Personal practice

Antibiotic use in the neonatal unit

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The changing pattern of organisms causing neonatal sepsis, from *Streptococcus pyogenes* in the 1930s to *Staphylococcus aureus* in the 1950s and more recently to Gram negative bacilli and the group B streptococcus,¹ has been reflected in the development of new antibiotics. In particular semi-synthetic penicillins and the so called third generation cephalosporins have been introduced, both with activity against a wide range of Gram negative as well as some Gram positive organisms.

There remains some uncertainty about whether it is best to use these antibiotics for all episodes of suspected sepsis or to reserve them for episodes not responding to more conventional antibiotics. In a recent survey of antibiotic use in neonatal units in the United Kingdom and Eire, conducted through the British Association of Perinatal Paediatrics, replies were received from 30 institutions, who regularly used 24 different antibiotic policies. This may reflect a rational approach to changing causes of sepsis and changing antibiotic resistance patterns but may equally be due to uncertainty over which of the many possible antibiotics to use.

The aim of this article is to review antibiotic options in the light of known causes of neonatal sepsis and our experience and to give a rational explanation of our own antibiotic policies.

Early onset sepsis

Most neonatal units use different antibiotics for babies with onset of sepsis within the first 48 hours of life (early onset) and those with sepsis starting after 48 hours (late onset). Early onset sepsis is almost invariably due to organisms acquired transplacentally or to ascending infection from the vaginal canal, whereas onset after 48 hours may be due to organisms acquired either at delivery or on the neonatal unit.¹

Early onset sepsis is usually treated with penicillin or ampicillin and an aminoglycoside, as group B streptococcal infection and infection with Gram negative organisms are currently the most com-

monly identified causes.¹ Babies with early onset sepsis may present with non-specific signs or may have a respiratory illness that, in the case of group B streptococcal infection, is clinically and radiologically indistinguishable from hyaline membrane disease.² In Britain the incidence of early onset group B streptococcal sepsis is about 0.3 cases per 1000 live births,³ considerably lower than in the United States where it is 2.0–3.7 per 1000.² It may rise sporadically to higher rates in some areas, and an incidence of 1.4 per 1000 was described in West Berkshire in 1978.⁴ The low incidence of group B streptococcal sepsis has meant that short term studies of the newer ureidopenicillins⁵ or third generation cephalosporins^{6,7} in the management of early onset sepsis have included very few cases of group B streptococcal disease. Thus the studies have been too small to show any difference between the newer antibiotics and penicillin, which is the treatment of choice for group B streptococcal sepsis.²

The main reasons proposed for researching alternative treatments to penicillin and an aminoglycoside are the potential ototoxicity and nephrotoxicity of aminoglycosides and the cost of monitoring blood concentrations. There is no evidence that aminoglycosides cause appreciable toxicity in neonates.^{8,9} We measure serum gentamicin concentrations after 48 hours when a steady state has been reached,⁹ and a decision is then made whether or not to stop antibiotics. This ensures early review of the necessity for antibiotics, often eliminates the expense of measuring concentrations, and minimises the risk of toxicity.

In the 18 months from 1 May 1984 to 31 October 1985 we have diagnosed 18 episodes of early onset sepsis. In this time there were 8708 live births at the hospital. There have been six cases of group B streptococcal sepsis, with four deaths. In addition, although not fulfilling our strict criteria of sepsis as positive blood or cerebrospinal fluid cultures, or both, two babies heavily colonised with group B streptococci but with negative blood cultures died from histologically proven pneumonia. Our current

policy is high dose penicillin (100 000 units/dose/kg every 12 hours) and gentamicin (2.5 mg/kg/dose intramuscularly every 12 hours for babies with birth weight over 1500 g, every 18 hours if under 1500 g) for suspected early onset sepsis. As group B streptococcal infection was the only detected infectious cause of early onset mortality it would be illogical for us to use any alternative to penicillin or ampicillin for the treatment of early onset sepsis. The fact that 50% or more of babies with early onset group B streptococcal sepsis still die despite early treatment with penicillin² suggests that alternative treatment strategies are needed. Boyer *et al* in Chicago have shown that among pregnant women colonised with group B streptococcus a group can be identified with preterm labour, rupture of membranes for greater than 18 hours, or maternal fever, whose infants comprise three quarters of all cases of early onset sepsis.¹⁰ Their recent study shows that the incidence of early onset group B streptococcus sepsis can be significantly reduced by giving the at risk mothers ampicillin during labour.¹¹

Some authors have advocated administration of a single dose of intramuscular penicillin to all newborns as prophylaxis against group B streptococcal infection. One group found that this significantly reduced colonisation and sepsis, but the slight improvement in mortality from organisms sensitive to penicillin compared with the control group was offset by a rise in mortality from organisms resistant to penicillin.^{12 13} In a separate study of high risk babies under 2000 g, single dose penicillin prophylaxis did not alter the incidence of, nor mortality from, group B streptococcal sepsis.¹⁴ It may be possible to identify term babies on the postnatal wards with group B streptococcal pneumonia by measuring their respiratory rate; a non-invasive method has been described.¹⁵

Ampicillin is widely used in the USA as an alternative to penicillin and is active against some of the Gram negative organisms causing early onset sepsis. It is possible, however, that the use of broad range antibiotics such as ampicillin and the third generation cephalosporins may be a factor in promoting systemic candidiasis and that use of ampicillin may encourage plasmid mediated multiple drug resistance. We feel justified in using the narrower range penicillin G in view of the lack of morbidity caused by organisms other than group B streptococci.

Late onset sepsis

Gram negative organisms are far more likely to cause late onset than early onset sepsis, and this has been the rationale for some units changing to third

generation cephalosporins for the treatment of suspected late onset sepsis.^{6 7} In particular *Pseudomonas aeruginosa*, which was reported by seven of the 30 British institutions to colonise many of their patients, has caused problems in many European countries, and the high activity of ceftazidime against *Pseudomonas* is attractive.

The initial treatment for late onset sepsis, excluding meningitis, in Oxford is flucloxacillin and gentamicin. The original basis for the use of flucloxacillin was the high incidence of infections with *Staph. aureus* in the 1960s. Although *Staph. aureus* is now an uncommon cause of late onset sepsis, many units have reported *Staph. epidermidis* to be their commonest cause of late onset septicaemia,¹⁶ even allowing for difficulty in interpreting the significance of blood cultures positive for what is also a common skin contaminant. In fact neither *Staph. aureus* nor *Staph. epidermidis* are common causes of late onset sepsis in Oxford (Table). A possible reason is that enteral feeds are begun very early in this unit and central venous catheters are rarely used, *Staph. epidermidis* being notorious for colonising venous catheters and other indwelling synthetic materials.

Twenty seven episodes of late onset sepsis occurred in 18 months in Oxford, nine being polymicrobial (Table). Gram negative organisms predominated, but faecal streptococci comprised the commonest single organism. The third generation cephalosporins are inactive against enterococci,¹⁷ and colonisation with faecal streptococci is common when these antibiotics are widely used.⁷ We would substitute a third generation cephalosporin for flucloxacillin if blood cultures were growing Gram negative bacilli and the patient was still unwell on flucloxacillin and gentamicin; this happened in six of the 27 episodes of septicaemia. We would not use third generation cephalosporins as first line treat-

Table Bacterial isolates in 27 episodes of septicaemia (nine polymicrobial) after 48 hours of age in the Neonatal Unit, John Radcliffe Hospital, Oxford, between 1 May 1984 and 31 October 1985

Organism	No
Faecal streptococci	11
<i>Pseudomonas</i>	9
<i>Klebsiella</i>	5
<i>Escherichia coli</i>	3
<i>Staphylococcus epidermidis</i>	3
<i>Serratia</i>	2
<i>Clostridium</i>	1
<i>Acinetobacter</i>	1
<i>Achromobacter</i>	1
Total	36

ment for suspected sepsis because of the high incidence of infection with faecal streptococci.

There were two deaths among the babies with late onset sepsis. One baby with *P. aeruginosa* meningitis and septicaemia died after treatment for 24 hours despite receiving ceftazidime and netilmicin from the time of diagnosis, while a preterm baby with cystic fibrosis and recurrent pneumonias not responding to treatment developed septicaemia with *P. aeruginosa* and *Str. faecalis* as a terminal event.

All other babies recovered. Colonisation of infants with aminoglycoside resistant strains was common. Up to 25% of *Pseudomonas* and up to 50% of coliforms were resistant to the aminoglycoside in use, but these strains rarely caused sepsis. Only two of the bacteria isolated from babies with septicaemia, a *P. aeruginosa* and an *Achromobacter xylosoxidans*, were resistant to aminoglycosides and one baby had a shunt infection with *P. aeruginosa* resistant to ceftazidime and piperacillin but not aminoglycosides. All three babies recovered. Other workers have found a similar lack of correlation between colonisation with resistant organisms and episodes of systemic sepsis.¹⁸ Our low mortality and morbidity from late onset sepsis do not warrant any change from our present policy of flucloxacillin and gentamicin for suspected sepsis after 48 hours of age. Continued surveillance of the outcome of late onset infections will determine the effectiveness of this approach. We reserve the use of third generation cephalosporins for severe Gram negative infections not responding to conventional treatment, with the aim of limiting the emergence of strains resistant to these important antibiotics.

Late onset pneumonia

Babies receiving artificial ventilation will often have episodes of increased pulmonary shadowing on x ray film, which could be due to infection or pulmonary oedema, and the distinction is often extremely difficult. When the shadowing resolves within 24 hours fluid seems the likely cause. Often, however, the diagnosis is unclear and empirical treatment with antibiotics is necessary. We base this treatment on the results of thrice weekly cultures of endotracheal secretions from artificially ventilated babies and would only treat if there were x ray changes and clinical deterioration. Some neonatal units treat endotracheal cultures regardless of the clinical picture or x ray appearance. As about 50% of our babies develop endotracheal tube colonisation with a potential pathogen that is not eradicated by antibiotics this practice will result in considerable overuse of antibiotics.

Duration of treatment

Altogether, 96% of blood cultures that grow an organism do so within 48 hours and 98% within 72 hours.¹⁹ Babies treated with antibiotics for over 72 hours are more likely to become colonised with Gram negative organisms.²⁰ Furthermore, the old idea that courses of antibiotics should be completed to prevent the emergence of resistant strains has been superseded by the realisation that increasing use of antibiotics selects for antibiotic resistant strains.²¹ We, therefore, stop antibiotics given for suspected early or late onset sepsis after 48 to 72 hours if blood cultures yield negative results. When pneumonia seems a strong likelihood but the results of blood cultures are negative we would usually give five days of antibiotics, but this duration of treatment is purely empirical and physiotherapy seems at least as important as antibiotics. Proven septicaemia is treated for at least 10 days and there have been no recurrences.

Surveillance

Unlike other workers²² we have not found that nasopharyngeal colonisation with a pathogen is a common antecedent of late onset septicaemia with the same organism. On the contrary, of the 26 episodes of late onset septicaemia in which the nasopharyngeal and surface colonisation of the baby was known, the bacteria isolated from blood cultures were only colonising the baby in 10 cases. Furthermore, although the results of endotracheal and surface cultures showed that resistance to aminoglycosides in colonising organisms was common, this was not reflected in episodes of sepsis with resistant organisms. Thus routine surveillance of surface or stool bacteria is not performed on our unit. We do, as stated previously, routinely culture endotracheal secretions as this often affects choice of treatment with antibiotics for pneumonia.

Bacterial meningitis

The treatment of proven or suspected bacterial meningitis will depend on the Gram's stain of the cerebrospinal fluid (CSF). In the absence of a shunt or of signs of disseminated staphylococcal sepsis, Gram positive cocci in the CSF will almost certainly be group B streptococci. The treatment for group B streptococcal meningitis is high dose penicillin G (150 000 to 250 000 units/kg/day) with or without gentamicin.²³

When Gram negative bacilli are seen in the CSF the optimum treatment is less clear cut. Most units in the United Kingdom still use chloramphenicol (de

Louvois J. Personal communication.), but results with this drug have not been impressive^{24, 25} and its toxicity has been a major problem.²⁶ Furthermore, *Pseudomonas* and many coliforms are fairly resistant to chloramphenicol.²⁵ The third generation cephalosporins have excited attention because of their excellent penetration of CSF and high activity against Gram negative organisms, although only ceftazidime is potent against *Pseudomonas*. Experience with these drugs, however, is very limited. Drug resistant strains may emerge during treatment.²⁷ Although bacteria are rapidly eliminated from the CSF, there is a worry that the rapid acquisition of high CSF cidal concentrations might itself be deleterious, in that rapid killing of large numbers of Gram negative organisms could cause massive release of endotoxin.²⁸ Previous attempts, by the Neonatal Meningitis Cooperative Study Group in the USA, to improve the delivery of antibiotics to the meninges and ventricles of neonates and infants with Gram negative enteric meningitis by the use of intrathecal²⁹ and intraventricular³⁰ administration of aminoglycosides have not improved outcome. But perhaps the most important finding in these studies was the low mortality and morbidity in the control group: babies who were treated with parenteral ampicillin and gentamicin alone. In the former study the mortality of the control group was 32%,²⁹ and in the intraventricular study was 12.5%, while eight of the 21 survivors were normal and eight had mild to moderate disability.³⁰ This was despite 46% of strains being resistant to ampicillin. The current multi-centre study from the same group is comparing moxalactam with ampicillin and gentamicin for the treatment of Gram negative meningitis. Until the results of this study are known, parenteral ampicillin and gentamicin is our treatment of choice for Gram negative meningitis. The use of third generation cephalosporins is understandable; use of the combination of chloramphenicol and a third generation cephalosporin is contraindicated because these drugs are antagonistic.

In roughly 20% of cases of bacterial meningitis the initial CSF Gram stain will not reveal organisms. In addition, neonates have often had intraventricular haemorrhages and when the red cells have degenerated the CSF white cell count can be artificially high. Thus it is not uncommon to have to prescribe 'blind' treatment for possible neonatal meningitis. Ampicillin and gentamicin, for the reasons outlined above, will be appropriate for Gram negative bacilli. They are also excellent treatment for group B streptococcal and listeria meningitis and toxicity is low. Alternative treatments sometimes used for suspected bacterial

meningitis with no organisms are chloramphenicol, with its risk of toxicity, and the third generation cephalosporins, whose activity against listeria and group B streptococci are in doubt.

Conclusion

The emergence of resistant bacteria, a high rate of bacterial infections in neonates, and the poor outcome of some of these infections mean that the antibiotics used in neonatal units need frequent scrutiny. Use of antibiotics should, however, be based on actual episodes of sepsis rather than patterns of colonisation and on the outcome of those episodes of proven sepsis. The temptation to use new antibiotics extensively should whenever possible await controlled studies of their efficacy that show their superiority to existing regimens. In the absence of such studies it might be sensible to restrict their use to babies not responding to conventional treatment.

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