

## ORIGINAL ARTICLE

## Bacteraemia and antibiotic use in respiratory syncytial virus infections

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**Aims:** To examine the frequency of and risk factors for bacteraemia in children hospitalised with respiratory syncytial virus (RSV) infection; and to determine current use of antibiotics in hospitalised children with RSV infection.

**Methods:** Retrospective study of all children, aged 0–14 years, admitted to a tertiary children's hospital with proven RSV infection over a four year period. Children with concurrent bacteraemia and RSV infection were identified, and risk factors examined for bacteraemia. The case notes of a randomly selected comparison sample of 100 of these RSV infected children were examined to assess antibiotic use and population incidence of risk factors for severe RSV infection.

**Results:** A total of 1795 children had proven RSV infection, and blood cultures were sent on 861 (48%). Eleven (0.6%) of the 1795 RSV positive children had bacteraemia. RSV positive children had a significantly higher incidence of bacteraemia if they had nosocomial RSV infection (6.5%), cyanotic congenital heart disease (6.6%), or were admitted to the paediatric intensive care unit (2.9%). Forty five (45%) of the random comparison sample of RSV infected children received antibiotics.

**Conclusions:** Bacteraemia is rare in RSV infection. Children with RSV infection are more likely to be bacteraemic, however, if they have nosocomial RSV infection, cyanotic congenital heart disease, or require intensive care unit admission.

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Respiratory syncytial virus (RSV) is a major cause of morbidity, including hospitalisation, of infants in industrialised and developing countries.<sup>1–4</sup> Hospitalised children with RSV infection are often given antibiotics,<sup>4–6</sup> although rapid detection techniques for RSV are routine,<sup>7</sup> and two randomised controlled trials have shown that antibiotics are of no added benefit in children with uncomplicated RSV infection.<sup>8–9</sup> Chest radiographs are unhelpful in distinguishing children with viral from those with bacterial pneumonia,<sup>10</sup> and thus determining which children will benefit from antibiotics.

If it were possible to identify groups of children with a higher incidence of bacteraemia, these children might be considered more likely to warrant antibiotic therapy. Yet we could find no previous studies which had examined risk factors for bacteraemia in RSV infection. We therefore undertook a retrospective chart review of children hospitalised with RSV infection over a four year period, to determine the frequency of, and risk factors for, concurrent bacteraemia. We also studied a comparison group of RSV infected children to assess antibiotic use and to determine the incidence of risk factors for severe RSV in the population of RSV infected children we are seeing.

## METHODS

### Patients

All children in The Children's Hospital at Westmead, from 1 January 1998 to 31 December 2001, with proven RSV infection, defined as positive RSV immunofluorescence or culture of RSV from nasopharyngeal secretions, were included in this study. Samples are routinely sent for RSV identification from children with suspected respiratory infections. The four year time period was used because of the availability of complete, computerised, pathology records. The children ranged in age from 0 to 14 years, and there were no clinical exclusion criteria. Blood cultures were performed on the children only if felt to be clinically indicated by the

attending physicians. We identified, from the pathology database, all RSV positive children who had a blood culture performed within 30 days of the positive RSV result. The clinical file of each RSV positive child with a positive blood culture within 30 days was hand searched. Positive blood cultures were classified as true bacteraemia associated with RSV, or other alternatives (see Definition of bacteraemia, below). The case notes of bacteraemic patients and their chest radiographs taken at the time of bacteraemia were reviewed.

### Random comparison sample

A computer generated, random number system was used to select a random comparison sample of 100 of all the RSV positive patients, whose clinical files were hand searched. Children with positive blood cultures were excluded from this group. Background information was obtained from each of the hand searched patient files and recorded on a data extraction sheet. This included history of potential risk factors for severe disease, for example, malignancy, immunodeficiency, congenital heart disease, cystic fibrosis, or preterm birth. Details of any admission to the paediatric intensive care unit (PICU) or neonatal intensive care unit (NICU) were recorded, including ventilatory support. Details of antibiotic use were obtained from medication charts.

### Laboratory tests

Respiratory syncytial virus infection was detected in nasopharyngeal secretions (NPS) using direct immunofluorescent antigen testing (Simulfluor, Light Diagnostics, USA) and

**Abbreviations:** CCHD, cyanotic congenital heart disease; CI, confidence interval; CPAP, continuous positive airways pressure; NICU, neonatal intensive care unit; NPS, nasopharyngeal secretions; OR, odds ratio; PICU, paediatric intensive care unit; RSV, respiratory syncytial virus

viral culture on monkey kidney cells. Blood cultures were performed using the Vital (BioMerieux, France) blood culture system. Cultures were continued for six days before being declared negative. Computerised pathology data (PathNet Clinical Systems, HNA Classic Version 306, Cerner Corporation, USA) were sourced to determine the number of positive RSV results for this period. If a second positive RSV result was obtained from the same patient within 30 days of the initial positive result, it was not considered to be a new infection. If the second positive RSV isolate occurred between 30 and 90 days after the initial positive, the patient's clinical file was hand searched to determine if the clinical data supported a single infection or a reinfection.

### Definition of community and hospital acquired RSV infection

Based on an incubation period of 2–7 days, all RSV infections were classified into:

- Community acquired infection: child admitted with respiratory symptoms (coryza, cough, wheeze, tachypnoea), or symptoms began less than 48 hours after admission and the child had not been in hospital within the preceding six days.
- Possible hospital acquired (nosocomial) infection: respiratory symptoms began either 2–6 days after admission or 2–6 days after discharge from hospital.
- Definite hospital acquired (nosocomial) infection: symptoms began after seven or more days in hospital, or within 48 hours of discharge.<sup>14 15</sup>

### Definition of bacteraemia

Each data extraction sheet from a child with concurrent RSV infection and bacteraemia was reviewed by two investigators (PB, DI) and classified, according to predetermined definitions, as:

- True bacteraemia: bacteraemia/septicemia with bacterium which is usually pathogenic (for example, *Streptococcus pneumoniae*, *Haemophilus influenzae*, group A streptococcus, *Staphylococcus aureus*), and in the absence of a central venous catheter.
- Contaminant: growth in the blood culture of a bacterium usually considered a contaminant (for example, coagulase negative staphylococcus, diphtheroids, and multiple organisms), in the absence of a central venous catheter.
- Catheter associated infection: growth of a potential pathogen (for example, coagulase negative staphylococcus and *Staphylococcus aureus*), in association with a central venous catheter.
- Coincidental bacteraemia: bacteraemia in association with a definite non-pulmonary focus (for example, urinary tract).

Data on patients with RSV admitted to the paediatric or neonatal intensive care units were obtained from specialised clinical audit databases (Clinical Report System version 3.11). The data included antibiotic use and the need for ventilatory support, either mechanical ventilation or continuous positive airways pressure (CPAP).

### Statistical methods

The relation between bacteraemia/septicaemia and the following potential risk factors was analysed statistically, using the Fisher's exact test. Results were expressed as

odds ratios (OR) and their 95% confidence intervals (95% CI):

- Age (0–3 months, 4–6 months, 7–12 months, 13–24 months, >24 months)
- Nosocomial infection
- PICU admission for RSV infection
- Ventilatory support for RSV infection
- Cyanotic congenital heart disease.

A Mann-Whitney U test was used to examine associations between age and bacteraemia/septicaemia. Logistic regression was used, where possible, to examine the data for collinearity. Values of  $p < 0.05$  were considered statistically significant.

The Ethics Committee of The Children's Hospital at Westmead granted approval for this study.

### RESULTS

There were 2014 positive RSV tests, representing 1827 separate infections with RSV over the four year study period. These infections occurred in 1795 different children. Blood cultures were performed on 861 (48%) of the patients with RSV infection within 30 days of the positive RSV result. There were 79 patients with positive blood cultures. However, only 11 children (0.6% of all RSV positive patients or 1.3% of those on whom blood cultures were performed) were considered to have true concurrent bacteraemia and RSV infection (table 1). The median age of the 11 patients was 4.7 months (interquartile range 24.7) which was not significantly different from that of the 1784 non-bacteraemic children with RSV infection of 6.2 months (interquartile range 12.4) ( $p = 0.42$ ).

The 11 children with bacteraemia all had chest radiographs within 24 hours of the positive blood culture. Seven of the radiographs were reported by a consultant radiologist to be consistent with bronchiolitis, with no areas of focal consolidation or collapse, whereas four had lobar consolidation (table 1). In addition, one child with lobar consolidation had concurrent pneumatoceles, while another had a pleural effusion as well as lobar consolidation.

Sixty two of the blood culture growths were contaminants. One patient had acute pyelonephritis with septicaemia due to *Escherichia coli*, and co-existing community acquired RSV infection. The remaining five patients had infection of indwelling central venous catheters with co-existing RSV infection (table 2).

Infection with RSV was hospital acquired in 93 children (5.2% of all RSV infections), definitely in 36 (2.0%), and possibly in 57 (3.2%). RSV was community acquired in the remaining 1702 children. Of the 11 children with true bacteraemia, three had definite and three had possible hospital acquired RSV infection. The incidence of bacteraemia in children with nosocomial RSV infection (defined as RSV infection acquired either definitely or possibly in hospital) was 6 of 93 (6.5%). This was significantly greater than children with community acquired RSV infection, of whom 5 of 1702 (0.3%) were bacteraemic (OR 23.4, 95% CI 7.0 to 78.2,  $p < 0.0001$ ).

Two of the 11 children with bacteraemia had cyanotic congenital heart disease (CCHD), but only two of 100 children in the comparison group. Extrapolating from these data, the incidence of bacteraemia in RSV positive children with CCHD is 6.6%. The incidence of bacteraemia is significantly higher in children with RSV infection and cyanotic congenital heart disease than in children without congenital heart disease (OR 10.8, 95% CI 1.4 to 85.9,  $p = 0.049$ ).

**Table 1** Characteristics of 11 children with concurrent true bacteraemia and RSV infection

Age (mth)	Relevant prior medical history	Hospital acquired RSV?	Blood culture organism	PICU	Ventilatory support	Consolidation	Other radiology
1	Nil	No	<i>S aureus</i>	Yes	No	RUL	Bronchiolitis
1	Preterm–30 weeks gestation	Yes	<i>S pneumoniae</i>	Yes	Yes	RUL	Pneumatocoels
1	Nil	No	<i>S pneumoniae</i>	No	No	No	Bronchiolitis
2	Nil	No	<i>S pneumoniae</i>	No	No	No	Bronchiolitis
3	Nil	No	<i>S aureus</i>	Yes	Yes	No	Bronchiolitis
4	Nil	No	<i>S pneumoniae</i>	No	No	LLL	Pleural effusion
4	Congenital asplenia	Possible	<i>S pneumoniae</i>	Yes	No	No	Bronchiolitis
4	Cyanotic heart disease	Yes	<i>S pneumoniae</i>	Yes	Yes	No	Bronchiolitis
8	Nil	Possible	<i>S pneumoniae</i>	No	No	LLL	Bronchiolitis
22	Cyanotic heart disease	Yes	<i>S pneumoniae</i>	Yes	Yes	No	Bronchiolitis
24	Leukaemia, neutropenia	Possible	<i>S pneumoniae</i>	No	No	No	Bronchiolitis

RUL, right upper lobe; LLL, left lower lobe.  
Bronch, radiological appearance of bronchiolitis without focal consolidation.

A total of 208 (11.6%) of the 1795 children with RSV infection were admitted to PICU at least once during their RSV infection. Six (2.9%) of the 208 RSV positive children admitted to PICU had bacteraemia (table 1) compared with 5 (0.3%) of 1587 children not admitted to PICU (OR 9.4, 95% CI 2.8 to 31.1,  $p = 0.001$ ). Ventilatory support was provided in PICU to 132 RSV positive children (101 mechanical ventilation and 31 continuous positive airways pressure), or 7.4% of the total of 1795 children with RSV infection. Four (3.0%) of the 132 children who received ventilatory support had bacteraemia, compared with 7 (0.4%) of the 1663 children not given ventilatory support (OR 7.4, 95% CI 2.1 to 25.6,  $p = 0.006$ ). There was strong co-linearity between PICU admission and ventilatory support as risk factors for bacteraemia, with PICU admission being the stronger independent variable. Antibiotics were administered to 145 (70%) of the PICU admissions and to 106 (80%) of the children given ventilatory support.

Thirty nine patients were admitted to the NICU with RSV infection. Antibiotics were administered to 29 (74%) of these infants. None of them had concurrent bacteraemia, and all recovered. Prematurity and immunodeficiency were not associated with bacteraemia (table 3).

Parenteral antibiotics were administered to 45 of the 100 randomly selected RSV positive patients at the time of RSV infection. Six of these were receiving antibiotics prior to the onset of RSV symptoms, 31 were commenced empirically prior to the RSV result (nine were subsequently ceased once the result was known), and a further eight were commenced after the RSV result was known. Thus, 89 patients had no known risk factors for severe RSV infection, but 38 of the 89 (43%) were given parenteral antibiotics.

## DISCUSSION

Respiratory syncytial virus infection is rarely associated with bacteraemia in hospitalised children, even those in a tertiary level children's hospital. Hall and colleagues<sup>10</sup> found 0.7% of 565 infants hospitalised with RSV infection had a positive culture of blood or cerebrospinal fluid. This compares closely with our study, in which 11 (0.6%) of 1795 patients with RSV infection had concurrent bacteraemia. We performed blood cultures on 47% of all RSV positive patients, so we may have underestimated the incidence of bacteraemia by as much as twofold. Purcell and Fergie<sup>11</sup> reviewed the records of 2396 infants and children admitted to hospital with RSV lower respiratory tract infection; they found 12 positive blood cultures from patients investigated for bacterial infection, but all were considered contaminants. Thus they identified no RSV positive children with true bacteraemia.

It is important to identify children with true bacteraemia, since they are likely to benefit from antibiotics. In our study, 9 of the 11 children had pneumococcal bacteraemia. Only 4 of the 11, and 3 of the 9 with pneumococcal infection had radiographic changes, such as consolidation, effusion or pneumatoceles, to suggest they had bacterial pneumonia complicating RSV bronchiolitis. Furthermore, previous studies have suggested that it is difficult to distinguish viral from bacterial pneumonia on radiological grounds, since purely viral pneumonia may sometimes cause lobar consolidation.<sup>12</sup> If antibiotics were reserved for RSV positive children with radiological changes suggestive of bacterial infection, we would not have treated 7 of our 11 bacteraemic children. Other criteria are needed if bacteraemia is not to go untreated.

Previous studies have identified prematurity, bronchopulmonary dysplasia, congenital heart disease, congenital or

**Table 2** Characteristics of five children with infected central venous catheters and RSV infection

Age (y)	Background medical history	Hospital acquired RSV?	Blood culture organism(s)	PICU admission	Ventilatory support
2	Chronic lung disease Preterm (29 weeks)	No	<i>Candida albicans</i>	No	No
2	Neuroblastoma, neutropenia	Yes	<i>Klebsiella pneumoniae</i>	Yes	No
3	Leukaemia	Possible	<i>Staphylococcus aureus</i> <i>Flavimonas oryzae</i> <i>Candida albicans</i>	No	No
5	NHL, neutropenia	Yes	<i>Streptococcus viridans</i> <i>Candida albicans</i>	Yes	Yes
10	NHL, neutropenia	No	<i>Escherichia coli</i>	No	No

NHL, Non-Hodgkin's lymphoma.



**Table 3** Risk factors for bacteraemia in children with RSV infection

Risk (or exposure) factor	Unadjusted OR (95% CI)	p value
Nosocomial RSV infection	23.4 (7.0 to 78.2)	<0.0001
PICU admission	9.4 (2.8 to 31.1)	0.001
Ventilatory support	7.4 (2.1 to 25.6)	0.006
Cyanotic congenital heart disease	10.8 (1.4 to 85.9)	0.049

acquired immunodeficiency, malignancy, and cystic fibrosis as risk factors for more severe RSV disease, in terms of need for mechanical ventilation, duration of oxygen therapy, and sometimes mortality.<sup>13</sup> It seems intuitive that these groups are at greater risk of bacterial infection complicating RSV infection, but there is little formal evidence to support this view. Five of 11 children with bacteraemia and RSV infection in our study had one or more previously recognised risk factors for severe RSV infection (congenital heart disease, chronic lung disease, prematurity, or immunodeficiency).<sup>13</sup> We do not know what proportion of all our RSV positive patients had the same risk factors, but it was 11% of the comparison group. Extrapolating from these figures predicts that 197 (11% of 1795) RSV positive children had underlying risk factors for severe disease, of whom five (2.5%) were bacteraemic. Conversely, only six (0.4%) children of 1598 children predicted to have no risk factors developed bacteraemia. Thus it seems logical to have a lower threshold for antibiotic use in RSV infected children with underlying risk factors for more severe disease.

We found nosocomial RSV infection was associated with an increased incidence of bacteraemia. This is not surprising. Children at risk of nosocomial infection are more likely to have underlying conditions predisposing them to prolonged hospital stay and increasing their susceptibility to bacterial co-infection.<sup>14</sup> Nevertheless, we could find no previous studies showing that children with nosocomial RSV infection are at greater risk of concurrent bacteraemia than those with community acquired RSV, although this knowledge might be important in deciding whether or not to prescribe antibiotics. The children with nosocomial RSV and bacteraemia in our study all had pneumococcal bacteraemia (see table 1), indicating that their bacteraemia is not merely line associated. Our finding also emphasises the importance of prevention of nosocomial RSV infections, using measures such as routine hand washing by staff, isolation of patients within hospital, and cohort nursing.<sup>14 15</sup>

Other groups of children with an increased incidence of bacteraemia in our study were those with cyanotic congenital heart disease, but not acyanotic heart disease, and PICU admission. The link between heart disease, particularly cyanotic, and severe RSV has been noted before.<sup>16</sup>

We found that children with uncomplicated RSV infection were often treated with antibiotics. This is consistent with similar studies from developed countries, which show high rates of antibiotic use in RSV infection,<sup>4-6</sup> despite evidence that they are not beneficial, at least in uncomplicated infection.<sup>8 9</sup> Antibiotics were continued in over two thirds of our comparison group after the positive RSV result was known. This appears to contradict one of the most important reasons given for using rapid viral diagnosis, to reduce unnecessary antibiotic use in viral infections. The clinical indications for antibiotics are difficult to evaluate retrospectively, but it seems likely that antibiotics could have been stopped in most if not all of the patients in whom they were continued. This confirms that antibiotics are generally

overused for children with RSV infection in our hospital, as they are in other hospitals.<sup>4-6</sup>

Conjugate pneumococcal vaccines are not widely used in Australia, although they are universally recommended for children in the USA. Their introduction may have a significant impact on the incidence of bacteraemia in RSV infection, if our finding that *Streptococcus pneumoniae* is by far the commonest cause of bacteraemia, is generally true.

On the basis of this and other studies, our recommendations regarding antibiotic treatment for children with RSV infection are to:

- Consider antibiotics for any child with nosocomial RSV infection (6% will have bacteraemia on our figures).
- Consider antibiotics for any child admitted to PICU with RSV, particularly if needing ventilatory support (3% will have bacteraemia).
- Have a low threshold for treating children who have underlying risk factors for severe RSV disease such as prematurity, bronchopulmonary dysplasia, congenital heart disease (particularly cyanotic), congenital or acquired immunodeficiency, malignancy, and cystic fibrosis (2.5% bacteraemia).
- Treat when there is a strong clinical suspicion of bacterial illness (for example, very high fever, toxicity, signs of sepsis).

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