Lower respiratory tract infection caused by respiratory syncytial virus. The short-term and the long-term efficacy of corticosteroids
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General discussion and summary
General discussion

RSV is the most common causative infectious agent of respiratory infections in infants and young children. In addition, in children that are hospitalised with bronchiolitis RSV is the most common causative agent. The number of bronchiolitis hospitalisations in the Netherlands has increased during the last decade of the 20th century to almost 3000 annually (Chapter 1). This increasing number of hospitalisations underscores the growing socio-economic impact of RSV disease and stresses the urgent need for an effective vaccine as well as adequate treatment for severe RSV-LRTI. Unfortunately, despite the large number of trials that have been performed in the search for therapeutic modalities for RSV-LRTI, up to date no adequate treatment for RSV-LRTI is available (Chapter 2). The explanation for this lack to control RSV infections probably is multifactorial. First, most intervention trials have focussed on treatment of bronchial constriction and airway inflammation, but probably also other factors related to the characteristics of the respiratory system in infants play a role in the pathogenesis of RSV-LRTI. Second, RSV infections are mild and self-limiting in the majority of the cases and it is likely that most benefit of treatment is to gain in patients with severe RSV infections. Finally, potential effective treatment for RSV-LRTI may be obscured by the heterogeneity of the investigated populations. This is caused by the lack of uniformity in the definitions of infant bronchiolitis and pneumonia, but also by the fact that RSV-LRTI is not an uniform disease and that inter-individual differences in the balance between viral cytotoxic and disease augmenting immunological phenomena strongly determine the pathogenesis and therefore the response to certain forms of treatment.

RSV-LRTI is, at least partially, an immune mediated disease. This pivotal role of the immune response is not only of importance during the acute phase but potentially also contributes to development of long-term airway morbidity. It is likely that in natural infection a fine balance exists between the immune response and viral cytopathic effects. Subtle changes in the interaction between inflammatory cells and opathogenetic effects or pronounced cytopathic viral effects depending on the overhand of one of these two factors. Evidence for the balance between viral injury and immune mediated phenomena stems from experimental, animal as well as human studies.

Experimental studies

Airway inflammation during RSV-LRTI is caused by direct cytopathic effects of the virus that consists of persistent degeneration and regeneration of bronchial epithelial cells, loss of ciliary activity and formation of syncytia.\textsuperscript{9,10} In addition, beside structural histopathological changes RSV may cause acute and chronic functional alterations in the neural control of the airways.\textsuperscript{11}

The immune response during RSV infection is in great extent orchestrated by the respiratory epithelial cells, that are able to attract and activate inflammatory cells upon exposure to RSV. Very interestingly, it has been shown that this pro-inflam-
matory response is also initiated by inactive RSV, supporting the concept of the possible overshoot of the immune response during RSV disease.\textsuperscript{12,13}

\textit{Animal studies}\n
The mouse model has been used in many studies to clarify the role of the individual inflammatory cells during RSV disease.\textsuperscript{14} In particular, the role of the individual T-cell subsets has been studied extensively in mice and results have helped to understand the vaccine debacle in the 1960s. In these studies it has been shown that FI-RSV elaborates mainly a Th-2 response and this unbalanced immune response leads to enhanced pulmonary pathology. It has been suggested that formalin inactivation of the virus changes epitopes within the F and G protein that normally generate the neutralising antibodies.\textsuperscript{15}

In this light it has been suggested that also wild type infection in some cases may give rise to a Th-2 reaction. However, most animal and human studies could not demonstrate that natural infection with RSV leads to a Th-2 response.\textsuperscript{16-19} Most likely, the immunology and immunopathology during RSV disease must be seen in a broader and more complex context than solely the Th-1/Th-2 paradigm.

Probably the vaccine triggered a rapid amplification of Th-2 lymphocytes in absence of neutralising antibodies and a adequate cytotoxic T-lymphocyte response, resulting in recruitment and activation of other inflammatory cells causing airway damage.

\textit{Human studies}\n
Our first intervention trial was conducted to evaluate the efficacy of oral prednisolone in hospitalised patients with RSV-LRTI, including patients that needed mechanical ventilation. Although we found no beneficial effect in the whole study cohort, in a post hoc analysis we found that prednisolone accelerated recovery in patients with severe RSV-LRTI. In particular, prednisolone shortened the duration of mechanical ventilation and length of stay in the hospital in mechanically ventilated patients (\textit{Chapter 3}). This is in contrast to many other studies that evaluated the efficacy of corticosteroids in RSV-LRTI. However, our study was the first that also included mechanically ventilated patients, as representatives of patients with most severe RSV disease. These results suggest that immune mediated processes may play a more prominent role in patients with severe disease than in milder cases.

In order to further assess the role of corticosteroids in patients that need mechanical ventilation for RSV-LRTI a new trial was undertaken. The aim of this trial was to evaluate the efficacy of dexamethasone in this particular group. Unexpectedly, the results of this trial did not confirm our previous findings, since no beneficial effect of dexamethasone could be demonstrated in the whole study cohort. Again, in a post hoc analysis a strong difference in efficacy between patients with bronchiolitis and those with pneumonia was found. Bronchiolitis and pneumonia are the two principal clinical manifestations of RSV-LRTI and were distinguished from each other on the base of oxygenation anomalies at presentation, as described before.\textsuperscript{20} In patients
who suffered from bronchiolitis dexamethasone led to more than 4 days shorter mechanical ventilation whereas in patients suffering from pneumonia there appeared to be no effect (Chapter 4).

Taken together our results suggest that immunologic mechanisms play a more prominent role during severe RSV bronchiolitis than during severe RSV pneumonia. One could hypothesise that in patients suffering from bronchiolitis the immune response leads to clearance of the virus, but a certain overshoot leads to disease enhancing effects, resulting in obstructive airway manifestations (i.e. bronchiolitis). If the immune response insufficiently leads to clearance of the virus, direct virological histopathological effects may prevail, resulting in restrictive airway manifestations, i.e. pneumonia (Figure 8.1). This could explain why corticosteroids are less effective in patients with pneumonia. Our hypothesis is supported by the finding that on admission the RSV load was lower, whereas several inflammatory variables, such as IL-8 level, white blood cell count in tracheal aspirate were higher in patients with bronchiolitis compared to those suffering from pneumonia (Chapter 5). A more outspoken cell mediated cytotoxic response in RSV bronchiolitis than in RSV pneumonia has also been described by others.21,22 Moreover, in autopsy series more abundant presence of virus during pneumonia in comparison to bronchiolitis has been described.23-25

Host factors, viral factors and environmental factors may influence the balance between viral effects and the immune response. In this view it is very interesting that besides pre-existing pulmonary or cardiac disease also prematurity and young age are risk factors for a severe course of RSV disease. Immaturity of the immune system might play a key role in this respect.26,27 The immaturity of the natural cellular immune response of preterm infants and neonates might lead to an inadequate immune reaction during RSV infection, potentially leading to diminished viral control and therefore to pneumonia. In our cohort we demonstrated that patients with bronchiolitis were older than patients with pneumonia although this difference was statistically not significant. Several other authors described that the clinical presentation of pneumonia is associated with prematurity and young age.28 In addition, immune compromised hosts tend to have severe RSV restrictive respiratory disease as well as prolonged viral shedding.10,29-31 In this respect the widespread occurrence of lower respiratory tract infections with RSV in elderly adults, in whom not only the presence of underlying heart and lung disease but also a declining immune system may play a role in the pathogenesis of RSV disease, is intriguing. Many aspects of the weaning immunity in the elderly are comparable with the immaturity of the neonatal immune system.57,58 On the other hand the high frequency of wheezing in the elderly during RSV infections also raises the possibility of an immune mediated pathogenesis.33

Other host factors such as asthmatic or atopic constitution may potentially influence the immune response and thus the pattern in which RSV-LRTI presents. However, in agreement with other studies we found no difference in the number of patients
with or without a positive family history of atopy or asthma between the bronchiolitis and the pneumonia group (Chapter 4). In addition, we found no association between a history of parental asthma and wheezing (i.e. bronchiolitis) during the acute phase of RSV infection, which is in agreement with a number of papers in the literature.\textsuperscript{2,34-36} A diminished lung function shortly after birth seems to be a more important host factor that predisposes for wheezing during the first lower respiratory tract infections, supporting the association between genetic factors and the clinical presentation of RSV-LRTI.\textsuperscript{37}

Viral factors, such as viral subtype, could influence the balance between the viral proliferation and the immune response. Reports on disease severity in relation to viral subtype are conflicting,\textsuperscript{38-41} and in addition, no study is available that has evaluated the relation between viral subtype and clinical pattern of RSV-LRTI. Finally, it is well known that environmental factors such as exposure to tobacco smoke and day care attendance predispose to more frequent episodes of lower respiratory tract infections with or without wheezing.\textsuperscript{42}

It seems to become important to discriminate between patients with an obstructive and those with a restrictive airway disease in order to administer adequate therapy. The definition of the clinical diagnosis bronchiolitis is characterised by many controversies.\textsuperscript{43} It may furthermore be very difficult to objectivate obstructive airway disease on auscultation, in particular when patients are on the mechanical ventilator.\textsuperscript{44} Tasker et al demonstrated by using chest radiography as golden standard, that the two clinical patterns can be distinguished on the base of the extent of oxygen anomalies on presentation. Interestingly, they also found an important shorter time course of disease in the bronchiolitis group compared to the pneumonia group.\textsuperscript{50} By applying their criteria we would have expected to find a similar difference between these 2 subgroups in the placebo treated patients, which was not the case and underscores the need for further studies on this topic. Beside chest radiographs, lung function measurements and flow-volume loops that are available on many mechanical ventilators nowadays, may be helpful tools to distinguish between the two clinical patterns.\textsuperscript{45}

The strong correlation between RSV-LRTI and subsequent respiratory morbidity during early childhood has been evident for many years. It is still a matter of debate whether RSV-LRTI is a first manifestation of asthma or whether non-atopic mechanisms contribute to RSV-LRTI and subsequent airway morbidity. Almost certainly the relation between RSV-LRTI and subsequent airway morbidity is multifactorial, in which host, viral and environmental factors interact.\textsuperscript{11,35} Nevertheless, since the immune response accounts, in part, for respiratory tract pathology during the acute phase we found it imaginable that corticosteroids also have a long-term effect. We demonstrated that corticosteroid treatment during the acute phase of RSV-LRTI is not effective in preventing wheezing in the first year after the infection or asthma at the age of 5 (Chapter 6). This suggests that other factors such as genetic factors or the direct viral injury may be more important in the development of increased
airway responsiveness after RSV-LRTI than the airway damage due to inflammation in the acute phase. However, it could have been that a beneficial effect of corticosteroids is masked by the heterogeneity of the study cohort. In analogy with our findings that corticosteroids during the acute phase are potentially beneficial in patients suffering from bronchiolitis one could imagine that corticosteroids also might prevent subsequent airway morbidity in particular in patients suffering from bronchiolitis. It has indeed been demonstrated that wheezing during the acute phase is a strong predictor for recurrent wheezing in later life.\textsuperscript{36}

The results of our studies suggest that the balance between viral cytopathic effects and the immune response might influence the clinical presentation of RSV infection of the lower respiratory tract. Much research has been performed to cytopathic and immunological phenomena in experimental settings, yet only limited data are available on this topic in the airways \textit{in vivo}.

The observation of a beneficial effect of corticosteroids in mechanically ventilated patients with RSV bronchiolitis was suggested in a post hoc analysis. This finding is only hypothesis generating and should be confirmed in a new intervention trial.

\textbf{Figure 8.1}

\textit{Hypothetical model of RSV lower respiratory tract infection.}
Summary

Respiratory syncytial virus (RSV) is the most important cause of respiratory infections in infants and young children. In the majority of the patients the infection is limited to the upper respiratory tract, but the lower respiratory tract becomes involved in about one third of the cases. RSV lower respiratory tract infection (RSV-LRTI) may present as mainly obstructive airway disease, classically known as bronchiolitis or mainly restrictive airway disease known as pneumonia.

To outline the magnitude of RSV disease in the Netherlands we performed an observational study to bronchiolitis hospitalisations in the Netherlands from 1991 through 1999 (Chapter 1). We found an increase in the number of bronchiolitis hospitalisations. This increase has a considerable socio-economic impact on the society, and underscores the need for further development of an effective vaccine against RSV as well as effective treatment for RSV-LRTI.

In the literature treatment for RSV-LRTI is surrounded by much controversies and attempts to find an effective therapy have been unsuccessful so far. In Chapter 2 we present a review of the studies that evaluated treatment possibilities for RSV-LRTI. RSV-LRTI is not only the result of direct cytopathic effects of the virus but a substantial body of evidence has shown that the immune response, in part, contributes to disease severity. Therefore, immune modulating drugs like corticosteroids are potentially beneficial for RSV-LRTI. To evaluate this a randomised controlled trial in children hospitalised for RSV-LRTI was performed. The results of this trial are discussed in Chapter 3. Briefly, we found only a modest effect of prednisolone in the cohort as a whole. However, in a post hoc analysis prednisolone seemed to be beneficial in patients that suffered from severe RSV-LRTI. In particular, in patients that needed ventilatory support, the duration of mechanical ventilation and length of stay in the hospital were shortened.

These results formed the basis for a new trial in which the efficacy of dexamethasone was evaluated in patients that needed mechanically ventilation for RSV-LRTI. The results of this trial are presented in Chapter 4. This double-blind multicenter randomised placebo-controlled trial did not confirm our previous findings. We could not demonstrate a difference in duration of mechanical ventilation in the study cohort as a whole. However, when the patients were stratified in those with RSV bronchiolitis at presentation and those with RSV pneumonia a striking difference in effect of dexamethasone was found. In patients with bronchiolitis dexamethasone shortened the duration of mechanical ventilation with more than 4 days whereas there appeared to be no effect in patients suffering from pneumonia. These results suggest that RSV bronchiolitis and RSV pneumonia have a different pathogenesis and that immune mediated phenomena play a more outspoken role in bronchiolitis than in pneumonia.

In order to find an explanation for the observed clinical effects we analysed inflammatory parameters and viral load in tracheal aspirates of those patients (n=22) who were included in the clinical trial in the Emma children's hospital. The results of this
analysis are presented in Chapter 5. Beside a faster decrease of interleukin(IL)-8 in the dexamethasone group compared to the placebo group no major differences were found in the time course of WBC count or RSV RNA concentration in tracheal aspirates. Interestingly, on admission RSV RNA concentration was lower, whereas IL-8 level and WBC count were higher in the patients suffering from bronchiolitis compared to those suffering from pneumonia. This finding indirectly supports our hypothesis that immunological phenomena are more important in bronchiolitis, whereas direct cytopathic effects seem to be more outspoken in pneumonia.

Follow-up studies have demonstrated that bronchiolitis caused by RSV is strongly associated with wheezing in the ensuing years. The pathogenesis of this long-term morbidity is still not clear, but both genetic predisposition and direct viral and immunological injury during the acute infection have been suggested as possible explanations. In order to evaluate the long-term effect of prednisolone during the acute phase on wheezing during the ensuing years, a follow-up study was performed (Chapter 6). We found that oral prednisolone during the acute phase of RSV bronchiolitis is not effective in preventing wheezing in the first year after bronchiolitis or asthma at the age of 5. This suggests that genetic factors or the direct viral injury may be of more importance in the development of increased airway responsiveness after RSV bronchiolitis than the airway damage due to inflammation.

In conclusion, ways to control RSV infections are limited. In the final chapter a contemplation on this lack to control RSV infections is presented (Chapter 7).
References


