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Case Report

Neonatal Respiratory Syncytial Virus Pneumonia: A Case Report and Review of Literature

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ABSTRACT

Respiratory Syncytial Virus (RSV) has been identified as the major causative organism of lower respiratory tract infection (LRTI) in neonates and infants.

***Case Report**: A 7 day old baby girl has born at 36+2 weeks of gestation presents with cough, cold, nasal congestion, difficulty in breathing and poor feeding since last 2 days. On examination, baby was dull, lethargic, had noisy breathing with moderate intercostal and subcostal retractions. X-ray showed bilateral hyper-inflated lung fields suggestive of bronchiolitis. Nasopharyngeal swab sent for respiratory viral panel PCR was positive for Respiratory Syncytial Virus. Baby responded to supportive management in the form of non-invasive ventilator (NIV) supports, nebulisation and chest physiotherapy. Baby was successfully discharged home on room air and exclusive breastfeeding by Day 12 of hospital admission.*

***Virus**: RSV is an enveloped, single stranded, negative strand RNA virus.*

***Epidemiology**: The highest hospitalization rates were seen during the first 6 months of life with peak rates of 25.9 per 1000 children seen in infants between 30 and 90 days of life. Risk factors include - prematurity, low birth weight, male gender, underlying lung or congenital heart disease, maternal smoking, lack of breastfeeding and over-crowding.*

***Pathogenesis**: RSV primarily spreads via air-borne droplets or via indirect contact with contaminated surfaces. Incubation period is between 2-8 days.*

***Clinical Presentation**: Neonates have atypical clinical manifestations and include afebrile cough, nasal congestion, choking on milk, spitting, rapid breathing and apnoea.*

***Diagnosis**: NICE recommends that the diagnosis of RSV infection should primarily be based on detailed history and physical examination. Additional radiological and laboratory investigations should be performed only in severe cases requiring intensive care management.*

***Prevention**: Basic hygiene rules such as frequent hand-washing, keeping surfaces clean and covering mouth and nose while coughing and sneezing is the most effective preventive measure. In inpatient setting, infected patient should be isolated with proper precautions.*

***Treatment**: Neonates with marked respiratory distress, saturation below 92% on room air, clinical dehydration and apnoea should receive inpatient management. Supportive care along with inhaled hypertonic saline and inhaled bronchodilator forms the standard of care.*

***Prognosis**: Most patients recover in 1-2 weeks. However, re-infections are common throughout life as RSV infection do not grant permanent immunity.*

KEYWORDS: Neonate, Respiratory Syncytial Virus, Pneumonia, Bronchiolitis, Palivizumab, Ribavirin

INTRODUCTION

Respiratory Syncytial Virus [RSV] has been identified as the major causative organism of lower respiratory tract infection [LRTI] in neonates and infants[1]. Respiratory Viral Infections [RVIs] in neonates continue to be the most under-diagnosed entity owing to their subtle clinical presentation and the absence of set protocols for viral pathogen testing in most of the NICUs[2]. This leads to increased length of hospital stay, unnecessary antimicrobial exposure and significant short- and long-term morbidity in preterm as well as term neonates[3]. Also, there is scarcity of Indian data on incidence, clinical profile and outcome of RSV pneumonia.

We present a case of Respiratory Syncytial Virus pneumonia in a 7 day old neonate. We also review the literature, discussing the risk factors, diagnosis and treatment of neonatal RSV.

CASE REPORT

A 7 day old baby girl was born at 36+2 weeks gestation to a primigravida mother through emergency caesarean section. Breastfeeding was initiated within 2 hours of birth. Baby was discharged home at 3rd day of life after receiving birth vaccination. At day 5 of life, baby was admitted to an outside NICU for neonatal jaundice and received phototherapy for 48 hours. Baby developed cough, cold and nasal congestion on 6th day of life which progressed in next 24 hours. Baby then developed poor oral intake and breathing difficulty for which baby was admitted to our NICU. Mother is a known case of asthma on SOS inhaled β2-agonist and inhaled corticosteroids. On general physical examination, baby was found to be dull, lethargic and had noisy breathing with moderate subcostal and intercostal retractions. Systemic Examination revealed no significant abnormality other than conducting sounds in bilateral lung fields. Baby was taken on non-invasive ventilation at optimal settings. Intravenous fluids and intravenous empirical antibiotics as per unit's protocol were started. Septic screen revealed thrombocytosis with negative C-reactive protein. X-ray chest showed developing consolidation in right para-cardiac region (Fig.1). Nebulisation with hypertonic saline and chest physiotherapy was started. On day 3rd of hospital stay, repeat X-ray chest showed bilateral hyper-inflated lung fields suggestive of bronchiolitis.

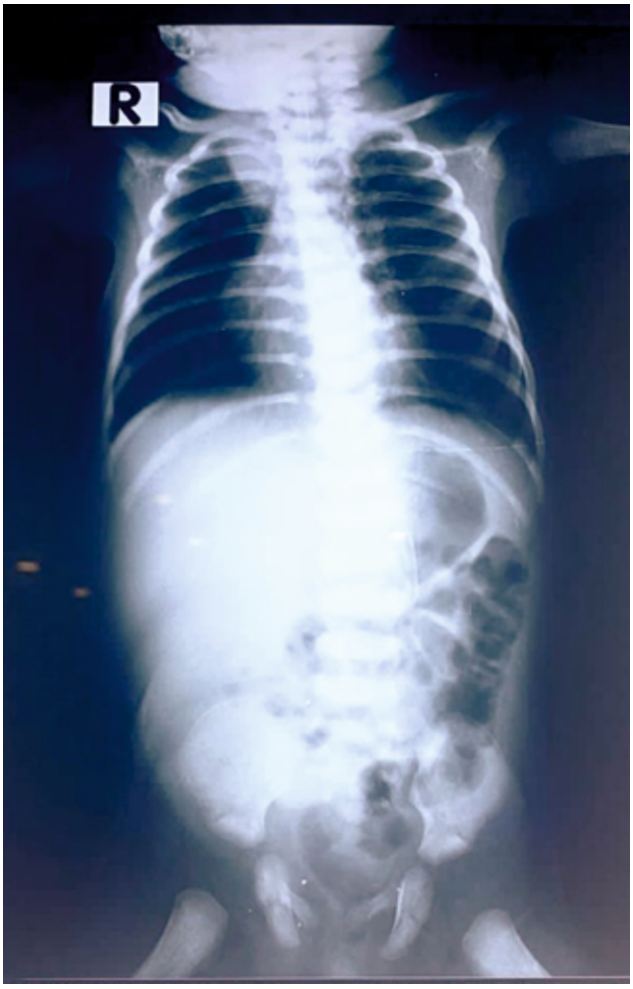

Figure 1: X-ray chest showing consolidation in right para-cardiac region

Intravenous Azithromycin was added. Nasopharyngeal swab sent for respiratory viral panel PCR was positive for Respiratory Syncytial Virus [RSV]. Supportive treatment in the form of non-invasive ventilator [NIV] support, nebulisation and chest physiotherapy was continued. Intravenous antibiotics were stopped after blood culture came out to be sterile. Baby had intermittent episodes of bronchospasm, characterised by worsening subcostal and intercostal retractions and bilateral wheeze on auscultation. These episodes warranted increase in NIV settings and nebulisation with corticosteroid [Budesonide], β2-agonist [Levosalbutamol] and Adrenaline was added. In view of persistent NIV requirement and oro-nasal copious secretion, HRCT-Chest was done which ruled out any associated lung anomaly and H-type tracheo-esophageal fistula. Supportive treatment was continued. Baby showed gradual improvement from 8th day of hospital stay [Day 10 of illness]. NIV support was gradually weaned and baby was taken on room air on day 11th of hospital stay. Baby was then started on breastfeeds which baby accepted well with no worsening respiratory distress. Baby was successfully discharged home by day 12 from admission.

REVIEW OF LITERATURE

Virus

Respiratory Syncytial Virus [Family – Pneumoviridae, Order – Mononegalevirales, Genus - Orthopneumovirus], primarily isolated from a Chimpanzee in 1956, is an enveloped, single-stranded, non-segmented, negative-strand RNA virus[4]. There are two main antigenic groups, A and B, based on surface glycoproteins. Subgroup-A infections are more common, severe, and contagious[5].

Epidemiology

The global annual rate of RSV hospitalization, as per a systematic review, was 4.4 per 1000 children aged <5 years. The highest hospitalization rates were seen during the first 6 months of life with peak rates of 25.9 per 1000 children seen in infants between 30 and 90 days of life6. RSV hospitalization rate was 4.6 per 1000 children in preterm neonates [<37 weeks gestation] which was nearly equivalent to rate of 5.2 per 1000 children for term neonates[7].

The under-developed neonatal airway, along with narrow internal diameter, poor elastic support and a tendency towards increased mucus secretion following inflammation, gets easily blocked as compared to older children. Preterm neonates, owing to their low levels of IgG antibody and immature immune system, are at an increased risk of severe and fatal RSV infections. Other risk-factors include – low birth weight, male gender, underlying lung disease or congenital heart disease, maternal smoking, history of atopy, lack of breast feeding, siblings attending daycare/kindergarten and over-crowding[8].

In India, seasonal outbreaks of RSV infection occur from October to April, with a peak observed in January or February.

Pathogenesis

RSV primarily spreads via air-borne droplets or via indirect contact with contaminated surfaces. Vertical transmission [respiratory tract of mother placenta transient RSV viremia developing foetal lung] as well as hematogenous spread from the primary site of infection to remote extra-pulmonary site can also be seen[9].The incubation period is usually between 2-8 days[10]. Viral shedding lasts for an average of 11 days. However, preterm neonates and immune-compromised hosts can stay infective up to 4 weeks.

RSV primarily infects ciliated cells of the upper respiratory tract, epithelium of the small bronchioles and type 1 pneumocytes. The predominant pathological findings include nasal and pharyngeal mucosal congestion, airway oedema, degeneration and necrosis of alveolar epithelial cells, shedding of necrotic cells and excessive mucus production that leads to bronchial narrowing, excessive aeration and disruption in gas exchange[11].

Both humoral and cellular immunity helps in clearing the RSV infection. Based on the disease severity, the body first mounts an interleukin-8 (IL-8) mediated neutrophil response. Pulmonary CD8+ T-cell response helps in viral clearing and is followed by systemic T-cell lymphopenia. Protective antibodies are produced by B-cell activating factors in the airway epithelium[12]. IFN-γ also plays a protective role but ultimately results in immunopathological injury of the lower respiratory tract.

Neonates can be effectively prevented from RSV infection by maternally transmitted antibodies. However, the degree of protection is directly proportional to the RSV antibody titre of the mother[13].

Clinical presentation in neonates

Clinical manifestation of RSV infection in neonates is often atypical and includes afebrile cough, nasal congestion, choking on milk, spitting, and rapid breathing. Apnoea can be the presenting feature in approximately 20% of neonates. On physical examination, features of rhinitis and pharyngitis along with conjunctival and tympanic membrane congestion may be seen. On auscultation, prolonged expiration, rales, inspiratory rhonchi, decreased lung sounds and increased aeration in lung periphery may be found[14]. Primary RSV infection in neonates causes severe lower respiratory tract infection, including bronchiolitis, bronchospasm and pneumonia. However, disease severity reduces with subsequent infection and LRTI is seen in only 50% of secondary infections[15].

Diagnosis

1. The National Institute for Care and Excellence16 recommends that the diagnosis of RSV infection should primarily be based on detailed history and physical examination. Additional radiological and laboratory investigations should be performed only in severe cases requiring intensive-care or in cases of atypical bronchiolitis.

2. Complete Blood Count is non-specific for RSV infection.
3. C-reactive protein can be mildly elevated.
4. X-ray chest shows hyper inflated lung fields, heterogenous infiltrates, patch-type atelectasis and increased peri-bronchial shadows. It also helps to rule out other differential diagnosis.
5. Serology – Direct Fluorescence Antibody Test with a sensitivity and specificity of 95% can provide results in 2-3 hours. But it has a limited role as a diagnostic tool as seroconversion takes approximately 2 weeks and maternally transferred antibodies are also present up to 6 months of age[17].
6. Rapid antigen diagnostic tests [RADT] have a sensitivity of 80% and a specificity of 97%[18]. They can provide results in shortest time [less than 30 minutes] and thus, can be used as screening tests. However, low sensitivity warrants negative results to be confirmed with PCR-based assays.
7. Reverse Transcriptase Polymerase Chain Reaction [RT-PCR] has a higher sensitivity as compared to rapid antigen detection test and viral culture18. Typically included as a part of multiplex PCR-based assays to detect multiple respiratory pathogens, it provides rapid and reliable results. The only disadvantage is that these assays are more expensive than RADT.
8. Viral Cell Culture demonstrating characteristic plaque morphology with syncytium formation is the gold standard test for the diagnosis of RSV infection. Rapid cell culture [shell vial] results are available within 48 hours as compared to classic cell culture that takes 4-8 days to yield result.

Prevention

A. Pertussis and Influenza vaccination during pregnancy – Maternal vaccination will provide passive immunity to newborn until they are themselves vaccinated. Currently there is no RSV vaccine available. However, preventing avoidable diseases will protect neonate's immune system and make it less vulnerable to RSV infection.

B. Hygiene and behavioural measures – As droplet infection is the major source of RSV transmission, basic hygiene rules such as frequent hand washing, keeping surfaces clean and covering mouth and nose while coughing and sneezing is the most effective preventive measure. Exclusive breastfeeding, not smoking near the child and avoiding exposure to crowded places also reduces the risk of RSV infection. In inpatient settings, infected patients should be isolated with standard and contact precautions.

C. Palivizumab prophylaxis – Palivizumab is a RSV-specific humanized IgG1 monoclonal antibody produced by recombinant DNA technology. It prevents adherence of virus to respiratory epithelium and thus, inhibits viral replication. Prophylactic Palivizumab administration is recommended during RSV season in neonates and infants who are at risk for high mortality and morbidity with RSV infection[19]. It is given intra-muscularly at a dose of 15ml/kg monthly for a total of five doses.

D. Nirsevimab – It is a recently approved monoclonal antibody that targets the RSV F-glycoprotein. It has a longer half-life and a single injection has been shown to prevent RSV-infection and hospitalization for 150 days in a multi-center, placebo-controlled RCTs[20,21].

Treatment

Neonates with marked respiratory distress, oxygen saturation below 92% on room air, clinical dehydration and apnoea should receive in-patient management[16].

A. Supportive Care: It includes respiratory support [ranging from supplemental oxygen via nasal cannula to mechanical ventilation], clearing secretions from airway, maintaining hydration, assisted feeding, chest physiotherapy and close monitoring of the clinical status. This forms the mainstay of treatment.

B. Medications**:**

1) Ribavirin – It is a synthetic nucleoside analogue licensed by FDA in 1993 against severe RSV infections. However, American Academy of Paediatrics (2021) guidelines does not recommend routine administration as it is expensive and must be given early in the disease course. Long-term aerosol administration and concerns for safety [haemolytic anaemia, leukaemia, bronchospasm, conjunctival irritation and teratogenic potential] also precludes routine use of Ribavirin in RSV pneumonia[22].

2) Inhaled hypertonic saline – AAP recommends that nebulized hypertonic saline can be administered to infants and children with RSV infection who require hospitalization[22]. Hypertonic saline increases mucociliary clearance and thereby helps in keeping the airway clean of mucus plugs.

3) Inhaled Bronchodilator [β-2 agonist like Albuterol, Salbutamol and Anticholinergics] –Bronchodilators may be tried if a strong personal or family history of atopy is present and wheezing is predominantly present. Routine use of bronchodilator therapy is not recommended[22].

4) Nebulized Adrenaline – Hartling et al[23] in their recent meta-analysis evaluated nebulized epinephrine vs. placebo in bronchiolitis and found no effectiveness of epinephrine in hospitalized patients on length of stay [LOS] or other inpatient outcomes. A recent, large, multi-center trial further demonstrated a longer LOS when epinephrine was used on a fixed-schedule as compared with an as-needed schedule[24].

Canadian Bronchiolitis Epinephrine Steroid Trial[25]compared hospitalization rates over a period of 7 days in 800 patients with bronchiolitis and found that the group of patients who received epinephrine in combination with corticosteroids had reduced hospital admission by day

7 than the double placebo group. However, the role of epinephrine in out-patient department remains controversial and a formal large, multi-center study is needed before a recommendation in this setting.

5) Inhaled or Systemic Corticosteroids –Although the Canadian Bronchiolitis Epinephrine Steroid Trial[25] showed a reduction in hospital admission rate 7 days after treatment with combined inhaled adrenaline and oral dexamethasone, a recent Cochrane Systematic Review[26] showed that corticosteroids neither reduced outpatient admissions when compared with placebo nor reduced LOS for inpatients.

In summary, infants with bronchiolitis do not benefit significantly with corticosteroids alone. However, there can be a potential benefit from combination of steroids with both α- and β-agonist agents and additional large trials are needed to clarify effectiveness of this therapy.

6) RSV-IVIG – It is a hyperimmune polyclonal immunoglobulin obtained from donors with high RSV neutralising antibodies. It has five-fold greater efficiency in neutralising RSV as compared with IVIG. RCTs showing no benefit along with other disadvantages like need for hospitalization, long-term infusion, high volume doses, sudden cyanotic episodes and necessity to avoid live-attenuated vaccines for at least 9 months precludes its use[27].

Prognosis

Most patients recover in 1-2 weeks. However, reinfections are common throughout life as RSV infection do not grant permanent immunity. Infants who required hospital admission because of RSV infection have been found to have significant long-term pulmonary sequelae, such as asthma, recurrent wheezing and impaired lung function, which may last for 10 years or longer[28].

CONCLUSION

Respiratory Syncytial Virus is the leading agent causing of respiratory illness associated hospital admissions in children under 12 months of age. It can lead to recurrent wheezing and asthma in later life. PCR-based viral detection methods should be considered in neonates with acute respiratory tract infection requiring NICU admission and those who are at high risk of RSV infection. Currently there are no vaccines available for the prevention of RSV infection. Supportive therapy in the form of respiratory support and maintaining hydration forms the mainstay of treatment in the absence of availability of specific treatment.

CONFLICT OF INTEREST: None

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