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Life-Threatening RSV Infections in Children

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1. Introduction

During the middle of the 20th century, Chanock and co-workers recovered an cytopathogenic agent from lung secretions of young infants with lower respiratory tract disease (LRTD). This agent was found out to be similar to an agent that was identified in an outbreak of infection in chimpanzees resembling the common cold (Chanock et al, 1957; Morris J.A. et al, 1956). Because of its characteristic cytopathologic findings in tissue culture where it forms syncytia of epithelial cells, the virus was named *respiratory syncytial virus* (Chanock et al, 1957). From serological studies it was observed that almost all children have been infected by RSV by the age of two years (Glezen et al, 1986). Since then, RSV has been identified as the most important causative agent of viral LRTD (Hall, 2001). Approximately 100.000 infants are annually admitted with RSV induced bronchiolitis in the United States, and the number of hospitalizations is increasing (Shay et al, 1999). Because of this, RSV associated disease imposes a major burden on health care resources (Leader et al, 2003). Furthermore, RSV is increasingly being recognized as an important pathogen causing severe LRTD in elderly and immunocompromised patients (Falsey et al, 2005).

This chapter reflects on the current knowledge about RSV in critically ill children admitted to the pediatric intensive care unit (PICU) and its possible therapeutic options.

2. Epidemiology of RSV

RSV (genus *pneumoviridae*, family of *paramyxoviridae*) is a single stranded enveloped RNA virus. The RSV genome codes for ten major proteins (Hacking et al, 2002). Of these proteins, the F (fusion) and the G (attachment) glycoprotein are the major surface antigenic determinants. Two antigenic strains of RSV, group A and group B, can be identified. Both groups co-circulate together but also independently from each other during annual epidemics (Hall et al, 1990). The clinical spectrum of RSV associated disease extends from mild upper respiratory tract infection to severe lower respiratory tract infection including bronchiolitis and pneumonia (Hall, 2001). Re-infections occur frequently, although they tend to be mild (Henderson et al, 1979).

Severe RSV infection necessitating mechanical ventilation (MV) occurs in 2 – 16% of previously healthy infants (Leclerc et al, 2001). This percentage may increase up to 30 – 35% among high-risk patients such as children with congenital heart disease (CHD), chronic lung disease (CLD), compromised immune function, postnatal age less than 6 weeks and

premure birth (i.e. less than 37 weeks gestational age) (Wang et al, 1996). The mean duration of conventional MV may be as long as 10 days, but in a proportion of ventilated patients alternatives mode such high-frequency oscillatory ventilation (HFOV) or extra-corporeal membrane oxygenation (ECMO) are necessitated when severe impaired oxygenation or ventilation persists (Guerguerian et al, 2004; Leclerc et al, 2001). Usually mortality rates are less than 1% for previously healthy infants, although these percentages may increase up to 10% among high-risk infants (Shay et al, 2001).

3. Clinical manifestations of RSV in the PICU

RSV LRTD is usually referred to as "bronchiolitis" because of the clinical presence of audible airflow limitation on expiration in a significant proportion of infected infants and the classic hyperinflation on chest radiograph. In infants admitted to the PICU an increase in total respiratory system resistance compatible with obstructive disease has also been demonstrated (Gauthier et al, 1998; Hammer et al, 1995; Hammer et al, 1997; Mallory Jr et al, 1989). Nevertheless, RSV LRTD is in fact a heterogeneous disease, implicating that it is incorrect to label all RSV LRTD as bronchiolitis (Isaacs, 1998). This is of importance because of the proposed differences in ventilatory strategies needed to treat obstructive or restrictive disease (Frankel et al, 1999). Furthermore, identification of the clinical phenotype aids in targeting a specific population of infants for a therapeutic modality.

In critically ill children RSV LRTD can also be characterized as a restrictive disease (Frankel et al, 1999). Hammer and co-workers evaluated 37 mechanically ventilated infants with RSV and were able to categorize them as having obstructive or restrictive disease based upon the findings from pulmonary function testing (PFT) (Hammer et al, 1997). Ten infants had decreased respiratory system compliance (Crs) compatible with restrictive disease in conjunction with four-quadrant alveolar consolidation on chest radiograph compared to healthy controls. The remaining 27 had increased respiratory system resistance (Rrs), compatible with obstructive disease. Infants with restrictive disease required prolonged ventilation compared to infants with obstructive disease. However, infants with underlying diseases such as prematurity and/or chronic lung disease were not excluded in their analysis. Especially among infants with restrictive disease there were three infants with CLD. By including these infants, it cannot be ruled out they had pre-existing lung abnormalities that might contribute to altered respiratory system mechanics. For instance, prematurely born infants with CLD have higher Rrs that predisposed them to suffer from symptomatic RSV LRTD compared to controls (Broughton et al, 2006). Hence, the issue of clinical phenotype is still subject of scientific debate.

Unfortunately, in most PICU's PFT is not done routinely. Alternatively, ventilatory indices characterizing the efficacy of gas exchange might be used. These include the oxygenation index (OI) and the alveolar-arterial oxygen gradient ($Aa\text{-}DO_2$). Tasker and co-workers found an $Aa\text{-}DO_2$ > 400 mmHg during the first 24 hours of mechanical ventilation and mean airway pressure (MAP) > 10 cm H_2O associated with radiographic appearances suggestive of RSV restrictive disease (Tasker et al, 2000). All infants were previously healthy, and had upon PICU admission four-quadrant alveolar consolidation on their chest radiograph. However, their definition of severe RSV LRTD was based upon a chest radiograph scoring system developed for prematurely born infants with infant respiratory distress syndrome (IRDS) and has not been validated for patients with RSV to our knowledge (Maconochie et

al, 1991). Furthermore, their findings have not been validated yet. We have retrospectively studied parameters for gas exchange in 53 mechanically ventilated infants with RSV LRTD admitted between 1995 and 2005, and were unable to detect significant differences in oxygenation index (OI) or alveolar-arterial oxygen gradient ($Aa\text{-}DO_2$) between infants with radiological classified restrictive disease and obstructive disease (manuscript in preparation). We further observed a comparable duration of MV between infants with obstructive and restrictive disease. Our findings strengthen our assumption that RSV LRTD is a heterogeneous disease that cannot be strictly dichotomized into a restrictive and obstructive disease.

RSV is also a neurotrophic virus. Our group has found that it causes apnoea (defined by a cessation of respiration or a bradycardia with accompanying cyanosis for a period of 20 seconds or longer) in approximately one out of every five patients presenting with RSV (Kneyber et al, 1998). In fact, apnoea may be the presenting symptom without any other symptoms of respiratory tract infection. The odds for MV were 6.5-fold increased among infants who present with RSV – associated apnoea. The exact mechanism underlying RSV-associated apnoea is unknown, although it has been observed that the apnoea is of central origin (Rayyan et al, 2004).

Cardiovascular compromise during RSV infection has been reported by various authors. Severe RSV infection may mimic shock (Njoku et al, 1993). Nearly half of all infants admitted to the PICU were found to have elevated cardiac enzyme levels (Checchia et al, 2000; Eisenhut et al, 2004). Cardiovascular support either by fluid boluses or inotropic drug use is not seldomly necessitated in ventilated infants (Checchia et al, 2000; Eisenhut et al, 2004; Kim et al, 1997). Life-threatening disturbances of the cardiac rhythm have also been described in critically ill patients with RSV (Playfor et al, 2005; Thomas et al, 1997).

There is much controversy whether or not severe RSV infection is associated with increased occurrence of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). One group of investigators have reported that 33% infants admitted to the PICU developed hyponatraemia (serum sodium < 136 mmol/L) (Hanna et al, 2003). Four of them had a hyponatraemic seizure upon PICU admission. Van Steensel-Moll and co-workers observed increased ADH levels in mechanically ventilated children compared with non-ventilated children (Steensel-Moll et al, 1990). However, these were not significantly correlated with serum sodium levels.

4. Bacterial co-infections

Many if not all infants admitted to the PICU with RSV LRTD have antibiotics prescribed. Clinicians often assume that a concurrent bacterial pulmonary infection is probably (partially) accountable for the development of respiratory failure due to RSV. Nevertheless, the occurrence of severe infections is low. Randolph *et al* retrospectively studied the number of positive cultures from blood, urine, cerebrospinal fluid and endotracheal aspirates upon PICU admission among 63 mechanically ventilated previously healthy infants (Randolph et al, 2004). All of these infants were treated with antibiotics. They observed a low percentage (< 2%) of concurrent bacterial blood stream infection. In addition, 24 (38.1%) had positive cultures from endotracheal aspirates that could be linked to either possible or probable bacterial pneumonia. These observations were supported by the findings of Bloomfield *et al*

(Bloomfield et al, 2004). They observed bacteraemia in 6 children out of 208 PICU admissions. Four infants were mechanically ventilated. All of them were prematurely born or had congenital heart disease. Our group has also studied retrospectively the occurrence of concurrent bacterial infection in 65 mechanically ventilated infants during 1996 – 2001 (Kneyber et al, 2005a). In 38 of these infants microbiological investigations were performed. All had antibiotics upon PICU admission. We found only one positive culture from blood and 37.5% positive cultures from endotracheal aspirates compatible with bacterial pneumonia. Infants with concurrent bacterial infection had similar CRP concentrations and white blood cell counts compared to infants with negative cultures. In addition, the presence of bacterial pulmonary infection upon PICU admission was undetectable by the OI as this was equal among infants with and without positive cultures. There were two additional remarkable finding from our study. First, concurrent bacterial infection occurred almost exclusively in previously healthy, term born infants. Second, infants with positive concurrent bacterial infection required prolonged ventilatory support (14.3 ± 2.4 versus 10.6 ± 1.0 days).

All retrospectively made observations were confirmed by a study from Thorburn *et al* (Thorburn et al, 2006). Their group prospectively collected endotracheal aspirates in 165 mechanically ventilated infants during three consecutive RSV seasons. They observed that 21.8% had concurrent bacterial pneumonia upon PICU admission. Strikingly, these infants also required prolonged ventilatory support compared to infants without bacterial pneumonia. Only 36% of these infants had antibiotics on PICU admission. The majority of bacterial pneumonias occurred in infants with pre-existing morbidity.

It may thus be concluded that at least in (significant) proportion of infants hospitalised to the PICU with severe RSV LRTD a bacterial pneumonia (partially) contributes to the development of respiratory failure. Whereas others report such findings among children with pre-existing morbidity, we were unable to confirm this. At present therefore, it seems rational to refrain from the routine use of antibiotics in children admitted to the PICU. Immediate investigation of the endotracheal aspirate may identify those children in whom antibiotics are justified, although this hypothesis calls for further study such as a randomized controlled trial.

5. Pathophysiology

The pathophysiological mechanisms underlying RSV-induced respiratory failure with subsequent necessitation of MV are not fully elucidated. Various pathways can be proposed that most likely interact with each other, including viral load and strain, pre-exististing structural abnormalities and the host immune response. Pre-existing structural abnormalities of the respiratory system may predispose prematurely born children and children with CLD or CHD to a severe disease course. Prematurely born but otherwise healthy infants have an underdeveloped respiratory system that is easily compromised by the direct toxic effects of an infectious agent, such as epithelial necrosis due to invading virus (Welliver, 2003). Young children with CLD have structural abnormal airways that collapse easily as well as structural pulmonary abnormalities predisposing them to severe disease necessitating MV (Welliver, 2003).

Viral strain is not accountable for disease severity. We observed that the need for PICU admission and MV is equally distributed among infants with RSV group A and B (Kneyber

et al, 1996). In contrast, the effect of viral load on disease severity is less clear. Conflicting data have been reported on differences in viral load between ventilated and non-ventilated infants. DeVincenzo *et al* were unable to find significant differences in viral load obtained from nasal washes between previously healthy ventilated (n = 22) and non-ventilated infants (n = 119) (5.185 versus 4.963 log pfu/mL) (DeVincenzo et al, 2005). Others, however, observed significantly higher nasal viral load among ventilated (n = 15) versus non-ventilated previously healthy infants (n = 24) (5.06 ± 0.34 vs. 3.91 ± 0.35 log pfu/mL, p = .022) (Buckingham et al, 2000). Only one group of investigators has exclusively focused on differences in viral load among ventilated infants. Van Woensel *et al* found a higher viral load in tracheal aspirates of infants (n = 14) who met criteria for "severe RSV LRTD" (PaO_2/FiO_2 ratio ≤ 200 mmHg and a mean airway pressure (MAP) > 10 cmH_2O (72.0 ± 28.0 RNA copies) compared to infants (n = 8) with "mild" disease (21.1 ± 9.2 RNA copies, p = .20) (van Woensel et al, 2003a). At present, there are no reports on differences in viral load among various categories of mechanically ventilated high-risk infants. Further studies are awaited.

Various authors have postulated that the immune response against RSV plays an important role in determining disease severity, especially when there is no pre-existing disease (Bont et al, 2002). It is subject of debate whether or not the immune response against RSV is protective or disease-enhancing. Results from animal studies have led to the assumption that an overshoot of the T-cell response towards a T – helper 2 profile may be responsible for severe disease (Cannon et al, 1988). This skwewing towards a T – helper 2 response has not been universally confirmed to occur in children with RSV LRTD (Bont et al, 2002).

A good humoral immune response is necessary to prevent severe RSV LRTD. Low titers of neutralising antibodies have been found to be associated with severe RSV LRTD (Glezen et al, 1981; Karron et al, 1999). Yet, this may specifically apply for infants born prematurely as in general they lack sufficient titers of protective immunoglobulin G neutralising antibodies because placental transport of IgG occurs late in gestation, near the end of the third trimester. Early post-natal life is associated with a physiological immune deficiency defined by hyporesponsiveness of mononuclear phagocytes to stimuli and a diminished T – cell response (Marchant et al, 2005; Marodi, 2006). This low level of immune response could very young previously healthy infants render susceptible for severe disease.

Next to this, a good cellular immune response is also necessary to prevent severe RSV LRTD. Low numbers of T – cells are found in peripheral blood samples of ventilated infants compared to non-ventilated infants, although this also may suggest recruitment of activated T – cells to the lungs (de Weerd et al, 1998). More importantly, low levels of IFN-γ (a T – helper 1 cell cytokine) were found in nasopharyngeal aspirates of mechanically ventilated children compared to non-ventilated children (Bont et al, 2001). In addition, monocyte-derived interleukin (IL) 12 was observed to be inversely related to the duration of MV. IL-12 promotes the differentiation of naïve CD4 –positive T cells into T-helper 1 cells (Ramshaw et al, 1997). Finally, mononuclear cells of ventilated infants exhibited diminished ex-vivo lymphoproliferative responses and the capacity to produce IFN-γ and IL-4 compared to non-ventilated infants.

It may thus be concluded that severe RSV LRTD in healthy term and pre-term born infants originates from an immature immune system so that they cannot neutralise the virus sufficiently. For children with pre-existing abnormalities of the respiratory system it is

probably the combination of both. In addition, it cannot be ruled out that genetic polymorphisms also play an important role in the host susceptibility for severe RSV LRTD. Future research should be directed towards understanding the pathophysiological mechanisms underlying severe RSV LRTD and are eagerly awaited.

6. Treatment of severe RSV LRTD

Therapeutic management of mechanically ventilated infants with severe RSV LRTD can either be curative or supportive. Curative treatment includes the virostatic drug ribavirin or corticosteroids, whereas bronchodilators and exogenous surfactant are supportive.

Three reports reporting the efficacy of ribavirin were reviewed systematically in a Cochrane review (Randolph et al, 2000). Results from a total number of 104 mechanically ventilated infants were pooled. The use of ribavirin was associated with a significant decrease in the duration of MV (mean difference 1.2 days (95% confidence interval -.2 to -3.4, p = 0.03). Normal saline was used as placebo in two studies, whereas sterile water was used in the third study. However, the beneficial effect of ribavirin was discarded when the one study using sterile water instead for normal saline for control was excluded from analysis. This could be explained by the serious side-effect of sterile water, being induction of bronchospasmn. Thus, there is not rationale for the use of ribavirin. Furthermore, is not easy to administer and is associated with teratogenic side-effects.

Others have explored the efficiacy of corticosteroids (Buckingham et al, 2002; van Woensel et al, 1997; van Woensel et al, 2003b; van Woensel et al, 2011). Unfortunately, the results of these studies cannot be easily compared because of the different dosing and duration of treatment. Van Woensel *et al* initially performed a post-hoc analysis of 14 mechanically ventilated infants in their original trial of prednisolone 1 mg/kg for seven days versus placebo in hospitalised children with RSV (van Woensel et al, 1997). They observed a non-significant difference in mean duration of MV (4.7 ± 2.91 versus 6.3 ± 4.23 days). Subsequently, they designed a randomised clinical trial in mechanically ventilated infants comparing dexamethason 0.15 mg/kg/day every 6 hours for 48 hours with placebo in 85 patients (van Woensel et al, 2003b). No significant difference in mean duration of MV between the two treatment arms was found. Yet, post-hoc analysis suggested that corticosteroids might be beneficial among ventilated infants who met criteria for mild disease as derived by Tasker *et al* (Tasker et al, 2000). Similar results were obtained in a study including 41 mechanically ventilated infants (Buckingham et al, 2002). Recently, Van Woensel *et al* have completed a third RCT (the so-called STAR-trial) based upon the post-hoc analysis from their second RCT (van Woensel et al, 2011). Eighty-nine patients were stratified according to oxygenation abnormalities: PaO_2/FiO_2 < 200 and MAP > 10 cmH_2O (N = 45) vs PaO_2/FiO_2 >200 and MAP < 10 cmH_2O (N = 44) and randomized to either dexamethason 0.15 mg/kg/day every 6 hours for 48 hours with placebo. The study showed that the duration of MV was not significantly reduced in both stratification arms by dexamethason. Hence, the use of corticosteroids cannot be supported.

The efficacy of bronchodilators for ventilated infants with RSV LRTD has been explored in three different studies (Derish et al, 1998; Hammer et al, 1995; Mallory, Jr. et al, 1989). Mallory and co-workers observed a ≥ 30% improvement of peak expiratory flow at 25% (MEF_{25}) of functional residual capacity (FRC) in 13 out of 14 mechanically ventilated

children with RSV LRTD (Mallory, Jr. et al, 1989). Pulmonary function was assessed by deflation flow-volume curve analysis. Hammer *et al* performed a more elegant study by excluding infants with restrictive disease (Hammer et al, 1995a). However, only 10 out of 20 infants with obstructive RSV LRTD responded to nebulised albuterol (defined by a ≥ 2-fold improvement of intra-individual coefficient of variation for MEF_{25} en Rrs. Derish *et al* included 25 infants and observed a significant increase in PEF at FRC and decrease in Rrs in some patients (Derish et al, 1998). Of note, all three studies incorporated infants with pre-existing morbidity, and none were designed to detect an effect on the duration of MV and/or PICU stay. The routine use of bronchodilators, therefore, seems unjustified. Recently, Levin and co-workers confirmed the absence of beneficial effect of bronchodilators (i.e. norepinephrine, levalbuterol, and racemic albuterol) (Levin et al, 2008).

Low levels of surfactant phospholipids and proteins as well as a diminished function of surfactant (lowering surface tension at the alveolar-capillary level) has been described (Kneyber et al, 2005b). Hence, the the use of exogenous surfactant seems highly rational. Its effect on disease course has been explored in three RCTs (Luchetti et al, 1998; Luchetti et al, 2002; Tibby et al, 2000). The group of Luchetti *et al* performed two studies investigating porcine surfactant versus no placebo (Luchetti et al, 1998; Luchetti et al, 2002). In their first study 20 children with bronchiolitis of whom 20% were RSV positive were randomized to receive either 50 mg/kg porcine surfactant once, or nothing (Luchetti et al, 1998). In their second, and methodologically more sound, study 40 children with RSV LRTD were randomized (Luchetti et al, 2002). Not only oxygenation improved in both studies, but the mean duration of MV was also significantly different between the surfactant and the placebo group (4.4 ± .4 vs 8.9 ± 1.0 days in the first study and 4.6 ± .8 vs 5.8 ± .7 days in the second study). These findings were confirmed by a study by Tibby *et al*, randomizing 19 infants to receive either 100 mg/kg bovine surfactant twice or air placebo (Tibby et al, 2000). Furthermore, a trend towards a reduced duration of MV was observed (126 hours vs 170 hours in the control group). Taken together, the findings of these three studies strongly call for a RCT with duration of MV as primary endpoint.

MV remains the mainstay of supportive therapy for infants with RSV – induced respiratory failure. Interestingly, there are no randomized controlled trials (RCT) on for instance various ventilatory strategies (volume controlled versus pressure controlled) or the level of positive end-expiratory pressure (PEEP) (Leclerc et al, 2001). MV with heliox has been scantily studied among infants with RSV LRTD. From a pathophysiological point of view MV with heliox seems rational. Heliox has a density that is one-seventh that of air, resulting in a decreased resistance to gas flow (Gupta et al, 2005). There is one trial investigating the effect of MV with heliox in various concentrations in ten infants with RSV LRTD (Gross et al, 2000). No beneficial effect could be demonstrated. As the study has methodological flaws, and no attempt was made to discriminate clinical phenotype of RSV LRTD, the role of MV with heliox requires further study. Our group has undertaken a pilot-study in 13 ventilated infants with RSV LRTD. Heliox 60/40 (i.e. 60% helium and 40% oxygen in the inspired gas) significantly reduced the Rrs compared with conventional gas mixture although CO_2 exchange was not improved (Kneyber et al, 2009). Our findings warrant follow-up in a large RCT.

Until now, the mainstay of therapy for mechanically ventilated infants with RSV LRTD has been symptomatic. Judging the outcomes of the various RCTs, it is highly unlikely that this

will change in the near future. The only promising therapeutic modality seems exogenous surfactant, although this has no direct curative effect.

7. Prevention

Vaccination against RSV will not readily be available, but passive immunisation can be applied (Kneyber et al, 2004). Passive immunization can be achieved through palivizumab, which is a monoclonal antibody directed against the F – glycoprotein. Presently, its use is advised for (a) infants not older than 12 months without CLD born after a gestation of 28 weeks, (b) infants not older than six months without CLD born after a gestation of 29 to 32 weeks, and (c) infants born after a gestation of 32 to 35 weeks with at least two of the following risk factors: attending child care, having school-aged siblings, being exposed to environmental air pollutants, having congenital abnormalities of the airways, or being diagnosed with severe neuromuscular disease. Palivizumab is also advised for children younger than two years of age with CLD or a hemodynamically significant CHD (Meissner et al, 2003).

The effect of routine passive immunization on the number of PICU admissions as well as duration of MV is not clear. In the IMpact study an overall reduction of 55% in hospitalizations was found among palivizumab recipients (N = 1002 vs 500 controls). However, the number of PICU admissions (1.3% vs 3%) or number of mechanically ventilated children (0.2% vs .7%) was not significantly affected (The IMpact-RSV Study Group, 1998). Children with congenital heart disease were separately studied (639 palivizumab recipients vs 648 controls) (Feltes et al, 2003). Again, the overall reduction of 45% in hospitalizations was not observed for the number of PICU admissions (2% vs 3.7%) or mechanically ventilated children (1.3% vs 2.2%). Two post-licensure studies after the introduction of palivizumab have been reported. Pedraz and co-workers studied the efficacy of palivizumab in four consecutive RSV seasons (non-prophylaxed children (N = 1583) admitted between 1998 – 2000, and prophylaxed (N = 1919) children admitted between 2000 – 2002) in Spain (Pedraz et al, 2003). The number of children admitted to the PICU (13% vs 20%) or requiring MV (8% vs 11%) were comparable. Similar observations were made in a national survey performed in Israel during two consecutive RSV seasons (2000 – 2002), including 296 children (Prais et al, 2005). It thus seems that monthly prophylaxis with palivizumab does not have an effect on the occurrence of severe RSV LRTD necessitating PICU admission and/or MV. This suggests that not only virological and/or immunological factors are (partially) responsible for the development of severe RSV LRTD.

8. Long term effects

Long-term follow-up studies of children hospitalised with RSV LRTD have irrespective of age consistently shown impaired pulmonary function compared with children who had no apparent infecting agent, mainly characterized by an obstructive pattern (i.e. increased airway resistance) (Cassimos et al, 2008; Dezateux et al, 1997; Singleton et al, 2003; Stein et al, 1999). This increase in airway resistance coincides with episodes of recurrent wheezing resembling childhood asthma in up to 50% of children, and not results in a high use of asthma medications but also in a substantial decrease in parental-reported health-related quality of life of the child (Bont et al, 2000; Bont et al, 2004; Kneyber et al, 2000; Stein et al, 2004). Importantly, in general there is no data available on pulmonary function after being

mechanically ventilated for RSV LRTD (Ermers et al, 2009). Mechanical ventilation is life-saving for patients with RSV induced respiratory failure. Yet, numerous experimental studies have shown that mechanical ventilation induces a pulmonary inflammation that aggravates lung injury leading to irreversible damage. This has been labelled "double-hit principle" (Tremblay et al, 1998; Tremblay et al, 2006). More specifically, lung inflammation and programmed cell death were enhanced by mechanical ventilation in a mouse model of RSV LRTD (Bem et al, 2009).

9. Conclusion

RSV is an important cause of serious morbidity annually occurring in paediatric critical care units. At present, the mainstay of therapy for mechanically ventilated infants is still symptomatic. The routine use of ribavirin or corticosteroids cannot be recommended. However, there are new and promising (supportive) treatment modalities emerging such as the use of exogenous surfactant or mechanical ventilation with heliox. Future research should also be directed towards a better understanding of the pathophysiological mechanisms underlying severe RSV LRTD to gain insight why infants need to ventilated and what the effects of mechanical ventilation in combination with RSV itself are on long term outcome. Only then it will be possible to develop new curative treatments and to identify patients who might benefit from such a treatment. In the mean time, we continue our endless care and devotion to these infants.

10. References

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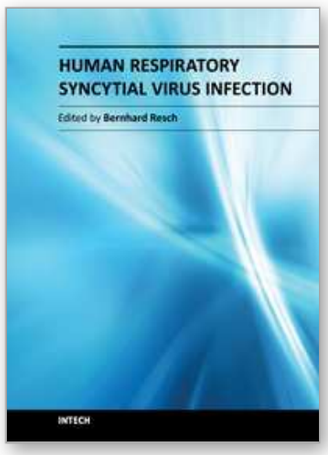

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In this online Open Access book on "Human RSV Infections", several distinguished authors contribute their experience in respiratory syncytial virology. A major focus lies on the fascinating pathophysiology of RSV and represents recent and actual work on different mechanisms involved in the complex pathogenesis of the virus. The second section elucidates epidemiologic and diagnostic aspects of RSV infection covering a more clinical view of RSV disease. At last, treatment modalities including the search for a vaccine that is still not in sight are discussed and conclude this book, thus building up a circle that runs from experimental models of RSV related lung disease over clinical aspects of disease to the latest news of therapeutic and prophylactic approaches to human RSV infection.

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