Lower respiratory tract infection caused by respiratory syncytial virus. The short-term and the long-term efficacy of corticosteroids
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The effect of dexamethasone on airway inflammation in mechanically ventilated children with respiratory syncytial virus infection

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Submitted
Abstract

Background
To assess the effect of dexamethasone on airway inflammation and viral concentration during mechanical ventilation for respiratory syncytial virus lower respiratory tract infection (RSV-LRTI) a randomised controlled trial was performed.

Methods
Patients received dexamethasone (0.6 mg/kg/24 hr, in 4 doses, for 48 hours) or placebo. Tracheal aspirates were analysed on RSV RNA concentration, interleukin (IL)-8 level and white blood cell (WBC) count.

Results.
The viral concentration decreased in a similar pattern in the dexamethasone (9 patients) and the placebo group (13 patients). IL-8 level decreased in the dexamethasone, but increased in the placebo group at 24 hr (change -1.3 vs. 0.9 ln ng/ml, p=0.024) and at 48 hr (change -2.3 vs. 0.4 ln ng/ml, p=0.032). When disease pattern on presentation was considered the RSV RNA concentration was lower (21.0 vs. 87.0 RNA copies×10^9/ml p=0.16), whereas the IL-8 level (827 vs. 570 ng/ml, p=0.60) and WBC count (6149 vs. 1197 cells×10^4/ml, p=0.06) were higher in 8 patients with bronchiolitis compared to 14 with pneumonia. RSV RNA concentration decreased in the bronchiolitis group, but increased during the first 48 hours in the pneumonia group independent of dexamethasone (mean change during first 48 hour -1.6 vs. 2.1 ln RNA copies×10^9/ml, respectively, p=0.013). Although dexamethasone led to a stronger decrease of tracheal IL-8 in the bronchiolitis group than the pneumonia group (change at 24 hr -2.8 vs. -0.6 ln ng/ml, p=0.014 respectively), we found no different effect on WBC count.

Conclusion
Dexamethasone inhibits parts of the immune response in the airways of patients mechanically ventilated for RSV-LRTI. Viral concentration was lower and inflammation parameters were higher in the bronchiolitis group than in the pneumonia group, suggesting a greater influence of inherent immune mediated inflammatory response in bronchiolitis.

Introduction
Respiratory syncytial virus (RSV) is the most common cause of respiratory infections in infants and young children.1 In the majority of the cases, the RSV infection is limited to the upper respiratory tract. If the lower respiratory tract is also involved (RSV-LRTI), severe respiratory insufficiency may develop, necessitating mechanical ventilation. Patients with RSV-LRTI may present with bronchiolitis (obstructive airway...
disease) or pneumonia (restrictive airway disease). It has been demonstrated that these two clinical patterns may differ in the initial presentation and the course of the disease.²

Airway inflammation during RSV-LRTI is to a great deal orchestrated by respiratory epithelial cells that are -either infected or not- able to attract and activate inflammatory cells through the production of chemokines, such as interleukin(IL)-8.³⁻⁵ IL-8 is an important chemoattractant for human neutrophils,³ that have been demonstrated to be the most prominent inflammatory cell in the airways during RSV-LRTI.⁶,⁷ Although the immune response leads to the clearance of the virus during RSV-LRTI, it has been shown that it also may contribute to disease severity per se.⁸ Therefore, immunosuppressive drugs such as corticosteroids may be an effective treatment for RSV-LRTI. In a recently performed intervention study we found strong indications that corticosteroids may be beneficial in a subgroup of mechanically ventilated patients, i.e. dexamethasone reduced the duration of mechanical ventilation in children who presented with a clinical pattern of bronchiolitis, in contrast to those who presented with the clinical pattern of pneumonia. The aim of the present study is to assess the effect of dexamethasone on viral concentration and inflammatory variables in the airways during mechanical ventilation for RSV-LRTI in relation to the clinical pattern.

**Methods**

**Study design**

The study was performed as part of a multicenter randomised controlled trial in which the clinical efficacy of dexamethasone was evaluated. In that multicenter trial all patients with microbiologically proven RSV-LRTI before the age of 2, who were admitted to the pediatric intensive care unit of one of the participating hospitals and needed mechanical ventilation were eligible for inclusion. Patients who were included in the Emma Children’s Hospital in Amsterdam were eligible for this part of the study. RSV was proven by direct immunofluorescence assay (Imagen, Dako, Denmark) of a nasopharyngeal aspirate. Patients were only included after written informed consent was obtained from their parents, after mechanical ventilation was started. Patients who had used systemic or inhaled corticosteroids within the 2 months before admission were excluded. All patients were ventilated with an Evita 4 ventilator (Dräger, Lübeck Germany) with a synchronised mandatory intermittent ventilation, pressure controlled mode. The decision to treat patients with antibiotics, bronchodilators and paralysing drugs was taken by the attending physicians. The study was approved by the medical ethical committee of the hospital.

RSV-LRTI may present as bronchiolitis or pneumonia. These 2 entities can be distinguished from each other on the basis of oxygenation anomalies on admission as
shown by Tasker et al.\textsuperscript{2} in analogy to that paper, patients in our cohort were stratified according to their PaO$_2$/FiO$_2$-ratio and mean airway pressure (MAP) on admission. If the PaO$_2$/FiO$_2$ was >200 mm Hg and/or the MAP was ≤10 cm H$_2$O patients were stratified to the bronchiolitis group and if PaO$_2$/FiO$_2$ was ≤ 200 mm Hg and the MAP was >10 cm H$_2$O to the pneumonia group.

Trial medication was intravenous dexamethasone for 48 hours, 0.6 mg/kg/24 hr, divided in 4 doses (8 doses in total) or placebo and had to be started within 24 hours after start of mechanical ventilation. Patients were allocated to the dexamethasone or placebo group by computerised block randomisation in groups of 10. The randomisation was performed by a pharmacist not involved in the care of the patients who kept the concealed randomisation list until the study was completed.

Tracheal aspirate was collected by gently suction with a sterile 6 French suction tube with mucus trap through the endotracheal tube. Suction was performed without previous installation of fluids and at least one hour after previous routine endotracheal suction was performed. The suction tube was not inserted deeper than the length of the endotracheal tube. Samples were immediately preserved in ice and transported to the laboratory. Samples were taken on the day of admission (before the first gift of the study medication) and daily thereafter for 4 days or until the patient was extubated.

**Efficacy analysis**

Variables that were measured were RSV RNA concentration, IL-8 as important chemotactant for WBC, in particular human neutrophils, and white blood cell (WBC) count and differentiation.

**Sample processing**

In the laboratory the weight of the tracheal aspirate was determined. An equal volume of cold 10 mM DTT (Sigma) in 100 mM Hepes pH 8.0 (buffered with NaHCO$_3$) was added to the aspirate on ice followed by occasional gentle mixing during 60 min. If the aspirate remained mucoid, DNase was added and left for 5 min in ice. Cells in the treated aspirate were collected by centrifugation (10 min, 450 g, 4°C). The supernatant of the treated aspirate was aliquotted (100 μl portions) and stored at -80°C. Cells were resuspended in PBS with 2% (w/v) human serum albumin and cytocentrifuged at 500 rpm for 2 minutes in a Shandon cytocentrifuge and stained with Romanovsky (Diff-Quick) and Jenner-Giemsa.

**Virus stocks**

Respiratory syncytial virus B9320 was propagated on Hep-2 cells and RSV A Long was propagated on human embryonic lung fibroblast cells at 35°C in Eagle minimal essential medium supplemented with 0.01 M HEPES, 0.084% bicarbonate, 100 U/ml of penicillin and streptomycin, 0.625 μg/ml fungizone and 0.2 M glutamine (SVM, foundation for the advancement of public health and environment,
Bilthoven, The Netherlands). After development of a cytopathic effect, supernatant was harvested and the virus particle count of each stock was determined by quantitative EM (Advanced Biotechnologies Incorporated, Columbia, Md).

**Viral RNA isolation and quantification.**
RNA was extracted from the cell-free tracheal aspirate using the MagnaPure LC Total Nucleic Acid Kit (Roche Diagnostics, Mannheim, Germany). RNA extraction was not affected by DTT and DNase pre-treatment. The isolated viral RNA was reverse transcribed using MultiScribe reverse transcriptase and random hexamers (TaqMan Reverse Transcription Reagents, Applied Biosystems International). Each 50 µl reaction contained 10 µl of eluted RNA, 5 µl of 10xRT buffer, 5.5 mM MgCl₂, 500 µM of each of the deoxynucleoside triphosphates, 2.5 µM random hexamer, 62.5 U MultiScribe RT and 20 U RNase inhibitor. Complementary DNA synthesis was performed in a GeneAMP PCR system 9600, according to the following procedure: annealing for 10 minutes at 25 °C, RT was carried out for 30 minutes at 48 °C, followed by RT inactivation for 5 minutes at 95 °C. The cDNA was stored at -70 °C before real-time TaqMan PCR.

Both RSV A and B were assayed in duplicate in a 25 µl reaction mixture containing 5 µl of cDNA, 12.5 µl 2xTaqMan Universal PCR Master Mix, 900 nM forward primer, 900 nM of reverse primer and 200 nM of the probe that are shown in Table 5.1. RNA extracts were substituted by RNase-free water in negative control reactions. The PCR mixture was incubated 2 minutes at 50 °C for AmpErase uracil-N-glycosylase mediated decontamination followed by 10 minutes at 95 °C to activate AmpliTaq gold DNA polymerase. Subsequently, a total of 45 cycles were performed, consisting of a denaturation step for 15 seconds at 95 °C and a combined annealing-extension step for 1 minute at 60 °C. During the annealing-extension step, the ABI Prism 7700 SDS (Applied Biosystems International) monitored real-time PCR amplification by quantitatively analysing fluorescence emissions. The threshold was set at 10-times the standard deviation of the mean baseline emission calculated between cycles 3 to 15. The threshold cycle number represented the refraction cycle number at which a positive amplification reaction was measured. The amount of RSV A or B was determined relative to the EM counted viral stocks.

**IL-8**

IL-8 in tracheal aspirate was measured by ELISA using IL-8 cytose t capture and detection from Biosource (Nivelles, Belgium). This ELISA is insensitive for the effects of DTT.

IL-8 plasma concentrations was analysed using commercially available ELISA's with detection limit 15.0 pg/ml (Central Laboratory of the Netherlands Red Cross Blood Transfusion Service CLB, Amsterdam, The Netherlands).
**Statistical analysis**

Statistical analysis was performed with SPSS for Windows, version 11.01 (SPSS Inc., Chicago, Ill.). The student’s t test was used to compare group means for normally distributed data, otherwise the Mann-Whitney U test was applied. Proportions were compared by the chi-square test. A two-sided p value of <0.05 was considered statistically significant. Data in the tables are given as mean ± standard error of the mean unless otherwise stated.

**Results**

From November 1999 through January 2001 tracheal aspirates were collected in 22 patients. Nine patients received intravenous dexamethasone and 13 placebo. There were no statistical differences in baseline characteristics between the two treatment groups (Table 5.2).

Since levels of viral RNA concentration and inflammatory variables were not normally distributed all variables were converted to natural logarithm. Comparisons of these variables between the treatment groups in time were made as changes from the level before the start of study treatment (i.e. baseline level).

The changes from baseline level in time of viral RNA concentration, IL-8 levels and WBC count in tracheal aspirate are shown in Figure 5.1 a-c. The viral concentration increased during the first 24 hour and decreased in a similar pattern to low levels thereafter in both the dexamethasone and the placebo group. Differences in change from baseline were not significant at any time point.

We observed a decrease in IL-8 levels in the dexamethasone group in the first 96 hours after start of treatment. In contrast, in the placebo treated patients IL-8 levels increased in the first 48 hour and slightly decreased thereafter. The differences in change from baseline between the dexamethasone and the placebo group were statistically significant at 24 hr (mean change from baseline -1.3 vs. 0.9 ln ng/ml in dexamethasone vs. placebo group respectively, p=0.046, 95% CI for difference: -4.5 to -0.1 ln ng/ml) and at 48 hour (mean change from baseline -2.3 vs. 0.4 ln ng/ml, in dexamethasone vs. placebo group respectively, p=0.032, 95% CI for difference: -5.3 to -0.3 ln ng/ml).

IL-8 levels in tracheal aspirates were at 1000-fold higher than the IL-8 levels in plasma measured upon admission, demonstrating the localised synthesis in the lungs (data not shown).

During the first 48 hour WBC count in tracheal aspirate did not change remarkably in the dexamethasone group, whereas WBC count increased in the placebo group. However, these differences in WBC count between the two treatment groups were not significant at any time point (p=0.41 and p= 0.55, at 24 and 48 hours respectively). Differential count before start of the study treatment showed that 88% of the WBC in the tracheal aspirates were neutrophils. This remained so during admission in both the dexamethasone group (mean fraction 88%, range 83% to 94%) as well as in the placebo group (mean fraction 87%, range 76% to 93%). Eosinophils were present...
in only 23% of the samples, with a low mean percentage of 0.9% (range 0.4% to 2.8%).

Eight patients suffered from bronchiolitis (4 receiving dexamethasone, 4 placebo) and 14 from pneumonia (5 receiving dexamethasone, 9 placebo). The RSV RNA concentration and the levels of the inflammatory variables in tracheal aspirate before the start of the study treatment are shown in Table 5.3. The viral RNA concentration was lower, whereas the IL-8 level and the WBC count were higher in the bronchiolitis group compared to the pneumonia group. Only the difference in WBC reached borderline statistical significance.

The changes from baseline of the variables stratified to the above mentioned clinical patterns, are shown in Figure 5.2 a-c. The course of the viral RNA concentration showed a different pattern in the bronchiolitis compared to the pneumonia group. This difference appeared to be independent of dexamethasone (Figure 5.2 a). In contrast to the progressive decrease in RSV RNA concentration in the bronchiolitis group, we observed an increase in the pneumonia group during the first 48 hours. This difference was highly significant: mean change in viral concentration from baseline up to 48 hours -1.4 vs. 2.2 ln RNA copies 10⁹/ml (p=0.018; 95% CI for difference: -6.6 to -0.7 ln RNA copies 10⁹/ml) in the bronchiolitis vs. pneumonia group. Only after 48 hours the viral RNA concentration also started to decrease in the pneumonia group.

In the bronchiolitis group a strong decrease in IL-8 level was observed in the dexamethasone treated patients compared to those who received placebo. In the pneumonia group the dexamethasone-associated decrease was far less outspoken: the change in ln IL-8 levels from baseline up to 48 hr -3.4 vs. -0.8 ln ng/ml (p=0.017; 95% CI for difference: -4.6 to -0.6 ln ng/ml) in the bronchiolitis vs. pneumonia group (Figure 5.2 b). No difference in the course of WBC count between the two clinical patterns was present (Figure 5.2 c).

Discussion
In this study we demonstrated that dexamethasone has no effect on the viral RNA concentration in tracheal aspirates of patients that need mechanical ventilation for RSV-LRTI, whereas the inflammatory response was inhibited.

This report is the first that used quantitative PCR to measure viral concentration in vivo in the lower airways in pediatric patients with RSV-LRTI. PCR is a fast, sensitive and specific method to detect RSV and forms an excellent tool to quantify viral concentrations in the airways of patients suffering from RSV infection. Several other assays, such as quantitative cultures or quantitative ELISA have been used to determine RSV concentrations in respiratory secretions.⁹⁻¹³ Quantitative cultures are laborious, liable to subjectivity in scoring, and therefore less precise.

The RSV RNA concentration in tracheal aspirates appeared not to be influenced by dexamethasone. We found an initial increase in the viral load during the first 24
hours of admission that was independent of dexamethasone administration. Thereafter RSV RNA concentration decreased in a comparable pattern in both treatment groups. The patterns of RSV concentrations in respiratory secretions over time as described by others, show inconsistent results.\textsuperscript{9,10,12} This may in part be explained by differences in technique, as well as the time lapse before the collection of the samples was started.

Dexamethasone led to a significant decrease of IL-8 level in tracheal aspirates, resulting in a stabilisation of infiltrating neutrophils in the airways. In the placebo treated patients IL-8 showed an increase that was accompanied by an increase in the tracheal WBC count. Neutrophils were the most prominent cells in the airways, whereas almost no eosinophils could be detected. Our findings underscore the role of IL-8 and neutrophilic granulocytes in RSV-LRTI, that also have been described by others in both experimental and human studies.\textsuperscript{3,4,6,14}

In this study, the patients tracheal aspirates positive for eosinophils did not represent a separate group of patients (dexamethasone or placebo treatment, bronchiolitis or pneumonia, data not shown). Whether these patients represent a cohort of children that will develop hyperreactivity or atopic disease in the ensuing years will be studied but is yet unknown.

The results of this study do not explain the clinical results of the multicentred clinical trial in which we found no beneficial effect of dexamethasone on clinical variables such as duration of mechanical ventilation and length of stay in the PICU in the study cohort as a whole. However, we only analysed part of the immune response, and other inflammatory and viral mechanisms may play a role and contribute to the pathogenesis of RSV infection. On the other hand RSV-LRTI might not be an uniform disease and differences in the balance between direct viral cytopathic effects, and the immune response may lead to different forms of airway disease.\textsuperscript{15,16}

This idea is also supported by the results of our subgroup analysis of the inflammatory markers and the viral concentration. On admission, the RSV RNA concentration in tracheal aspirates was lower whereas IL-8 levels and neutrophil count were higher in the bronchiolitis group, in comparison with the pneumonia group. This suggests a more outspoken cell-mediated response in RSV bronchiolitis, while the cytopathic effects of the virus predominate in RSV pneumonia. Autopsy series in children also demonstrated a lower viral concentration in the lungs of children dying from RSV bronchiolitis and abundant virus loads in the lungs of those who died from RSV pneumonia.\textsuperscript{17,18} Hall et al demonstrated that cyanosis and pulmonary consolidation was associated with higher titers compared to patients without pulmonary consolidation.\textsuperscript{9,10}

In a post hoc analysis of the multicentred trial we found that dexamethasone leads to a significant shorter duration of mechanical ventilation compared to placebo in patients suffering from bronchiolitis, whereas there appeared to be no effect in the pneumonia group (van Woensel et al, submitted for publication). In the present study we showed that the RSV RNA concentration during admission strikingly
differed between bronchiolitis and pneumonia independent of the administration of dexamethasone. In addition, dexamethasone treatment resulted in a more dramatic decrease of IL-8 in the bronchiolitis group than in the pneumonia group, without comparable effects on WBC counts, suggesting that other factors influence also migration and activation of inflammatory cells during RSV disease. Our findings support the idea of differences in pathogenesis between RSV bronchiolitis and RSV pneumonia and argue for a distinct therapeutic approach. In case of bronchiolitis immune modulation may be beneficial, whereas antiviral therapy would be justified in RSV pneumonia.

The results should be interpreted with caution, because of the limited number of patients. In addition, in some patients RSV may not have been the sole pathogen and superimposed bacterial infection can never be completely excluded. However, we found neither a difference between the 2 treatment groups in the number of patients that had a positive sputum culture nor in the number of patients that received antibiotics (Table 5.2). Despite these limitations independent confirmation is warranted.

In conclusion, we found that dexamethasone inhibits parts of the immune response in the airways of patients that need mechanical ventilation for RSV-LRTI. In addition, viral concentration was lower and the extent of inflammation was higher in patients suffering from bronchiolitis than those with pneumonia. Together with a more outspoken anti-inflammatory effect of dexamethasone in bronchiolitis compared to pneumonia our findings suggests that the immunopathogenic mechanisms of inflammation predominate in bronchiolitis in contrast to cytopathicity in pneumonia.
Table 5.1

Primers and probe used for RSV detection.

<table>
<thead>
<tr>
<th>Primer / probe</th>
<th>RSV A</th>
<th>RSV B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forward</td>
<td>5'-AGA TCA ACT TCT GTC ATC CAG CAA</td>
<td>5'-AAG ATG CAA ATCATA AAT TCA CAG GA</td>
</tr>
<tr>
<td>Reverse</td>
<td>5'-TTC TGC ACA TCA TAA TTA GGA GTA TCA AT</td>
<td>5'-TGA TAT CCA GCA TCT TTA AGT ATC TTT ATA GTG</td>
</tr>
<tr>
<td>Probe</td>
<td>5'-CAC CAT CCA ACG GAG CAC AGG AGA T</td>
<td>AGG TAT GTT ATA TGC TAT GTC CAG GTT AGG AAG GGA A</td>
</tr>
</tbody>
</table>
Table 5.2
Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=9</td>
<td>n=13</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>9</td>
<td>0.66</td>
</tr>
<tr>
<td>Age, weeks</td>
<td>7.4 (1.7)</td>
<td>11.3 (2.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>Risk group*</td>
<td>3</td>
<td>4</td>
<td>0.63</td>
</tr>
<tr>
<td>Duration of symptoms, days</td>
<td>3.3 (0.8)</td>
<td>4.4 (0.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>PRISM score†</td>
<td>10 (7 – 18)</td>
<td>8 (7 - 11)</td>
<td>0.95</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio, mm Hg</td>
<td>155 (17)</td>
<td>155 (15)</td>
<td>0.75</td>
</tr>
<tr>
<td>MAP, cm H2O</td>
<td>12 (10 – 14)</td>
<td>14 (11-16)</td>
<td>0.10</td>
</tr>
<tr>
<td>Time between start mech. vent. and trial medication, hr</td>
<td>14 (2.6)</td>
<td>10 (1.9)</td>
<td>0.21</td>
</tr>
<tr>
<td>Antimicrobial therapy on or &lt; 24 hr of admission</td>
<td>8</td>
<td>11</td>
<td>0.64</td>
</tr>
<tr>
<td>Sputum culture positive, n/N§</td>
<td>1/6</td>
<td>3/9</td>
<td>0.46</td>
</tr>
<tr>
<td>Viral RNA copies, 10⁹/ml</td>
<td>60 (38)</td>
<td>73 (52)</td>
<td>0.85</td>
</tr>
<tr>
<td>IL-8 in tracheal aspirate, ng/ml</td>
<td>703 (302)</td>
<td>636 (330)</td>
<td>0.89</td>
</tr>
<tr>
<td>WBC in tracheal aspirate, 10⁴/ml</td>
<td>3596 (2881)</td>
<td>1991 (816)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

PRISM: Pediatric Risk of Mortality Score⁹
* Premature (defined as a gestational duration of less than 36 weeks), chronic heart or lung disease
† Median (interquartile range)
§ Sputum cultures were performed in 15 patients. Haemophilus influenza was cultured in 3 patients, Streptococcus pneumoniae in 1

Table 5.3
Baseline values of inflammatory variables and viral concentration in relation to clinical pattern.

<table>
<thead>
<tr>
<th></th>
<th>Bronchiolitis n=8</th>
<th>Pneumonia n=14</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral RNA copies, 10⁹/ml</td>
<td>18.0 (6.1)</td>
<td>96.0 (48.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>IL-8, ng/ml</td>
<td>827 (351)</td>
<td>570 (300)</td>
<td>0.60</td>
</tr>
<tr>
<td>WBC count, 10⁴/ml</td>
<td>5737 (3188)</td>
<td>797 (237)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

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Figure 5.1
Change from baseline of RSV RNA concentration, IL-8 level and WBC count in tracheal aspirates in the dexamethasone (\(^{-\Delta-}\)) and the placebo group (\(\square\)). Levels are given as mean and standard error of the mean.
Difference in change of IL-8 was significant at 24 and 48 hour (* \(p=0.046\), ** \(p=0.032\))

A. RSV

Lower respiratory tract infection caused by respiratory syncytial virus
The short-term and long-term efficacy of corticosteroids
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Figure 5.2

Change from baseline of RSV RNA concentration, IL-8 level and WBC count in tracheal aspirates stratified to clinical pattern.

Bronchiolitis dexamethasone group (□) and bronchiolitis placebo group (○); Pneumonia dexamethasone group (▲) and pneumonia placebo group (■). Levels are given as mean and standard error of the mean.

* mean change up to 48 hr: -1.4 vs. 2.2 ln RNA copies 10^9/ml (p=0.018, bronchiolitis vs. pneumonia group)

** mean change from baseline up to 48 hr: -3.4 vs. -0.8 ln ng/ml (p=0.017, bronchiolitis vs. pneumonia group)
Chapter 5  
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References


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