Neonatal pneumonia

S Webber, A R Wilkinson, D Lindsell, P L Hope, S R M Dobson, D Isaacs

Abstract

All babies admitted to the neonatal unit during a period of 41 months were prospectively studied to find out the incidence, aetiology, and outcome of neonatal pneumonia, and the value of routine cultures of endotracheal tubes. Pneumonia of early onset (before age 48 hours) occurred in 35 babies (incidence 1·79/1000 live births). In 20 (57%) it was caused by group B streptococci. Blood cultures showed the presence of organisms in 16 of the 35 (46%).

There were 41 episodes of pneumonia of late onset in 39 babies. Thirty six of the 39 were preterm, and 34 were artificially ventilated (10% of all ventilated babies). Endotracheal tube colonisation had occurred in 94% of these, most commonly by Gram negative organisms and *Staphylococcus epidermidis*. In only one of seven cases with simultaneous bacteraemia was the same organism grown from cultures of the blood. After controlling for gestational age and duration of artificial ventilation there was no difference in the incidence or timing of endotracheal tube colonisation between babies who did and did not have pneumonia of late onset.

Ten babies with pneumonia of early onset (29%) died; all were preterm infants. Only one death (2%) was associated with an episode of pneumonia of late onset. Routine surveillance cultures were not helpful in predicting and managing pneumonia of late onset.

There are serious problems in defining neonatal pneumonia and in determining its causes.[1] This has led to a paucity of data, particularly about those infants who survive. Disease of early onset is most commonly caused by ascending infection from the maternal genital tract across the membranes,[2] and the baby is often septicaemic at birth.[3] Pneumonia of late onset is usually caused by nosocomial infection, but occasionally by 'auto infection' from maternal organisms that colonised the infant at birth. Many of the reports about the bacteriology of neonatal pneumonia concern cultures taken at necropsy.[4–7] The results of these studies have shown that though most babies with pneumonia do have bacteria in their lungs at the time of death, so do many babies who die without contracting pneumonia.[4 6 7]

Routine surveillance screening by culture of aspirates from endotracheal tubes and swabs of the skin is commonplace among babies on neonatal units.[8] Several early studies reported that this was useful both for predicting the occurrence, and defining the aetiology, of early and late neonatal sepsis.[9–14] Recent studies, however, have cast doubt on its value in neonatal septicaemia of late onset.[8 15–17] The value of surveillance cultures in relation to pneumonia of late onset had not specifically been studied.

We have prospectively studied all babies admitted to our neonatal unit during a period of 41 months to find out the incidence, bacterial aetiology, and outcome of neonatal pneumonia. The value of routine surveillance cultures of aspirates from endotracheal tubes from babies being artifically ventilated was also studied.

Patients and methods

All babies admitted to the neonatal unit at this hospital during the 41 months from May 1984 to 30 September 1987 were studied. Pneumonia was defined as respiratory distress associated with changes on the chest radiograph that suggested pneumonia and that persisted for at least 48 hours. We therefore attempted to exclude transient episodes of atelectasis or collapse caused—for example—by misplacement of endotracheal tubes, and consolidation thought to be the result of pulmonary oedema. Recognised changes on chest radiographs included nodular or coarse patchy infiltrates, diffuse haziness or granularity on an air bronchogram, perihilar interstitial streaking, and lobar or sublobar consolidation.[18] All radiographs were reviewed by one consultant paediatric radiologist who did not know the clinical findings. It was often difficult to distinguish pneumonia from hyaline membrane disease. In such cases additional evidence such as the presence of neutropenia, appearances on the chest radiograph that were not completely typical of hyaline membrane disease, or other clinical and laboratory data that supported a diagnosis of pneumonia, were sought. When doubt existed, the baby was always treated with appropriate antibiotics but was not included as a case of definite or probable pneumonia for the purposes of this study. Thus for example, a newborn baby with classical hyaline membrane disease who was subsequently shown to be colonised with group B streptococci but whose blood cultures showed no bacteria was not included as a case of probable or definite pneumonia. Cases were labelled as 'definite' pneumonia only if a respiratory pathogen was isolated from the blood. Cases were labelled as 'probable' pneumonia if blood cultures failed to show a pathogen. In these cases identification of a likely causative organism was based on the results of cultures of endotracheal tube aspirates, nasopharyngeal aspirates, and skin.

John Radcliffe Hospital, Oxford, Neonatal Unit, Department of Paediatrics
S Webber
A R Wilkinson
P L Hope
S R M Dobson
D Isaacs

Department of Radiology
D Lindsell

Correspondence to:
Dr A R Wilkinson, John Radcliffe Hospital, Neonatal Unit, Department of Paediatrics, Headington, Oxford, OX3 9DU.

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Cases of pneumonia were divided into those of early or of late onset. Pneumonia of early onset was defined as the onset of symptoms during the first 48 hours after birth. Pneumonia of late onset was defined as the onset of illness more than 48 hours after birth.

Routine surveillance consisted of taking bacterial cultures of endotracheal tube aspirates from artificially ventilated babies three times a week. In infants in whom pneumonia was suspected, which included any newborn baby with respiratory distress, specimens were obtained by cotton wool swabs from nose, throat, eye, ear, rectum, and umbilicus; specimens of urine, blood, and cerebrospinal fluid were also collected. Collection of cerebrospinal fluid was sometimes delayed for one or more days in infants who were critically ill.

Specimens were inoculated on to blood agar plates aerobically and anaerobically, McConkey plates, chocolate agar plates in 5% carbon dioxide, and into cooked meat broth. Organisms were identified according to standard laboratory techniques.[19] Sensitivities to antibiotics were determined by the method of Stokes and Ridgway.[20] Blood cultures were regarded as 'positive' if there was a growth of a likely pathogen within 72 hours in at least one of two bottles. Cultures of *Staphylococcus epidermidis* from blood were, however, only considered important if growth occurred rapidly (within 48 hours) in both bottles, and if the organisms showed identical antibiotic sensitivities. Probable contaminants (for example, α-haemolytic streptococci and diphtheroids) were not regarded as pathogenic.

Patterns of endotracheal tube colonisation were studied by comparing babies who had pneumonia with controls who did not, and who were matched closely for gestational age and duration of artificial ventilation. Controls were chosen by selecting the next admission to the unit who was matched to within one week for gestational age and to within two days for duration of artificial ventilation (or to within seven days for babies who were artificially ventilated for more than 28 days). The significance of differences between colonisation rates was assessed by the χ^2 test, and those in mean time to colonisation by the paired t test.

Results

PNEUMONIA OF EARLY ONSET

During the study period of 41 months there were 19596 liveborn deliveries in this hospital, which is a tertiary care referral centre catering for high risk pregnancies; 1960 of these deliveries (10%) were to mothers referred from outside the area. There were 35 cases of pneumonia of early onset in these babies, giving an incidence of 1·79/1000 live births. Sixteen cases (46%) of pneumonia of early onset were 'definite': that is, clinical and radiological features of pneumonia were associated with positive blood cultures. There were also 19 cases of probable pneumonia. Of the 16 definite cases, 11 (69%) were caused by group B streptococci, although *Streptococcus pneumoniae* infection occurred in three and untypable *Haemophilus influenzae* in two babies. Five babies with pneumonia caused by group B streptococci, two in whom it was caused by *S pneumoniae*, and one in whom it was caused by *H influenzae* died, giving a mortality of 50% for definite pneumonia. None of these babies had meningitis. Of the 16 babies with definite pneumonia, 15 had a full set of cultures obtained from sites on the skin, and nasopharyngeal and endotracheal tube aspirates. Nasopharyngeal aspirates were positive for the organism obtained from blood cultures in 12 of 15 cases (80% sensitivity for predicting septicaemia). If all sites were included this rose to 13 cases (87% sensitivity).

Table 1 Potential risk factors for sepsis in 35 babies with pneumonia of early onset

	Total No	*No with only one risk factor*
Spontaneous onset of preterm labour	23	17
Prolonged rupture of membranes (>18 hours)	9	2
Maternal fever (>37·5°C)	3	1
Smelly liquor	2	0
No risk factors	8	—

Among the cases of probable pneumonia, cultures of endotracheal or nasopharyngeal secretions, or superficial sites, or both, grew a potential pathogen in 10 of 19 cases (53%). Group B streptococcus was the organism isolated in nine cases, group F streptococcus in one, and no organism in nine cases. Two babies with probable group B streptococcal pneumonia died. The overall mortality from pneumonia of early onset (both definite and probable) was 10 of 35 (29%). The signs and symptoms of those babies who died was similar whether the disease was caused by group B streptococci, *S pneumoniae*, or *H influenzae*. Deterioration was generally rapid, and both the course and the radiological appearances closely mimicked those of severe hyaline membrane disease. Twenty three cases of pneumonia of early onset (66%) occurred in preterm infants of less than 37 weeks' gestational age at birth, and 10 (43%) died. None of the 12 who had been born at term died.

Potential risk factors are shown in table 1. In eight cases (23%) there were no clear risk factors for the early development of sepsis. In 20 cases (57%) there was only one risk factor, and in seven cases (20%) there were two or more risk factors. Where a single risk factor was identified, this was usually the spontaneous onset of preterm labour (85%). It was noteworthy that in those babies for whom spontaneous onset of preterm labour was the only risk factor, the diagnosis by the admitting junior doctor was almost invariably that of hyaline membrane disease alone. Sepsis had, however, been included in the initial differential diagnosis for all babies with other risk factors for infection such as prolonged rupture of membranes or smelly liquor.

PNEUMONIA OF LATE ONSET

Forty one episodes of pneumonia of late onset

occurred, in 39 babies (tables 2 and 3). Thirty six of these babies (92%) were preterm. Four had already had episodes of pneumonia of early onset. Thirty four (87%) were being artificially ventilated at the time they developed pneumonia. The indication for artificial ventilation was hyaline membrane disease in all except one baby, who had been born at term and had meconium aspiration syndrome. The mean gestational age of these babies was 28 weeks and the mean time to onset of pneumonia was 35 days. Two thirds had been artificially ventilated for more than 21 days. Pneumonia of late onset developed in 36 of 358 (10%) babies who were artificially ventilated for more than 24 hours. Only one baby died of pneumonia in this group—a baby with cystic fibrosis who has previously been described.[21] Several babies died later, however, of extreme prematurity.

Seven episodes (17%) of pneumonia of late onset were definite, with positive blood cultures (table 2). In all cases the organisms grew rapidly within 48 hours in both bottles. Two of the babies (one of whom died) each grew two organisms from blood cultures, and these were not thought to be contaminants. In one instance was the same organism grown from the blood cultures and from the endotracheal or nasopharyngeal secretions. In three of the other six cases antibiotic treatment for suspected pneumonia based solely on cultures of endotracheal aspirates would have resulted in inappropriate antibiotics being given.

Table 2 Bacterial isolates from seven babies with pneumonia of late onset (presenting after 48 hours of age)

Case No	From blood culture	From culture from nasopharynx or endotracheal tube
1	*Pseudomonas aeruginosa, Achromobacter xylosoxidans*	No growth
2*	*P aeruginosa, Streptococcus faecalis*	No growth
3	*S epidermidis*	*S aureus*
4	*S epidermidis*	Coliform sp *S faecalis*
5	*P aeruginosa*	*P aeruginosa*
6	*S epidermidis*	*P aeruginosa* Coliform sp
7	*S epidermidis*	Coliform sp

*Baby subsequently diagnosed as having cystic fibrosis and died.

Table 3 Bacterial isolates from nasopharyngeal or endotracheal secretions of 32 babies during 34 probable episodes of pneumonia of late onset

Gram negative bacilli:	30
Coliform sp	15
P aeruginosa	12
Escherichia coli	2
Proteus mirabilis	1
S aureus	5
S epidermidis	2
Group B streptococcus	1
H influenzae	1
No organism identified	4

The organisms isolated from endotracheal tube cultures in 34 babies with probable pneumonia of late onset are shown in table 3. It can be seen that Gram negative bacilli predominate, although *Staphylococcus aureus* was also found fairly often. Multiple isolates were common.

Endotracheal tube colonisation was present in 34 of the 36 intubated babies who developed pneumonia of late onset (94%) compared with only 80 of 194 babies ventilated during the study period (41%) ($p<0{\cdot}001$, table 4). After controlling for duration of artificial ventilation and gestational age, however, it was found that there was no significant difference between the rate of colonisation in the two groups (only 30 of the babies could be appropriately matched). Furthermore, there was no difference in the average time to colonisation between babies who did and did not have pneumonia, nor was there any difference between the different organisms that were cultured from the endotracheal tube aspirates in the two groups.

All cases of pneumonia of late onset were initially treated with flucloxacillin and either netilmicin or gentamicin given intravenously. An increase in ventilatory support was usually necessary. In seven of 41 episodes (17%) one or more of the organisms from the endotracheal tube was resistant to the particular antibiotics being used. Most babies recovered rapidly and it was rarely necessary to change the antibiotics.

Discussion

The diagnosis of neonatal pneumonia is difficult and though there is much information from necropsy reports there is little from clinical and laboratory studies of surviving babies. One area of difficulty is the close similarity between hyaline membrane disease and neonatal pneumonia, with or without hyaline membrane disease. Our case definition of pneumonia is fairly rigorous, and the incidence of neonatal pneumonia has probably been underestimated. We have not been able to show clearly the aetiological agent in those babies who we thought had pneumonia but who had negative blood cultures. In pneumonia of early onset when babies are heavily colonised with pathogenic bacteria such as group B streptococci, it seems likely that in most cases this is the relevant pathogen. In nine early cases and four late

Table 4 Colonisation of endotracheal tubes in babies who were artificially ventilated for longer than 24 hours, and presence of pneumonia of late onset

	No who had pneumonia	*No (%) colonised*	*No who did not have pneumonia*	*No (%) colonised*	*p Value*
Before controlling for gestational age and duration of ventilation	36	34 (94)	194	80 (41)	<0·001
After controlling for gestational age and duration of ventilation*	30	28 (93)	30	25 (83)	0·4

*Mean (range) times to colonisation in those with and without pneumonia were 8 (1–15) and 10 (2–39) days, respectively ($p>0{\cdot}05$).

cases, however, no organism was cultured either from blood or surface cultures.

In this study we have not specifically investigated the role of other pathogens, which are now attracting increasing interest from various investigators. These organisms include *Ureaplasma urealyticum, Mycoplasma* sp, *Chlamydia trachomatis, Pneumocystis carinii,* and viruses.[22–24] It is possible that some of these organisms were responsible for infection in cases of pneumonia in which the blood culture was negative.

In early disease, the group B streptococcus remains the most important pathogen in our unit. As there is much local variation in the range of organisms causing sepsis it is important that each neonatal unit monitors its own predominant organisms. An increase in the proportion, for example, of *H influenzae* infections may suggest the initial antibiotic policy should be reviewed.

Although the overall mortality for pneumonia of early onset remains high, it is encouraging to note that in the study period no deaths occurred in babies born at term who had pneumonia of early onset. This must partly reflect the increased awareness of sepsis by midwifery and junior medical staff in our maternity and neonatal units. It is important to recognise, however, that risk factors are often absent in babies who develop pneumonia of early onset, and that spontaneous onset of preterm labour is in itself an important risk factor. Our findings support the practice of many units that all preterm babies with respiratory distress should be given antibiotics intravenously for at least 48 to 72 hours until the results of blood cultures are available.

We have shown that endotracheal tube colonisation occurs equally in babies whether or not they have pneumonia of late onset. There seems to be a poor correlation between blood cultures and cultures of endotracheal and nasopharyngeal aspirates in these babies. This casts doubt on whether the organisms cultured from the nasopharynx or endotracheal tube are truly those causing the pneumonia. Clearly babies should not be treated for 'pneumonia' because of endotracheal colonisation with a potential pathogen if there are no accompanying radiological changes. Furthermore, reliance on the results of cultures from endotracheal tube aspirates and the accuracy of their antibiotic sensitivities will often lead to inappropriate antibiotic treatment.

Although there are some published data to support the practice of taking endotracheal cultures from babies with suspected sepsis at birth,[12–14] there is conflicting evidence about the role of routine surveillance in predicting and managing neonatal sepsis of late onset.[8–11 15–17] The practice of routine surveillance of endotracheal tube aspirates is widespread.[8] We have previously shown that routine surveillance cultures are an inefficient means of predicting the aetiology of late septicaemia, and that considerable caution should be exercised in making decisions about antibiotic treatment based on colonisation patterns in neonatal units.[16] Two other studies have recently been published supporting this view. Evans *et al* analysed their experience of surveillance cultures from over 3000 infants,[8] and showed that the sensitivity, specificity, and positive predictive value of such cultures are generally poor and of limited value in predicting the aetiology of neonatal sepsis, as well as being expensive. Slagle *et al* from New York have investigated the role of routine endotracheal tube cultures in the prediction of late sepsis (though not specifically pneumonia) in artificially ventilated babies.[17] In their study, an organism was isolated from both the blood culture and the endotracheal tube aspirate culture in only five of 26 cases of proved sepsis (19%), though in a further seven cases the organism in the blood was also found as one of multiple isolates in the endotracheal tube culture. They also showed that inappropriate antibiotic treatment would have been given in a large number of cases (42%) if the antibiotic choice had been based on the sensitivity of the predominant isolates from the endotracheal culture.[17] Our data also suggest that routine surveillance cultures contribute little to the prediction and management of pneumonia of late onset, and may even be misleading. A baby with pneumonia should be treated according to the unit's antibiotic policy rather than its own surveillance cultures. There may, however, be some role for more limited surveillance of the organisms colonising the highest risk babies in the neonatal unit, because their resistance patterns may help to formulate antibiotic policies.[25]

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