LETTERS TO
THE EDITOR

Respiratory rate and pneumonia in infancy

Sir,—Dr Berman et al have presented an interesting and comprehensive paper about the use of respiratory rate in infants in the diagnosis of pneumonia.1 This is an important topic because counting respiratory rate is a critical aspect of the World Health Organisation acute respiratory illness programme. One of the difficulties has been that the normal range of respiratory rate had not previously been defined. The object of our paper was to define the normal range of respiratory rate in infants when they were awake.2

Berman et al suggested that their results (mean (SD) 61 (18)/minute) were too high because they did not compare with studies using electronic monitoring. Unfortunately, electronic monitoring is not a satisfactory gold standard for respiratory rate because studies in awake babies have movement artefact and the study of sleeping babies is not appropriate for routine clinical practice. Our range of respiratory rate for sleeping babies was similar to those in the published literature (42 (12)/minute).

They suggest that the use of a stethoscope or a hand on the chest for counting the respiratory rate in our study may have stimulated the infants to breathe faster than normal. Their own observation with studies using electronic monitoring is not a satisfactory gold standard for respiratory rate because studies in awake babies have movement artefact and the study of sleeping babies is not appropriate for routine clinical practice. Our range of respiratory rate for sleeping babies was similar to those in the published literature (42 (12)/minute).

We used this technique simply because we found it very difficult to count respiratory rate by observation and wanted to use a technique that could easily be used in all babies regardless of their state. It was our experience that respiratory rate could be counted by observation accurately in sleeping or ill babies because they lie still and often have increased respiratory effort. It was surprisingly difficult in lively healthy babies because they move approximately once a second and also breathe shallowly and irregularly.

Berman et al compare our data with a study in which respiratory rate was counted by observation in a community in Peru. Unfortunately, even that data can not be considered to represent the respiratory rate range of normal infants because the children were selected for the study only if they had a cough.

Unfortunately, the authors make a common statistical mistake when calculating sensitivity, specificity, and predictive values for pneumonia using respiratory rate above or below 50 or 60 breaths/minute. Their data were collected only from selected children seen in hospital. In their Denver study the infants were only seen if they had a cough or congestion and in the Vellore study the infants presented with a runny nose or cough.

The authors had no data from normal infants. Sensitivity, specificity, and predictive values are accurate only for the populations from which the data were derived and cannot be applied to populations in the community. Even using this selected data the sensitivity of a respiratory rate of 60 or more for lower respiratory infection was only 63% in Denver and 58% in Vellore. To be a useful screening test for pneumonia, respiratory rate measurement must have a much higher sensitivity.

Before it can be claimed that respiratory rate is a useful screening tool for pneumonia data must be presented using a simple technique of proved accuracy and repeatability from children with pneumonia and normal children in the communities where it will be used.

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Dr Berman and Simoes comment:
We appreciate the opportunity to respond to Dr Morley's comments on our annotation. The issue of the usefulness of simple clinical signs to identify pneumonia is important and we agree that it is necessary to document the range of respiratory rate counts in infants with and without acute respiratory infections. Interpretation of studies is impaired by the use of different counting methods. Unfortunately there is no counting method that can be considered a gold standard. It is possible that differences in respiratory rates reported in studies may partially reflect the different methods used to obtain them. Our own study comparing simultaneous counts obtained by observation and electronic pneumography tracing documents differences between these methods.1 Our annotation pointed out that counting with a stethoscope or by placing a hand on the abdomen may itself result in differences compared with obtaining counts by other methods. The use of a 15 second counting interval would also increase any consistent difference by a fourfold factor. We agree with Dr Morley that respiratory rates in very active 'lively' infants is difficult regardless of the counting method. Our recently completed study corroborates this finding.

The World Health Organisation (WHO) chose to develop respiratory rate thresholds based on data obtained using 60 second observed counts. This choice was made for operational reasons, based on the need to train community health workers to count respiratory rates without using a stethoscope.

The WHO respiratory rate thresholds have been designed to be used on subjects who have respiratory symptoms of cough or coryza. The case management guidelines are not relevant for healthy infants and children without respiratory symptoms. It is for this reason that sensitivity, specificity, and predictive value should be calculated on populations with respiratory symptoms. The predictive value of the respiratory rate threshold for pneumonia will vary with the prevalence of the pneumonia in the population with respiratory symptoms. It was not our intention to generalise sensitivity, specificity, and predictive value to the total population of children with and without respiratory symptoms.

We agree that the sensitivity and specificity of the WHO respiratory rate threshold applied to infants under 2 months of age is not as good as that in older infants and children. Further research is needed to evaluate the usefulness of the threshold in association with other clinical signs to diagnose pneumonia in that age group. Studies are underway in the Gambia and the Philippines to clarify these issues.


Diagnosis of pneumothorax by echocardiography

Sir,—Over the last 18 months we have performed frequent echocardiograms on ventilated neonates as part of a study on haemodynamics.2 Pneumothorax is common in this setting. We report three cases where pneumothorax was first suspected on echocardiography.

Case reports

Case 1
This infant, born at 41 weeks' gestation weighing 2370 g, was ventilated after birth asphyxia and meconium aspiration. A chest x-ray picture at 4 hours showed no air leak. At 22 hours the heart was difficult to see echocardiographically and was best seen from the right sternal edge. There was no clinical deterioration. Transillumination was negative. A further chest x-ray picture showed a small left pneumothorax which was managed conservatively. Five hours later, radiographs showed no air leak and echocardiographically the heart was easily seen and normally positioned.

Case 2
This infant, born at 25 weeks' gestation weighing 785 g, was ventilated for hyaline membrane disease. There was no air leak on a chest x-ray picture at 4 hours. At 16 hours, on echocardiography, the heart was difficult to see and displaced to the right. Transcutaneous carbon dioxide had risen from 4·5 to 6·9 kPa over the previous half hour. Transillumination showed left tension pneumothorax. After drainage, the heart was no longer displaced on echocardiography.

Case 3
This infant, born at 27 weeks' gestation weighing 1040 g, was ventilated for hyaline membrane disease and birth asphyxia. A chest x-ray picture at 10 hours showed no air leak. Echocardiography at 14 and 36 hours showed poor myocardial function. From 48 to 52 hours systolic blood pressure fell from 40 mm Hg to 32 mm Hg despite support. At 52 hours the heart was difficult to see echocardiographically but was displaced to the left with the apex tilted cranially. Transillumination showed right tension pneumothorax. After drainage the blood pressure rose to 58 mm Hg; echocardiography showed an easily seen, normally positioned heart.

The heart is normally easy to see echocardiographically in the neonate ventilated for hyaline membrane disease. In these three cases the heart was difficult to see from the left sternal edge, and was displaced laterally away from the air leak; this was presumably due to a combination of mediastinal shift and interposing air, which is impervious to ultrasound.

Unilateral pulmonary interstitial emphysema has mimicked these findings, hypertonated
lung lying in front of the heart. With other causes of mediastinal shift the heart should be easily seen unless there is air in front of it; in diaphragmatic hernia the heart should be visible in its displaced position until bowel gas accumulates.

Ultrasound is therefore a new technique to diagnose pneumothorax, but it is clearly not the best, and any suspicion should be confirmed using conventional methods before treatment. Nevertheless, pneumothorax can be a catastrophic complication of hyaline membrane disease, and those performing echocardiography on sick, ventilated neonates should be aware of this, so if the heart is difficult to visualise, or is laterally displaced, the attending clinicians can be informed immediately.

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Fluconazole in neonatal disseminated candidiasis

Sir,—We report the case of an infant, born at 28 weeks' gestation weighing 900 g, who on the 22nd day of life had thrombocytopenia and leucocytosis. Urine and blood cultures isolated Candida albicans. Amphotericin B was raised to 1.0 mg/kg/day by day 4 and on day 5, fluconazole 25 mg/kg every six hours was added and a brovicath catheter inserted. Peripheral and central blood cultures on the 7th, 14th, and 18th days of treatment with amphotericin B continued to yield C albicans, and cultures of abscesses on the forehead and arm yielded C albicans on day 18. Ultrasound of the kidneys, head, and abdomen as well as an ophthalmologic examination, gallium scan, and culture of the cerebrospinal fluid were negative. Amphotericin B and fluconazole were discontinued after 18 and 12 days, respectively. The catheter was removed and intravenous fluconazole (6 mg/kg/day) initiated. The catheter was replaced on day 4 of fluconazole. On day 5 of fluconazole peripheral and central blood cultures were negative for C albicans. Fluconazole was discontinued after 20 days with cultures remaining negative during four months of follow up.

Fluconazole serum concentrations three hours after the infusion and before the next dose on day 7 of treatment were 10.30 and 6.98 μg/mL. Amphotericin B concentrations were 0.21 μg/mL on day 14 of treatment and 0.12 μg/mL 30 days after discontinuation. A first order, one compartment model was used in the following pharmacokinetic parameters for fluconazole:

\( t_{1/2}=37.4 \text{ hours, } aVd=1.2 \text{ L/kg, } CL=0.02 \text{ L/kg/hour}. \) (Where \( t_{1/2} \) is terminal elimination half life, \( aVd \) is the apparent volume of distribution, and \( CL \) is clearance.) This indicates a larger \( aVd \) and a longer \( t_{1/2} \) as compared with adults (9.7 (0.06) L/kg and 22 (3.5) hours). The activities of four antifungal drugs against the isolate of \( C \) albicans from this patient are indicated in the table. These results do not necessarily reflect therapeutic efficacy. Because of the vitamin D deficiency, the amphotericin B during and after fluconazole, one could speculate that fluconazole and amphotericin B acted synergistically. Other factors, however, may have also contributed to eradication of \( C \) albicans. Further studies of fluconazole's efficacy in immunocompromised adults with invasive fungal disease are needed before studies in neonates are considered.

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Fluconazole

<table>
<thead>
<tr>
<th>Minimum inhibitory concentration and minimum lethal concentration of four antifungal drugs (concentrations in μg/mL)</th>
<th>Amphotericin B</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Schering 39304</th>
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<tr>
<td>Minimum inhibitory concentration:</td>
<td>24 hours</td>
<td>48 hours</td>
<td>24 hours</td>
<td>48 hours</td>
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<tr>
<td>&lt;0.01</td>
<td>&lt;0.29</td>
<td>&gt;80.00</td>
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<td>5.00</td>
<td>12.00</td>
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<td>Minimum lethal concentration:</td>
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<td>&gt;0.01</td>
<td>&gt;2.51</td>
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<td>5.00</td>
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Children and adults infected with \( C \) albicans and \( C \) glabrata are treated with fluconazole. Fluconazole's efficacy in children, however, is not well documented. Oral fluconazole is absorbed and undergoes a first order, one compartment model with a half life of 28 hours. Fluconazole's bioavailability ranges from 51% to 69% in adults, and it is extensively distributed (oral volume of distribution of 1.12 L/kg). Daytime plasma drug concentrations range from 2.2 to 11.6 μg/mL, and 24-hour concentrations range from 0.2 to 0.8 μg/mL. Plasma levels of fluconazole are not consistent with therapeutic effects, and these levels are achieved after five days of therapy. The drug is rapidly eliminated from the body. In adults, the volume of distribution is 1.2 L/kg, and the half life is 28 hours. In neonates, the volume of distribution is 1.12 L/kg and the half life is 28 hours. The drug is rapidly eliminated from the body. In adults, the volume of distribution is 1.2 L/kg, and the half life is 28 hours. In neonates, the volume of distribution is 1.12 L/kg and the half life is 28 hours. In adults, the volume of distribution is 1.2 L/kg, and the half life is 28 hours. In neonates, the volume of distribution is 1.12 L/kg and the half life is 28 hours.

The paediatric departmental library

Sir,—Dr Clayton is, I fear, somewhat optimistic when he suggests that we are 'on the brink of a breakthrough in data retrieval' by which we will 'access original articles and learned reviews at the touch of a few buttons . . . so the medical library will pass into the mists of memory'. Clearly this sort of thing is on the horizon. I already spend nearly as much time advising doctors on suitable