

## PENICILLIN (Commentary)

**Protecting babies from maternally acquired, early onset, bacterial infection**

**Group B streptococcal infection:** A range of bacteria commonly colonise the vagina, and colonise the baby at birth, but it is rare for any to infect the baby during delivery. Indeed viral infections, such as hepatitis B and HIV, are much more often acquired by the baby during delivery. While group B streptococcus (GBS) infection is but one of many potential bacterial pathogens, it is the single commonest pathogen, and the pathogen on which most attention had been focused in the last twenty years. Indeed prenatal screening for this condition is now established practice in North America, Australasia and many parts of Europe.<sup>6</sup> The UK and Finland stand out as the only two countries to have consciously resisted this trend,<sup>11,12</sup> and this is, at least in part, because the incidence of early onset neonatal infection in the UK is less than a third of what it was in America before clinicians in that country started to offer regular screening and intrapartum prophylaxis.

Policy in the USA since 2002, has been to recommend universal rectal and vaginal culture-based screening at 35–37 weeks, and to give IV antibiotics (usually penicillin or ampicillin) every four hours during labour to all who prove culture positive.<sup>2</sup> Antibiotics are also often given to those who present in labour before screening has been done and, as a result, between a third and a half of all women now get prophylactic intravenous antibiotics during labour or delivery.<sup>3</sup> However, risk factors for early onset neonatal infection are not the same in the UK as they are in America. Recent studies have shown that 37% of neonates with early onset infection in the UK are born preterm, but only 14% in America; 45% have had prolonged rupture of the membranes in the UK, but only 14% in America.<sup>7</sup> The implication is that what may be a cost effective strategy in America is not necessarily a cost effective strategy in the UK, and a study recently completed as part of the UK's Health Technology Assessment (HTA) Programme has now shown that this is indeed the case.<sup>13,14</sup> If this is true for the UK it may also be true for other countries where GBS infection is less common than it is in America.

Cost effectiveness is, however, only one consideration. Such a policy certainly further medicalises pregnancy, and only works if women can be prevailed upon to come into hospital at the first sign of labour. The added value of such a policy is also diminished in a climate where, as a result of the ORACLE trial findings, oral antibiotics are increasingly being used to delay labour when pregnancy is complicated by preterm pre-labour rupture of membranes.<sup>5</sup> Infection of intrapartum origin is a relatively uncommon cause of disability, and seldom causes death in the term baby, but it is often lethal in the preterm baby, and screening does not pick these up. Widespread antibiotic use could also have adverse consequences, and there is already concern that it may be starting to cause other, more resistant, pathogens to become more common.

The HTA report also concluded that the strategy currently recommended in the UK (an *intravenous* antibiotic for every mother who had had a previous baby with GBS infection, or an earlier vaginal swab or urine culture that was GBS positive and every mother who became pyrexial during labour, and an *oral* antibiotic for every mother experiencing preterm pre-labour rupture of membranes) is not cost effective either.<sup>4</sup> It concluded that it **would** be cost effective to give penicillin or ampicillin to *all* mothers being delivered before 37 weeks gestation, but the suggestion that this should even apply to babies born by elective Caesarean section is known to have been reached by a misreading of the available data. While there are good grounds for giving cefoxitin to every mother having a Caesarean delivery immediately after the baby is delivered, this is done to minimise the risk of post-operative *maternal* complications (as the *Formulary's* monograph on that antibiotic makes clear). There is no evidence that such a policy is of any benefit to the baby.

It is certainly true that infection of intrapartum origin is commoner after preterm delivery, and that any infection is much more likely to cause disability or death when it occurs to a preterm baby. Infection is, however, excessively rare after elective caesarean delivery, and relatively uncommon after premature labour unless the membranes ruptured before labour started. It is certainly commoner when the mother is pyrexial in labour, but fever is very uncommon in early labour and the commonest cause of fever in late labour is epidural analgesia (where temperature typically rises by 1°C within seven hours). The prime indication for giving an antibiotic during preterm labour is when the membranes are known to have ruptured before labour began. Controlled trial evidence suggests that, in this situation, oral erythromycin (q.v.) may well delay delivery for long enough to be of some real benefit,<sup>5</sup> but it is doubtful whether any oral antibiotic is the most secure way of preventing some maternal pathogen from infecting the baby during delivery. If such treatment is merited it should almost certainly be given parenterally.

**What about other pathogens?** GBS is but one of a range of pathogens capable of infecting the baby during delivery, as several surveys have shown. Only about a third of all the potentially lethal pathogens are sensitive to penicillin, and only about two thirds are sensitive to ampicillin<sup>1</sup> (a fraction that seems to have declined significantly during the last ten years<sup>8-10</sup>). It seems illogical, therefore, to use an antibiotic that is only effective against half to two thirds of the organisms that may be threatening the baby's very survival at this time. The more logical approach would be a combination of IV penicillin (or ampicillin) and IV gentamicin. The findings of two recent UK studies (see table) strongly support such an approach.<sup>1,15</sup>

## Organisms responsible for sepsis of intrapartum origin in the UK

Provisional data in early sepsis collected by the NeonIN Collaborative Group's in 2006-7,<sup>15</sup>  
and from a study of all perinatal death in the north of England 1981-2005<sup>1</sup>

Organism	Culture proven early sepsis <sup>15</sup>		Intrapartum or neonatal death from sepsis <sup>1</sup>	
Group B <i>Streptococci</i>	39	49%	82	38%
Other <i>Streptococci</i>	6	7%	16	7%
<i>Listeria monocytogenes</i>	3	4%	11	5%
<i>Haemophilus influenzae</i>	1	1%	6	3%
<i>Staphylococcus aureus</i>	12*	14%	3	1%
<i>Escherichia Coli</i>	13	16%	32	15%
<i>Bacteroides</i>	0	-	5	2%
Other gram negative organisms	4	5%	13	6%
Viral, protozoal or fungal infection	2	3%	12	5%
Unequivocal sepsis, organism undetermined	-	-	37	17%
<b>Total</b>	<b>80</b>	<b>100%</b>	<b>217</b>	<b>100%</b>

\* 10 of these were coagulase negative Staphylococci

**Conclusion:** To minimise these risks this *Formulary* has, for the last seven years, recommended that “all women going into unexplained spontaneous labour before 35 weeks gestation should be given both IV penicillin and IV gentamicin” and that, “in pregnancies more mature than this there are good grounds for giving IV penicillin throughout labour to reduce the risk of GBS infection if the membranes are known to have ruptured more than 6 hours before labour starts.” IV penicillin “should also be offered to all known carriers, and to mothers becoming pyrexial ( $\geq 38^{\circ}\text{C}$ ) during labour.” Even this policy results in antibiotics being given to between 40 and 60 women during labour to provide optimal treatment for just one baby with bacterial sepsis of intrapartum origin. However most other policies result in antibiotics being given to many more women than this. Indeed it is said that a third of all women in America are currently being treated with either penicillin or ampicillin during labour,<sup>3</sup> and this could be one reason why an increasing number of babies are presenting with ampicillin-resistant *E coli* septicaemia when three or more days old.<sup>16</sup> What is also clear is that the baby also needs treatment for 7 days if symptomatic even if no pathogen is grown.<sup>17</sup>

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## Speed of administration

Benzylpenicillin is an extremely nontoxic drug (if the risk of hypersensitivity developing in response to previous exposure is discounted). It is, however, known that it can be epileptogenic when CSF levels exceed 10 mg/l, and that penicillin is much more neurotoxic than any of the other related beta-lactam antibiotics. An intrathecal injection can also cause the patient to become drowsy and hyperreflexic. Hallucinations have been described, while coma and death have occurred when levels are exceedingly high. (See the review by Schliamser in 1991 for a discussion of these issues.) Such problems are **very** rarely encountered with IV administration because CSF penetration is poor even in patients with meningitis (~5% of plasma levels). However, toxicity does still occur occasionally when repeated large doses are given to patients in severe renal failure despite the fact that the drug is known to be almost entirely eliminated by the kidney. The main factor known to precipitate neurotoxicity with high dose treatment is some disturbance to the blood-brain barrier – the commonest causes being an intracranial tumour, cranial irradiation and microembolic damage during cardiac surgery. These findings account for the advice that direct intrathecal treatment is unwise, and that the dosage level must be halved when there is severe renal failure.

The findings do not, however, explain why almost all reference texts say that high IV doses, of the type recommended in the neonatal period (especially where group B streptococcal meningitis is a possibility), must be given slowly – typically over 15–30 minutes. The advice almost certainly stems from a statement in the manufacturer's Data Sheet (SPC) that adult doses in excess of 1.2 g should be given at a rate not exceeding 300 mg/min "to avoid high levels causing irritation to the central nervous system". Such advice is almost certainly generated by a misplaced concern that even transient high plasma levels will be translated into high CSF levels. The recommendation persists, nevertheless, and gets copied uncritically from text to text despite the lack of any reports of rapid administration causing any trouble. Similar, legally-inspired, long-discounted, concern for ototoxicity underpins the recommendation that all aminoglycosides should also be infused slowly over a 30 minute period when given IV in North America – a recommendation that has no counterpart in the advice the companies give when marketing the same products in Europe. More recently advice has begun to appear in the UK to the effect that fluxcloxacillin has to be given slowly over 30–60 minutes (*BNF for children*, 2008), but the evidence for this advice seems to be equally unlocatable.

Manufacturers offer similar advice in respect of a range of other antibiotics and, on inquiry, it often transpires that this is merely because that was how the product was first administered experimentally while under development. Were all such advice to be followed scrupulously it would greatly increase the work of nursing staff, leaving them with even less time to complete their many other duties and responsibilities. In fact many tens of thousands of rapid antibiotic injections have been given IV to small children over the years without a single adverse reaction ever being reported. Rapid delivery has become an inevitable consequence of the move towards giving almost all parenteral medication IV in the last 20 years – a strategy that nurses, in particular, see as a way of minimising the pain associated with IM injections. Rapid administration is unavoidable when a drug has to be given through a 'stopped off' IV cannula left in place specifically to make such treatment possible, and years of experience testify to the safety of this approach when giving a wide range of drugs.

That no problem has ever been recognised does not of course, of itself, mean that rapid bolus injection should be employed when an alternative exists. It is, however, perfectly possible to give any small volume (< 2 ml) injection to a small baby IV without setting up a separate line and syringe pump by following the advice given in the introduction to this *Formulary* as long as there is an IV infusion already running. A 60 mg/kg IV dose of benzylpenicillin when so given will not usually be infused at a rate that exceeds 6 mg/kg.min (the equivalent of a rate of 300 mg/min in a 50 kg adult). Mechanical infusion pumps need, of course, be used whenever a slow, controlled or continuous infusion is required, as Roberts was the first to recognise (Roberts, 1981). For all the products mentioned in this *Formulary* where such a need exists specific advice to this effect is given in the relevant monograph.

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