

CHLORAMPHENICOL (Comment)

Treating severe pneumonia in a resource-poor country

UNICEF, the United Nations Children's Fund, have called pneumonia the "forgotten killer" because there is good evidence that it is still killing two million young children every year. While intervention has caused a marked fall in the number of children dying from gastrointestinal infection and diarrhoea in the first five years of life in the last twenty years, there has been no decline in the number of deaths from pneumonia. Many of these deaths could be prevented if sustained breast feeding was more widely practised, and if vaccines for measles, *Haemophilus influenzae* type B (HiB) and *Streptococcus pneumoniae* were more widely available. Better nutrition would also leave children less vulnerable. However, while prevention must remain one important aim, those who **do** become ill need treatment, and treatment is never going to reach many of these children if first-level health care workers have to refer every child with obvious features of pneumonia to a qualified doctor for treatment (Peterson, *et al.*, 2004). Even fewer will get the care they need if they have to be admitted to hospital simply because of the belief that antibiotic treatment can only be relied upon if given as an intramuscular injection.

What colleagues from Pakistan have recently shown in a large, randomised, open-label, equivalency trial involving 2037 children presenting with severe pneumonia when between 3 and 59 months old, is that ambulatory treatment with high-dose oral *amoxicillin* (40–45 mg/kg twice a day) for five days can be just as effective as hospital admission so that the first four doses of the same five day course can be given IM (Hazir *et al.*, 2008). Indeed for children with non-severe pneumonia (some of whom will, admittedly, not have a bacterial infection) half this dose by mouth for just three days may be just as effective as a higher dose for five days (Bhutta, 2007).

Chloramphenicol remains the most commonly used antibiotic for treating pneumonia in resource-poor countries however, and this strategy still has the backing of the World Health Organisation because chloramphenicol is widely available, relatively cheap, and well absorbed when given by mouth. A large international trial (the SPEAR study) involving 958 hospitalised children 2–59 months old has recently concluded that there are advantages in using a combination of ampicillin and gentamicin rather than chloramphenicol when treating severe pneumonia (Ashgar *et al.*, 2008), but the outcome in the two trial groups was only marginally different. Indeed, a statistically significant result was only obtained by using a composite end point (the number of children who had died or were not getting better, plus the number who had had their antibiotic regimen changed within five days). However, this had, inevitably, been an unblinded trial, and the 'poorer' outcome seen in those given chloramphenicol was entirely due to the fact that almost twice as many of the children started on chloramphenicol had had their treatment changed within five days by the medical staff as those started on amoxicillin and gentamicin (9% v. 5%). There was *no* difference in the number who had died (3% v. 2%), or who were still showing no signs of improvement after five days (3% v. 4%). Neither do the authors comment on the fact that, in the only other large trial to date, reporting the outcome of a study involving 1116 1–59 month old children from Papua New Guinea (Duke *et al.*, 2002), death rates in the two trial groups had been identical (6% v. 5%), and slightly *fewer* of those started on chloramphenicol had had their treatment changed (9% v. 11%).

Clearly, even in very ill children (all the children in Duke's trial had a fractional oxygen saturation of less than 85% on admission), the two treatment strategies deliver very similar outcomes, and there can certainly be no good reason to stop using chloramphenicol to treat children who are *less* severely ill, especially if this means that treatment can be started more promptly and delivered without the need for hospital admission.

Duke T, Poka H, Dale F, *et al.* Chloramphenicol versus benzylpenicillin and gentamicin for the treatment of severe pneumonia in children in Papua New Guinea: a randomised trial. *Lancet* 2002;**359**:474–80. [RCT]

Peterson S, Nsungwa-Sabiiti J, Were W, *et al.* Coping with paediatric referral – Ugandan parents' experience. *Lancet* 2004;**363**:1955–6.

Hazir, T, Qazi SA, Nisar YB, *et al.* Comparison of standard versus double dose of amoxicillin in the treatment of non-severe pneumonia in children aged 2-59 months: a multi-centre, double blind, randomised controlled trial in Pakistan. *Arch Dis Child* 2007;**92**:291–7. [RCT]

Bhutta ZA. Dealing with childhood pneumonia in developing countries: how can we make a difference? *Arch Dis Child* 2007;**92**:286–8.

Atkinson M, Lakhanpaul M, Smyth A, *et al.* Comparison of oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia (PIVOT trial): a multicentre randomised controlled equivalence trial. *Thorax* 2007;**62**:1102–6. [RCT]

Hazir T, Fox LA, Nisar YB, *et al.* Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalency trial. *Lancet* 2008;**371**:49–56. [RCT] (See also 7–8.)

Asghar R, Banajeh S, Egas J, *et al.* Chloramphenicol versus ampicillin plus gentamicin for community acquired very severe pneumonia among children aged 2-29 months in low resource settings: multicentre randomised controlled trial (SPEAR study). *BMJ* 2008;**336**:80–4. [RCT] (See also 57–8.)