Archives of Disease in Childhood 1993; **69**: 156–157

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 IgG_{1-4} 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.[4] 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,[5] 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

Department of Paediatrics, Erasmus University and University Hospital Rotterdam/ Sophia Children's Hospital, Rotterdam, The Netherlands
W J E Tissing
H A van Steensel-Moll
M Offringa

Centre for Clinical Decision Analysis, Erasmus University Rotterdam
M Offringa

Correspondence to:
Dr H A van Steensel-Moll, Sophia Children's Hospital, Gordelweg 160, 3038 GE Rotterdam, The Netherlands.

Accepted 15 March 1993

Immunoglobulin and IgG subclass concentrations (in g/l) in relation to severity of respiratory syncytial virus infection; values are mean (SD)

	No	*IgG*	*IgA*	*IgM*	*IgG_1*	*IgG_2*	*IgG_3*	*IgG_4*
Diagnosis*:								
URI	12	5·58 (2·75)	0·45 (0·76)	0·59 (0·25)	3·93 (1·96)	0·99 (0·69)	0·30 (0·13)	0·19 (0·26)
LRI	74	5·87 (2·22)	0·36 (0·34)	0·82 (0·48)	4·22 (1·85)	0·83 (0·54)	0·33 (0·21)	0·17 (0·20)
Chest radiography:								
Normal	10	5·74 (2·41)	0·58 (0·80)	0·70 (0·26)	4·21 (1·70)	1·06 (0·72)	0·33 (0·17)	0·23 (0·28)
Hyperinflation	10	6·58 (2·24)	0·27 (0·09)	0·69 (0·30)	4·69 (1·61)	0·80 (0·42)	0·25 (0·10)	0·22 (0·16)
Atelectasis/consolidation	63	5·74 (2·19)	0·36 (0·37)	0·82 (0·51)	4·09 (1·87)	0·85 (0·56)	0·34 (0·22)	0·16 (0·20)
No chest radiograph	3							
Mechanical ventilation (age <90 days):								
Yes	12	5·61 (2·48)	0·23 (0·09)	0·70 (0·52)	3·86 (1·67)	0·85 (0·48)	0·19 (0·07)	0·18 (0·16)
No	38	5·76 (2·17)	0·27 (0·33)	0·57 (0·21)	4·12 (1·72)	1·07 (0·59)	0·25 (0·12)	0·18 (0·14)
Duration of hospitalisation:								
≤7 days	43	5·59 (2·15)	0·38 (0·34)	0·81 (0·41)	4·05 (1·93)	0·84 (0·62)	0·36 (0·21)	0·15 (0·16)
>7 days	43	6·07 (2·42)	0·36 (0·50)	0·76 (0·51)	4·31 (1·79)	0·87 (0·52)	0·30 (0·19)	0·19 (0·24)

*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,[2 6 7] although in some studies the concentration of respiratory syncytial virus specific antibodies was not related to the severity of disease.[8] The role of IgG subclasses in respiratory syncytial virus infections has not been clarified.[6]

The therapeutic role of intravenous immunoglobulin in respiratory syncytial virus infections was studied in animal models and in a small number of infants.[2] 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 immoglobulin 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 Thoorenenbergen, and G J M Boerma) for analysis of the serum immunoglobulin concentrations.

1 Brunell PA, Daum RS, Giebink GS, *et al.* (Committee on infectious diseases 1986–1987.) Ribavirin therapy of respiratory syncytial virus. *Pediatrics* 1987; **79**: 475–8.
2 Hemming VG, Prince GA. Immunoprophylaxis of infections with respiratory syncytial virus: observations and hypothesis. *Rev Infect Dis* 1990; **12**: s470–5.
3 Tissing WJE, Steensel-Moll HA van, Offringa M. Risk factors for mechanical ventilation in respiratory syncytial virus infection. *Eur J Pediatr* 1993; **152**: 125–7.
4 Rowe DS, Grab B, Anderson SG. An international reference preparation for human serum immunoglobulins G, A and M: content of immunglobulins by weight. *Bull World Health Organ* 1972; **46**: 67–79.
5 Leibl H, Mannhalter JW, Eibl M. IgG subclass determination in human sera with commercially available reagents: comparison of different assay systems. *European Journal of Clinical Chemistry and Clinical Biochemistry* 1992; **30**: 85–93.
6 Everard ML, Milner AD. The respiratory syncytial virus and its role in acute bronchiolitis. *Eur J Pediatr* 1992; **151**: 638–51.
7 Ogilvie MM, Vathenen AS, Radford M, Codd J, Key S. Maternal antibody and respiratory syncytial virus infection in infancy. *J Med Virol* 1981; **7**: 263–71.
8 Toms GL, Webb MSC, Milner PD, *et al.* IgG and IgM antibodies to viral glycoproteins in respiratory syncytial virus infections of graded severity. *Arch Dis Child* 1989; **64**: 1661–5.