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# Surfactant Replacement Therapy in RSV-Induced Acute Respiratory Distress Syndrome (ARDS)

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## ABSTRACT

**Acute respiratory distress syndrome (ARDS) associated with severe respiratory syncytial virus infection is rare. We report a 5-month-old Indian girl who was admitted to our intensive care ward with severe respiratory failure who fulfilled the criteria for ARDS using both Murray's Lung Injury Score of > 2.5 and the American-European Consensus Conference definition for ARDS. She developed diffuse bilateral alveolar infiltrates, severe hypoxaemia ($PaO_2/FiO_2 < 100$) and required high PEEP (> 15 cm $H_20$) 24 hours after admission. RSV was isolated from her nasopharyngeal secretion. She also had clinical features suggestive of a primary immunodeficiency and had laboratory evidence of combined T and B cell defect. There was unsustained clinical improvement with a dose of surfactant administered at 36 hours of PICU stay, and she continued to deteriorate and succumbed after 19 days in the PICU.**


**Keywords: acute respiratory distress syndrome (ARDS), surfactant, respiratory syncytial virus (RSV)**

## INTRODUCTION

RSV is a major cause of respiratory tract infection in infants and young children[1,2]. The majority of patients present with signs of a mild respiratory illness ie. upper respiratory tract infection, croup or bronchiolitis. Recognised conditions predisposing to severe respiratory distress with RSV infection include a young age, ex-premature infants, congenital heart disease, and underlying immunodeficiencies[1-4]. Only a small proportion of infants require mechanical ventilation for respiratory failure and apnoea. The mortality rate in these critically ill infants remained low. Progression into ARDS with RSV-infection is rarely documented in the literature[5].

ARDS, a process of non-hydrostatic pulmonary oedema due to a variety of pulmonary and non-pulmonary insults, continues to have a high mortality rate despite advances in critical care management. The study of ARDS has been fraught by heterogeneity of definitions. Two of the most commonly employed definitions of ARDS are: 1) Murray's Lung Injury Score[6] of > 2.5 (Tables I and II) and the American-European Consensus Conference Definition[7] for ARDS (Table II). Aetiology of ARDS with regards to causation have always been categorised together as pneumonia when it involves a primary disorder in the lungs. Hence the incidence of RSV bronchiolitis leading to ARDS is not well studied.

New and innovative therapies for ARDS have been gaining more attention. With the success of exogenous surfactant replacement therapy in infant respiratory distress syndrome (IRDS), trials are being carried out in ARDS using the information gained from animal models of acute lung injury. We report a case of a 5-month-old Indian infant with ARDS associated with RSV infection treated with exogenous surfactant replacement therapy.

## CASE REPORT

A 5-month-old Indian infant was admitted to the Paediatric Intensive Care Unit in University Hospital, Kuala Lumpur after a short bout of cough and fever. She was delivered at term via spontaneous vaginal delivery with a good birth weight of 3 kg. Her problems began at the age of 3 months when she presented with recurrent episodes of chest infection. This required frequent consultation with her general practitioner who prescribed her antibiotics after each consultation. Her BCG vaccination was given at birth, and three doses of hepatitis B vaccination were given as scheduled. She was the youngest of two children born to consanguineous parents. Her elder sibling is well. There was no history of recurrent abscesses, eczema or diarrhoea and she had no history of prior cardiopulmonary disease. The current admission was preceded by a short upper respiratory tract infection which worsened causing respiratory failure which required intubation and mechanical ventilation in a neighbouring hospital. She was transferred to our PICU for further care on her first day of illness.

On admission, she was a small child (weight of 5 kg, below the third centile for her age) with marked respiratory distress and cyanosis on positive pressure ventilation. Her chest expansion was poor bilaterally with widespread inspiratory crepitations. She was ventilated with pressure controlled ventilation using a Bear Cub pressure limited infant ventilator. Intravenous midazolam and vecuronium were used for sedation and muscle paralysis to aid patient ventilator synchrony. Cefuroxime and clarithromycin

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**Table I – Lung injury score**

| | Value |
|---|---|
| Chest roentgenogram score | |
| No alveolar consolidation | 0 |
| Alveolar consolidation in one quadrant | 1 |
| Alveolar consolidation in two quadrants | 2 |
| Alveolar consolidation in three quadrants | 3 |
| Alveolar consolidation in four quadrants | 4 |
| Hypoxaemia score | |
| $PaO_2/FiO_2 > 300$ | 0 |
| $PaO_2/FiO_2$ 225 – 299 | 1 |
| $PaO_2/FiO_2$ 175 – 224 | 2 |
| $PaO_2/FiO_2$ 100 – 174 | 3 |
| $PaO_2/FiO_2 < 100$ | 4 |
| Positive end-expiratory pressure score (when ventilated) (cm $H_2O$) | |
| < 5 | 0 |
| 6 – 8 | 1 |
| 9 – 11 | 2 |
| 12 – 14 | 3 |
| > 15 | 4 |
| Respiratory system compliance score (when ventilated) (mL/cm $H_2O$) | |
| > 80 | 0 |
| 60 – 79 | 1 |
| 40 – 59 | 2 |
| 20 – 39 | 3 |
| < 19 | 4 |
| Final score | |
| No lung injury | 0 |
| Acute lung injury | 0.1 – 2.5 |
| Severe injury (ARDS) | > 2.5 |

The final score is derived by dividing the aggregate sum by the number of components used.

**Table II– The American-European Concensus Conference definition of ARDS, 1994**

| | |
|---|---|
| Oxygenation | $PaO_2/FiO_2 > 200$ (regardless of positive end-expiratory pressure level) |
| Chest radiograph | Bilateral infiltration seen on frontal chest radiograph |
| Pulmonary artery occlusion pressure | ≤ 18 mm Hg when measured or no clinical evidence of left atrial hypertension |

were added for antibacterial coverage. She continued to be hypoxaemic despite being on an $FiO_2$ of 1.0. Her $PaO_2/FiO_2$ ratio was constantly < 100. Bilateral diffuse alveolar infiltrates consistent with pulmonary oedema was seen on frontal chest radiograph. A gradual addition of positive end expiratory pressure (PEEP) up to 16 cm $H_2O$ finally improved her oxygenation. The definition of ARDS was met using the criteria recommended by the American-European Consensus Conference on ARDS: Acute disease onset; $PaO_2/FiO_2$ ratio ≤ 200 mmHg; bilateral infiltrates on radiograph (Fig 1); and absence of clinical evidence of left atrial hypertension. She also met the criteria of the lung injury score (LIS) for ARDS with a LIS of 3.0. Respiratory syncytial virus was identified using immunofluorescence antibody technique and viral cultures from her nasopharyngeal secretions on three occasions from day one to three. In addition, she had a hepatosplenomegaly of 4 cm and 3 cm respectively and there was no BCG scar noted. There were no areas of eczema, petechial rash or oral candidiasis.

Laboratory investigations showed severe hypoxaemia and respiratory acidosis. There was a mild hypochromic microcytic anaemia of 10 g/L, lymphocytopaenia with a white count of 6.2 x $10^9$/L, a differential count with neutrophils of 88%, lymphocytes of 16% (absolute lymphocyte count of 990/$mm^3$; normal for age 1500 – 3000/$mm^3$) and monocytes of 3%. Echocardiography revealed normal left ventricular function. Bronchoalveolar lavage for pneumocystis carinii and cytomegalovirus were negative. Serology for chlamydia and mycoplasma were also negative. An associated primary immunodeficiency was suspected due to the severe nature of her respiratory illness, history of recurrent infections as well as failure to thrive. There was no seroconversion to hepatitis B immunisation. The HIV antibody status using ELISA was negative. The immunoglobulin assay revealed hypogammaglobulinaemia with an IgG of 100 mg/dL (age-related normal range 345 – 1213 mg/dL), IgA: 228 mg/dL (14 – 106 mg/dL), IgM: 118 mg/dL (43 – 173 mg/dL). A T- and B-lymphocyte cell function done revealed 80% CD2 (+) cells (790/$mm^3$), 25% CD3 (+) T cells (245/$mm^3$), 20% CD4 (+) helper-inducer T cells (190/$mm^3$), 6% CD8 (+) suppressor-cytoxic T cells (59/$mm^3$), 2% CD20 (+) B cells (20/$mm^3$) and 48% CD56 (+) natural killer cells (470/$mm^3$). There were no facilities to test for red cell adenosine deaminase enzyme activity in our hospital. The combined B- and T- cell deficiency and hypogammaglobulinaemia was consistent with a probable diagnosis of severe combined immunodeficiency (SCID). The immunological evaluation only returned after the patient had succumbed precluding the use of intravenous immunoglobulins. Her respiratory status worsened over the intervening days with a maximal peak pressure requirement of 45 cm $H_2O$ and a PEEP of 16 cm $H_2O$. A dose of artificial surfactant (Survanta, Abbot Laboratories) at 4 mL/kg/body weight was administered intrathecally over 10 minutes on the second day. She showed a transient improvement with a promising reduction in oxygen requirement as well as peak inspiratory pressures. However these changes were unsustained and she subsequently deteriorated after 2 hours of administration of Survanta (Fig 2). The repeat chest radiograph showed no improvement as well (Fig 3). Her clinical status continued to deteriorate despite maximal support with development of pulmonary interstitial emphysema, cystic lung changes and pneumomediastinum. She succumbed on the 19th day of PICU stay.

## DISCUSSION

RSV infection in children typically causes an acute respiratory illness with approximately 5% of these patients developing severe illness and a smaller proportion of these requiring ventilation for respiratory failure[8]. The typical clinical feature is due to widespread inflammation, mucosal oedema and

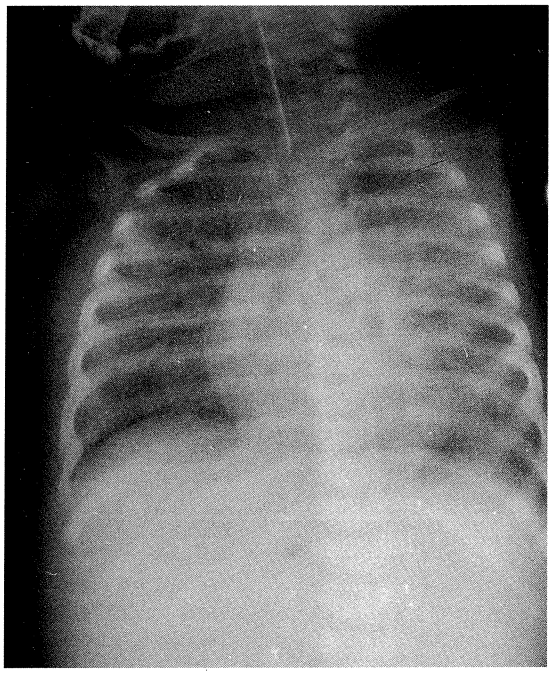

**Fig 1** – Bilateral infiltrates on radiograph.

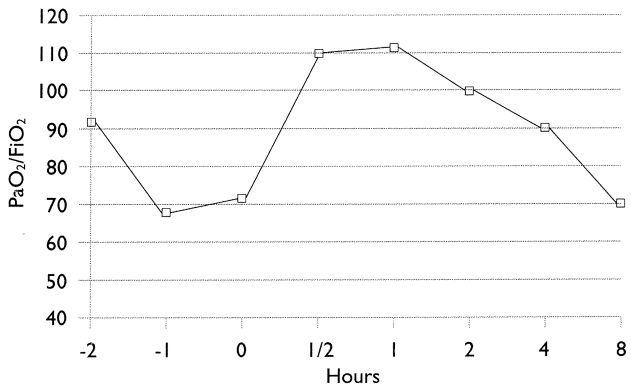


**Fig 2** – Oxygenation index after administration of surfactant.

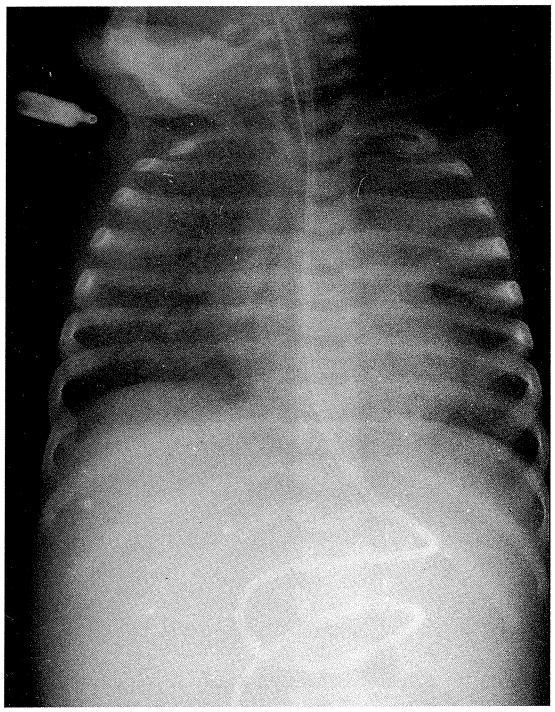

**Fig 3** – Repeat chest radiograph.

exudates in small calibre bronchi and bronchioles resulting in small airway obstruction and air trapping. Progression into ARDS with its accompanying pulmonary oedema is rarely reported[5,9,10]. The majority of patients with RSV-induced ARDS in the literature had an underlying illness and were usually less than 6 months of age. Our patient was five months old and had a clinical picture suggestive of a primary immunodeficiency (probable SCID). It appeared that severe RSV pneumonia led to the cascade of events that resulted in direct pulmonary injury with alveolar capillary disruption, permeability pulmonary oedema, hypoxaemia and decreased lung compliance characteristic of ARDS. Concerns have arisen that severe pneumonia should be excluded as a cause of ARDS. However it was agreed during the American-European Consensus Conference that diffuse lung infection should be considered as ARDS if the physiologic criteria listed were met.

It is recognised that there are two distinctive patterns of respiratory tract disease in infants with RSV-induced respiratory failure: 1) the more common obstructive small airways disease and 2) the rarer restrictive, parenchymal lung disease[10]. Patients with severe parenchymal lung disease as seen in our patient tended to have a longer course of illness and were more likely to fulfil the diagnostic criteria for ARDS. The choice of ventilation strategy depends on the type of defect seen. Hyperinflation and obstruction of small airways would require low PEEP and small tidal volume ventilation to prevent dynamic hyperinflation. On the other hand, the use of PEEP to restore functional residual capacity (FRC) and correct hypoxaemia is well recognised in cases of acute lung injury (ALI) and ARDS. Modes for ventilation of children with severe restrictive parenchymal disease include using techniques that use a level of PEEP necessary to correct hypoxaemia, limiting both fraction of inspired oxygen and tidal volume and allowing higher levels of arterial partial pressure of carbon dioxide.

The mainstay of treatment in RSV-induced respiratory failure is still conventional mechanical ventilation. Failure of conventional ventilation is an uncommon occurrence[8]. Recent studies have shown patients with ARDS to have both surfactant deficiency and inactivation. Both surfactant protein A and surfactant protein B as well as lecithin/sphingomyelin ratios were decreased[11]. These findings have formed the basis of surfactant replacement therapy in ARDS but to date results have been mixed. Current studies suggest that rapid instillation is more effective than aerosolised or slow intratracheal instillation. Early administration is also more effective than therapy late in the course of the disease and natural surfactant appears to be better than artificial surfactant due to the presence of SP-B and SP-C that prevent inhibition of exogenous surfactant by the protein rich alveolar exudates[12-15]. Survanta, an artificial surfactant was administered to our patient within 12 hours of the development of ARDS but her clinical improvement in oxygenation was disappointingly transient. Future areas of work include optimal dosage, timing and route

of administration, and diagnostic group of patients in whom surfactant would be beneficial. Exogenous surfactant may prove to be a beneficial adjunct to therapy either by directly improving pulmonary mechanics, or by allowing adequate reductions in ventilator requirement sufficient to reduce barotrauma.

Extra-corporeal membrane oxygenation (ECMO) may be needed in some cases to provide lifesaving support for RSV-infected patients. Three retrospective cohort studies have shown different survival rates, 50% in two studies and 96% in the third[16-18].

It is unsure whether ECMO improves survival in these critically ill children. Inhaled nitric oxide is another promising modality of treatment but the number of treated patients have been too small to make any definitive conclusions[19]. The mortality in ARDS remains high despite advances in intensive care. There is however reasons to believe that ARDS caused by RSV carries a more benign course particularly in those without an underlying illness[10]. Previous reports showed that severe RSV infection in SCID patients were uniformly fatal (2 cases)[9,10]. RSV infection was more severe in those with underlying illness like congenital heart disease, chronic lung disease and immunodeficiency.

## CONCLUSION

We described a well documented case of RSV-induced ARDS in an infant with underlying immunodeficiency in whom surfactant replacement therapy showed no beneficial effect. ARDS although rare, can occur in severe RSV infection and often presents with a severe restrictive parenchymal lung disease requiring a different ventilator strategy from other cases of RSV-induced respiratory failure. Mortality rates remain high especially in infants with underlying diseases. It remains unclear if early institution of separate modes of therapy like surfactant replacement therapy, inhaled nitric oxide or extracorporeal membrane oxygenation would alter the outcome.

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