Severity of respiratory syncytial virus infections and immunoglobulin concentrations

W J E Tissing, H A van Steensel-Moll, M Offringa

Abstract
In a prospective study in 86 children with respiratory syncytial virus infections, no relation was detected between the severity of infection (based on diagnosis, chest radiography findings, need for mechanical ventilation, and duration of hospitalisation) and serum concentrations of IgG, IgA, IgM, and IgG₁⁺ on admission.

(Arch Dis Child 1993; 69: 156-157)

Respiratory syncytial virus causes a substantial amount of morbidity in young infants during yearly epidemics. Several factors contribute to the pathogenesis of severe respiratory syncytial virus infections: a small airway diameter, pulmonary hypertension due to congenital heart disease, bronchopulmonary dysplasia, and immunodeficiency status.¹

The role of both humoral and cellular immunity is not fully understood. In recent years Hemming et al administered intravenous immunoglobulin for prophylactic and therapeutic purposes in children with respiratory syncytial virus infections.² However, no prior low concentrations of immunoglobulins or specific immunoglobulins have been reported in these patients.

As part of a larger project,³ the present study was initiated to evaluate whether low serum concentrations of IgG, IgA, IgM, and IgG subclasses are associated with more severe respiratory syncytial virus infections.

Patients and methods
Eighty six patients with respiratory syncytial virus infections who were admitted to the Sophia Children’s Hospital because of apnoea, dyspnoea, or feeding difficulties were included in a prospective study (October 1987 to April 1988 and October 1988 to April 1989). Respiratory syncytial virus infection was proved by a positive direct immunofluorescence test of nasopharyngeal secretion (Boots Cell Tech) and culture of the virus by standard methods. Data on postnatal age, corrected for gestational age, were registered on admission.

SEVERITY OF DISEASE
Respiratory syncytial virus infections were divided in two diagnostic groups: lower respiratory tract infections, that is pneumonia and bronchiolitis, and upper respiratory tract infections where patients showed no signs of pneumonia or bronchiolitis. The diagnosis of bronchiolitis was based on clinical features: tachypnoea, retractions, wheezing, and diffuse fine rales. Chest radiography findings were defined as normal or with hypertranslucency, consolidation, and/or atelectasis.

The need for mechanical ventilation and the duration of hospitalisation were recorded. Indications for mechanical ventilation were prolonged episodes of apnoea, hypoxaemia (oxygen saturation <90% with a fractional inspiratory oxygen of 40%), or hypercapnia (carbon dioxide tension >6·67 kPa), or sudden clinical deterioration.³

MEASUREMENT OF IMMUNOglobulins AND IgG SUBCLASSES
Total serum immunoglobulins were measured by a turbidimetric assay using the Cobas-Bio centrifugal analyser. The reagents used were provided by the Central Laboratory of Bloodtransfusion (CLB) (Amsterdam, the Netherlands), and the calibration was carried out with standards from Boehringer Mannheim GmbH (product 852643). The values were traceable to the World Health Organisation (WHO) international reference preparations 67/86 and 67/99.¹ IgG subclasses were measured quantitatively by radial immunodiffusion using the reagent provided by the CLB, Amsterdam, and were expressed in g/l. Standard serum H0001234, standardised on the WHO serum 67/69,³ was used.

Internal quality control of the immunoglobulin samples showed a SD between 0·006 and 0·27. Serum immunoglobulin and IgG subclass concentrations in the study population were compared with age adjusted reference concentrations (department of paediatrics, University Hospital, Leiden).

STATISTICAL ANALYSIS
As immunoglobulin concentrations are age dependent, age distributions in the different severity of disease subgroups were compared, before comparison of immunoglobulin concentrations. For comparison of the different subgroups, the Mann-Whitney U test was used; p values <0·05 were accepted as being significant.

Results
The median age on admission was 63 days (range 16 to 864); 27 (31%) were younger than 30 days. Twenty two (26%) patients were born prematurely. The age adjusted serum immunoglobulin and IgG subclass concentrations in the total study population did not differ from age adjusted reference concentrations.

The relation between serum immunoglobulin concentrations and severity of infection is shown...
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**Immunoglobulin and IgG subclass concentrations (g/l) in relation to severity of respiratory syncytial virus infection; values are mean (SD)**

<table>
<thead>
<tr>
<th>Diagnosis*</th>
<th>No</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>URI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LRI</td>
<td>12</td>
<td>5.58 (2.75)</td>
<td>0.45 (0.76)</td>
<td>0.59 (0.25)</td>
<td>3.93 (1.96)</td>
<td>0.99 (0.69)</td>
<td>0.30 (0.13)</td>
<td>0.19 (0.26)</td>
</tr>
<tr>
<td>Chest radiography:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>74</td>
<td>5.87 (2.22)</td>
<td>0.36 (0.34)</td>
<td>0.82 (0.48)</td>
<td>4.22 (1.85)</td>
<td>0.83 (0.54)</td>
<td>0.33 (0.21)</td>
<td>0.17 (0.20)</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>10</td>
<td>5.74 (2.41)</td>
<td>0.58 (0.80)</td>
<td>0.70 (0.26)</td>
<td>4.21 (1.70)</td>
<td>1.06 (0.72)</td>
<td>0.33 (0.17)</td>
<td>0.23 (0.28)</td>
</tr>
<tr>
<td>Atelectasis/consolidation</td>
<td>63</td>
<td>5.74 (2.19)</td>
<td>0.36 (0.37)</td>
<td>0.82 (0.51)</td>
<td>4.09 (1.87)</td>
<td>0.83 (0.56)</td>
<td>0.34 (0.22)</td>
<td>0.16 (0.20)</td>
</tr>
<tr>
<td>No chests radiograph</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Mechanical ventilation (age &lt;90 days):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12</td>
<td>5.61 (2.48)</td>
<td>0.23 (0.09)</td>
<td>0.70 (0.52)</td>
<td>3.86 (1.67)</td>
<td>0.85 (0.48)</td>
<td>0.19 (0.07)</td>
<td>0.18 (0.16)</td>
</tr>
<tr>
<td>No</td>
<td>38</td>
<td>5.76 (2.17)</td>
<td>0.27 (0.33)</td>
<td>0.57 (0.21)</td>
<td>4.12 (1.72)</td>
<td>1.07 (0.59)</td>
<td>0.25 (0.12)</td>
<td>0.18 (0.14)</td>
</tr>
<tr>
<td>Duration of hospitalisation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1-7 days</td>
<td>43</td>
<td>5.59 (2.15)</td>
<td>0.38 (0.34)</td>
<td>0.81 (0.41)</td>
<td>4.05 (1.93)</td>
<td>0.84 (0.62)</td>
<td>0.36 (0.21)</td>
<td>0.15 (0.16)</td>
</tr>
<tr>
<td>&gt;7 days</td>
<td>43</td>
<td>6.07 (2.42)</td>
<td>0.36 (0.50)</td>
<td>0.76 (0.51)</td>
<td>4.31 (1.79)</td>
<td>0.87 (0.52)</td>
<td>0.30 (0.19)</td>
<td>0.19 (0.24)</td>
</tr>
</tbody>
</table>

*URI=upper respiratory tract infection, LRI=lower respiratory tract infection.*

In the table. As the mechanically ventilated patients were younger than the non-ventilated patients, the immunoglobulin concentrations of mechanically ventilated patients (n=12) were compared with those of an age matched group of non-ventilated patients (n=38, both groups younger than 90 days). The age distribution in the other severity of disease groups was similar and no age matched controls were necessary. No relation between severity of disease and the concentrations of IgG, IgA, IgM, and IgG subclasses was found.

**Discussion**

This study shows two remarkable results: all immunoglobulin and IgG subclass serum concentrations in patients with respiratory syncytial virus infections matched normal age standardised ranges. No relation between the severity of infection, based on clinical diagnosis, chest radiography, the need for mechanical ventilation, or duration of hospitalisation and immunoglobulin or IgG subclass serum concentrations could be demonstrated.

So far, most studies have shown a protective function for respiratory syncytial virus specific humoral immunity in relation to the occurrence and severity of respiratory syncytial virus infection, although in some studies the concentration of respiratory syncytial virus specific antibodies was not related to the severity of disease. The role of IgG subclasses in respiratory syncytial virus infections has not been clarified.

The therapeutic role of intravenous immunoglobulin in respiratory syncytial virus infections was studied in animal models and in a small number of infants. Respiratory syncytial virus shedding was reduced and oxygen saturation levels were increased in children treated with intravenous immunoglobulin. However, the duration of hospitalisation and the duration of clinical symptoms were not reduced.

More research seems necessary to determine the mechanisms and indication for intravenous immunoglobulin in serious infections and its role in the prevention of severe morbidity in the defined risk groups. A hyperimmune status may influence the course of disease in serious infections. Infants with normal immunoglobulin concentrations but low respiratory syncytial virus specific antibodies might be susceptible to serious infections in a way remediable by intravenous immunoglobulin. We conclude that severe morbidity in infants with respiratory syncytial virus infections is not related to immunoglobulin deficiency on admission.

We are grateful to the paediatric residents for collecting the blood samples and to the laboratory of clinical chemistry (Drs J Lindemans, A W van Thoorenbergen, and G J M Boerman) for analysis of the serum immunoglobulin concentrations.

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