe ADVP need some form of respiratory support beyond simple oxygen therapy. In our cohort, most of them were initially tried with HHFNC or NIV falling of which we put them on invasive mechanical. ventilation. Min Jae Cha et.al. showed a high rate of respiratory failure[5] similar to our study. Out of 29 children, 25(86.2%) required invasive mechanical ventilation followed by noninvasive ventilation and high flow nasal cannula, also 42% of children required inotropic support. We strongly recommend early initiation of HHFNC or NIV to avoid invasive mechanical ventilation related adverse effects.

None of our children received any antiviral therapy, as currently there are no consensus guidelines about the use of any antiviral agents in severe adenoviral diseases in immunocompetent kids. There are few isolated case reports and series about the use of antiviral agents in severe ADVP in immunocompetent kids. Ganapathi L et.al. showed clearing of the viral load from blood with the use of Cidofovir but yet there is no change in mortality[15]. Jin Kim et.al. found early use of Cidofovir in severe ADVP had a favorable outcome[16] as compared to previous studies like Barker JH et.al.[17], Hakim FA et.al[18]. and Dudding BA et.al[19] where most patients received antiviral including Cidofovir had a poor outcome. Also, there is a case report showing improvement in respiratory distress with the use of oral Ribavirin[20]. A newer antiviral agent Brincidofovir lipid ester of cidofovir, less nephrotoxic than Cidofovir has been studied and has been shown to have enhanced in vitro action against adenovirus. The points against not using Cidofovir in our cases were Cidofovir is not easily available in our part of the country and had to be

imported at a very high cost. Potential nephrotoxicity had been another concern.

There had been an interest in using corticosteroids in cases of severe ADVP but still today there are no definitive consensus guidelines had been there and more ever which steroid and which doses to be used had not been clarified. In our study corticosteroids was used in 24 children (72.7%) between 1st and 2nd week of disease. Takahashi et.al. found better relief from respiratory distress in severe adenoviral pneumonia with hypercytokinema[21 after steroid therapy. Several studies showed the use of steroids especially pulse Iv Methylprednisolone with or without Intravenous Immunoglobulin had a favorable outcome in severe ADVP complicated with hypercytokinemia and hyperferritinemia[22,23]. In our series, we did not find any significant benefit from corticosteroid use except in hyperferritenemic conditions. A steroid may decrease the fever spikes as well as wheezy symptoms but was not effective to resolve the ARDS part as well as to prevent the long-term sequelae.

Out of 33 children, 9 children expired making our case fatality ratio to be 27.3% which is almost equal to the study by Li Min Lim where mortality was 26.3% in a severe group[4]. Hsiu-Lin Chen reported favorable outcomes with no mortality in their study[9]. Mortality and morbidity ranging from 20-50% can occur in severe adenoviral infection especially where nosocomial infection is involved, it also depends upon the immunity of the host, virulence of viral agents, and presence of risk factors [4,9].In our cohort, we have found late presentation, as well as bilateral patchy opacities in chest X-ray, had been associated with poor outcomes.

.Adenoviral LRTI is notorious to produce long term respiratory sequelae in the form of recurrent or persistent wheezing without any significant CT changes or in the form of PIBO or bronchiectasis [14,24]. In our cohort 81% of the survivors from severe ADVP had sequelae. The percentage of respiratory sequelae in our series is more than other studies involving adenoviral infection, a study from Malaysia had respiratory complications of 22% which they quoted to be much higher than similar previous studies[4].Li-MinLim et.al.[4] explained that PICU care, the need for ventilation, and the preexistence of Asthma as risk factors for developing complications and sequelae. Saleh Alharbi et.al. from Canada found that preexisting

lung conditions may predispose for developing complication especially for developing bronchiectasis [25] but in our study, none had preexisting lung diseases. Adenovirus is one of the common organisms implicated in PIBO[26]. Diagnosis of PIBO should be confirmed by histopathology but usually based on history, clinical, and CT findings as per criteria[26]. There are few serotypes like 3,5,7h,and21 that have been associated with a higher incidence of PIBO[27,28]. Treatment of PIBO is limited by the usage of inhaled and systemic steroids, intermittent use of inhaled bronchodilators. Oral Hydroxychloroquine and Azithromycin both had been used as an immunomodulatory in cases of PIBO with mixed results[29]. Azathioprine though used successfully in post lung transplant bronchiolitis obliterans, but use in PIBO in children is limited[27,30]. Most of the kids in our series with PIBO had been treated with inhaled steroids and bronchodilators as well as with oral Hydroxychloroquine and Azithromycin.

The main limitation in our study is the unavailability of serotype analysis and the inability to show the association of certain serotypes with clinical presentation, outcomes, and development of PIBO.

6. CONCLUSION

Contrary to the popular beliefs, adenovirus LRTI/ADVP can be life-threatening in immunocompetent kids too especially in the Infancy. Not resolving pneumonia with high-grade temperature along with wheezy symptoms with elevated TLC, CRP and SGPT should prompt a clinician to suspect ADVP early. Those who presented late with bilateral patchy opacities in Chest X-ray have a bad prognosis. The role of corticosteroids as well as specific antiviral agents like Cidofovir and Brincidofovir in severe ADVP in immunocompetent kids is still not well substantiated. Most of the severe ADVP, especially those who needed mechanical ventilation in the acute phase develop sequelae in the form of PIBO.

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8. What is already known?

Adenoviral pneumonia is mainly trivial and severe infection mainly occurs in immunocompromised children.

9. What this study adds?

Adenoviral lower respiratory tract infection can be severe and life threatening even in immunocompetent kids specially in infancy. Most of the survivors of severe adenoviral pneumonia develops bronchiolitis obliterans as a sequelae.

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