Infection with *Ureaplasma urealyticum*: is there a specific clinical and radiological course in the preterm infant?

**U Theilen, A J Lyon, T Fitzgerald, G M A Hendry, J W Keeling**

**Background:** Despite having mild early respiratory disease, many preterm babies develop chronic lung disease (CLD). Intrauterine infection with *Ureaplasma urealyticum* has been associated with preterm labour and CLD.

**Objective:** To test the hypothesis that infection with *U urealyticum* results in a specific clinical and radiological picture in the first 10 days of life.

**Methods:** Retrospective study of 60 ventilated babies < 30 weeks gestation, who had tracheal secretions tested for *U urealyticum*. Placental histology was reviewed by a paediatric pathologist for signs of chorioamnionitis. Chest radiographs were independently reviewed by two paediatric radiologists according to previously agreed criteria. All reviewers were blinded to the infection status of the babies.

**Results:** Twenty five babies were *U urealyticum* positive. These were more likely to experience chorioamnionitis (p = 0.004), premature rupture of membranes (p = 0.01), and spontaneous vaginal delivery (p = 0.09). *U urealyticum* positive babies had fewer signs of respiratory distress syndrome on early chest radiographs (p = 0.038), and they could be weaned from their ventilation settings (fraction of inspired oxygen (FiO₂) and mean airway pressure) more quickly in the first few days. Subsequently *U urealyticum* positive babies deteriorated clinically and radiologically. More often they required ventilation to be restarted (p = 0.051), a higher proportion being ventilated on day 10 (p = 0.027) with higher FiO₂ (p = 0.001) and mean airway pressure (p = 0.002). Their chest radiographs showed more emphysematous changes as early as day 5 (p = 0.045), with a pronounced difference by day 10 (p = 0.009).

**Conclusions:** Preterm ventilated babies with *U urealyticum* in their tracheal secretions have a different clinical and radiological course, with less acute lung disease but early onset of CLD, compared with those with negative cultures.
Clinical and ventilation data from the first 10 days of life were obtained by reviewing medical and nursing notes.

Placental histology was reviewed for features of chorioamnionitis. The pathologist was blind to the infection status and clinical course of the baby.

All babies had routine chest radiography but this was performed at different times depending on clinical need. Radiographs were divided into three time groups: day 1, those taken on day 1 or 2; day 5, taken on days 3–6; day 10, taken on days 7–14. Random radiographs from these time periods were reviewed independently by two paediatric radiologists, both blind to the infection status and the clinical course of the baby. Radiographs were scored for diffuse granular changes indicative of acute respiratory distress syndrome, alveolar changes characteristic of emphysema or cysts, and interstitial changes associated with developing fibrosis. The film was divided into four quadrants, and each feature scored as 0 (absent) or 1 (present) in each quadrant. This gave a total score of 0–4 for each feature in each radiograph.

$\chi^2$ and Wilcoxon rank tests were used to compare the groups.

The level of agreement between the two radiologists was assessed using Cronbach’s $\alpha$ test of reliability.

Logistic regression was used to explore the association between the development of significant emphysematous change on the radiographs on day 10 and gestation, birth weight, U urealyticum, prolonged rupture of membranes, and chorioamnionitis.

RESULTS

In the two year period, there were 89 eligible inborn babies. Secretions had been cultured for U urealyticum in 60. Twenty five were U urealyticum positive, and 35 were negative. There were no differences between the groups with respect to proportion of boys or multiple deliveries. In each group, 75% of the mothers had received at least one dose of amniatal steroids, and all babies were given replacement surfactant. In 54 babies, the surfactant was given within 15 minutes of delivery. There was no difference between the groups with respect to total number of doses of surfactant.

The babies in the U urealyticum positive group had a significantly lower gestational age. There was a trend to a lower birth weight but this did not reach significance (table 1).

Preterm premature rupture of membranes (more than 24 hours before delivery) was significantly more common in the U urealyticum positive group. There was also a trend towards vaginal delivery being more common in the U urealyticum positive group (table 1).

Placental histology was available in 24 of the U urealyticum positive group and 30 of the negative group. Table 1 shows that chorioamnionitis was significantly more common in the U urealyticum positive group. Of the 18 mothers in the study who had evidence of chorioamnionitis, 13 (72%) of the babies grew U urealyticum in the tracheal secretions.

Table 2 shows that the U urealyticum positive group had significantly higher total white cell and neutrophil counts during the first 10 days. There was a trend for an earlier peak of the white cell count in U urealyticum positive babies. This did not reach significance. There was no difference between the groups in the occurrence of positive cultures in tracheal secretions or blood for organisms other than U urealyticum.

The babies in the U urealyticum positive group were still on a ventilator and needed more support on day 10. There was a significant difference in the FIO2 (median 42 (interquartile range 31–48) between the two groups.

By 10 days of age, significantly more of the U urealyticum positive group needed to be ventilated, after a period of extubation of at least 24 hours (table 3). By this age, more of the positive group were still on a ventilator and they needed significantly higher levels of inspired oxygen and mean airway pressures than those who were U urealyticum negative (table 3).

Table 2 Early clinical course

<table>
<thead>
<tr>
<th></th>
<th>U urealyticum positive</th>
<th>U urealyticum negative</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum WCC (cm)</td>
<td>28 (24–44)</td>
<td>19 (14–29)</td>
<td>0.015</td>
</tr>
<tr>
<td>Maximum neutrophil count (x10^9/L)</td>
<td>20 (16–34)</td>
<td>13 (8–20)</td>
<td>0.013</td>
</tr>
<tr>
<td>Day of max WCC (x10^9/L)</td>
<td>8 (2–9)</td>
<td>9 (4–10)</td>
<td>0.087</td>
</tr>
<tr>
<td>Day of lowest FiO2 (%)</td>
<td>2 (1–3)</td>
<td>3 (2–6)</td>
<td>0.052</td>
</tr>
<tr>
<td>Day of lowest MAP (cmH2O)</td>
<td>4 (3–6)</td>
<td>6 (4–9)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Table 3 Clinical course after 10 days

<table>
<thead>
<tr>
<th></th>
<th>U urealyticum positive</th>
<th>U urealyticum negative</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reventilated after 24 hours off ventilator</td>
<td>8 (32)</td>
<td>4 (11)</td>
<td>0.051</td>
</tr>
<tr>
<td>Still ventilated on day 10</td>
<td>19 (75)</td>
<td>16 (55)</td>
<td>0.027</td>
</tr>
<tr>
<td>FiO2 on day 10</td>
<td>39 (31–47)</td>
<td>25 (23–32)</td>
<td>0.001</td>
</tr>
<tr>
<td>MAP on day 10</td>
<td>7 (6–8)</td>
<td>5 (4–7)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are median (interquartile range). p Value was obtained with the Wilcoxon test.

WCC, White cell count; FiO2, fraction of inspired oxygen; MAP, mean airway pressure.

Table 1 Patients and perinatal course

<table>
<thead>
<tr>
<th></th>
<th>U urealyticum positive</th>
<th>U urealyticum negative</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>25</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>25 (25–26)</td>
<td>26 (25–27.5)</td>
<td>0.016†</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>770 (710–900)</td>
<td>890 (700–985)</td>
<td>0.085*</td>
</tr>
<tr>
<td>PPROM</td>
<td>13 (52)</td>
<td>7 (21)</td>
<td>0.01†</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>13 (54)</td>
<td>5 (17)</td>
<td>0.004†</td>
</tr>
<tr>
<td>Spontaneous vaginal delivery</td>
<td>17 (68)</td>
<td>16 (46)</td>
<td>0.09†</td>
</tr>
</tbody>
</table>

Values are median (interquartile range) or number (%).

PPROM, Preterm premature rupture of membranes.

*Wilcoxon test.
†$\chi^2$ test.
Infection with *U urealyticum*

*U urealyticum* positive babies were still ventilated (16 v 9, p = 0.089) and needed a higher mean airway pressure (median 7 (interquartile range 6–8) v 5 (3–8), p = 0.076).

Looking at the outcome beyond 10 days of life in the entire study group, the total number of days of ventilation was significantly higher in the *U urealyticum* group (median 33 days (interquartile range 10–39) v 12 days (5–22), p = 0.015). More patients from the positive group were given postnatal steroids (7 v 2, p = 0.015).

At 36 weeks corrected gestation, there was no significant difference between the groups (91% in the survivors who were culture positive compared with 82% in those who were culture negative).

There were no differences between the groups with respect to need for inotropes or incidence of patent ductus arteriosus, necrotising enterocolitis, or intraventricular haemorrhage. In the *U urealyticum* positive group, there was a trend towards an increase in periventricular leucomalacia, but this did not reach significance (4 v 1, p = 0.072).

**Radiology**

The level of agreement between the radiologists was good for all features, with Cronbach’s α of 0.84 for diffuse granularity, 0.9 for emphysematous changes, and 0.9 for interstitial changes. For further analysis, the scores from the two radiologists were averaged.

Table 4 shows the results for the three time periods. The *U urealyticum* negative group showed significantly more changes characteristic of respiratory distress syndrome, as shown by the degree of diffuse granularity, on the first radiographs (fig 1). By day 5 the *U urealyticum* positive group was showing early emphysematous changes (fig 2), which were more obvious by day 10 and significantly different from the *U urealyticum* negative babies (fig 3).

There was an increasing trend to interstitial changes in fibrosis in the *U urealyticum* positive group by day 10, but this did not reach significance.

**Logistic regression**

*U urealyticum* colonised infants were less mature and had a higher incidence of chorioamnionitis and prolonged rupture of membranes. In a logistic regression model using emphysematous change on day 10 as the dependent variable with gestation, birth weight, *U urealyticum*, preterm prolonged rupture of membranes, and chorioamnionitis as covariates, only *U urealyticum* and chorioamnionitis remained as independent variables.

**DISCUSSION**

This was a retrospective study and not all ventilated babies were cultured for *U urealyticum*. It is possible that those not cultured included a number of *U urealyticum* positive babies who were well and had no significant radiological changes. However, in those cultured, the presence of *U urealyticum* in tracheal secretions resulted in a significantly different clinical and radiological course from similar babies who were culture negative.

The mothers of the *U urealyticum* positive babies had a higher incidence of preterm rupture of membranes, were more likely to have chorioamnionitis on placental histology, and vaginal delivery was more common. There was an 80% chance of finding *U urealyticum* in tracheal secretions if there was histological evidence of chorioamnionitis and preterm premature rupture of membranes or spontaneous vaginal delivery. This increased to 90% for babies of 24–26 weeks...
gestation. A higher proportion of *U urealyticum* infection in less mature preterm babies has been shown in other studies.10 Despite the significantly lower gestation of the *U urealyticum* positive group, these babies had milder acute lung disease, with less widespread radiographic changes associated with respiratory distress syndrome and more rapid weaning of initial ventilation. By 10 days, however, the positive group had worse respiratory problems than the negative group. This was confirmed in the subgroup of babies of less than 27 weeks gestation, where no difference in the gestational age was observed. This suggests that the clinical difference is an effect of infection with *U urealyticum*. Clinical deterioration correlated with radiological changes associated with emphysema seen in the *U urealyticum* positive group.

Others have reported an association of chorioamnionitis with less severe acute but more chronic lung disease.2 Antenatal infection matures the fetal lung at the expense of a disturbance in long term alveolar development. This is exacerbated after delivery by persistent inflammation in the airways, which is the precursor of chronic lung damage.11 It is not surprising that *U urealyticum* and chorioamnionitis remain covariates in a logistic regression model, as *U urealyticum* is a common cause of ascending infection in the mother and is often a factor in the preterm onset of labour. In this group of babies, the development of significant emphysematous radiographic change by day 10 was independent of gestation.

There is no universally accepted scoring system for neonatal radiographs, although other workers have used similar systems to the one devised for this study.12 There was very good agreement between the two independent radiologists for all the features, and we believe that the scoring system gave an accurate representation of the radiographic changes in these babies. The obvious changes in the *U urealyticum* positive group suggest quite significant lung damage in these babies in the first 10 days. Crouse et al13 have previously reported a higher incidence of pneumonia and precocious bronchopulmonary dysplasia in radiographs of neonates under 1250 g birth weight who had *U urealyticum* in tracheal aspirates.

Despite the clinical and radiological deterioration seen by day 10, we did not find a significant increase in the number of babies in the culture positive group who developed chronic lung disease, defined by oxygen requirement at 36 weeks corrected gestation. However, this was a small, retrospective study and not powered to look at the incidence of chronic lung disease.

*U urealyticum* is an important causative factor in preterm labour and development of chronic lung damage in the immature infant. The ORACLE study14 showed a slight benefit for the baby if mothers received erythromycin, but only if there was premature preterm rupture of membranes. There was no reduction in chronic lung disease alone, defined as oxygen dependence at 36 weeks gestation, but there was
improvement in the composite outcome, which included CLD as one of the components.

At present, there is no good evidence that treatment of the baby after delivery reduces the risk of chronic lung damage. It may be that antenatal infection has already activated the inflammatory cascade and started the lung injury sequence. Treatment after delivery may be too late. However, with a deteriorating clinical and radiological picture, it is difficult not to try to eradicate any organisms found in the respiratory tract, at least until better evidence is available from clinical trials.

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REFERENCES