CHLORAMPHENICOL (Comment)

Side effects of treatment

Haemolytic anaemia may occur in patients with the Mediterranean variant of G6PD deficiency. There is also a risk of bone marrow suppression at any age if high doses are prescribed for more than 1-2 weeks, but the resultant neutropenia and thrombocytopenia and reduced reticulocyte count are reversible once treatment is withdrawn. Irreversible aplastic anaemia, on the other hand, is not dose-related and typically occurs after therapy is over. There is some suggestion that susceptibility may be genetically determined. Luckily, it only occurs about once every sixty thousand times the drug is prescribed. Both these problems are more commonly seen in children than in neonates. The main toxic symptom of high-dose medication in infancy is the 'grey baby' syndrome with abdominal distension and vasomotor collapse after 2-3 days. Acute toxicity can effectively poison all drug oxidation by the liver for up to three days, and there is no treatment of proven value. Even charcoal haemoperfusion is largely ineffective.

Blood levels

It is probably only worth measuring the peak level (if this can be done) when the drug is used in children less than 4 weeks old. Some texts recommend that trough and peak levels should both be monitored, and there are theoretical reasons for this, because trough levels in excess of 5mg/l can cause damage to cell mitochondria. It is, however, often unrealistic to insist on such a low trough level in the neonate, because biological activation of the administered 'prodrug' proceeds too slowly for the drug to have a definable half life. This is particularly true following oral administration.

Management of neonatal meningitis

A study by Holt (2001) shows that group B streptococci are still the commonest cause of neonatal meningitis. Coliform infection is also common. Cefotaxime (q.v.) is now the drug most frequently used to treat an as yet undiagnosed organism (together with ampicillin or amoxicillin because infection with Listeria or enterococci is a real possibility), and mortality has declined since this became the usual approach to treatment. Some 15% of babies still die however, and most survivors suffer some disability. Treatment with vancomycin (q.v.) only seems appropriate once staphylococcal infection has been identified (which is uncommon except as a complication of shunt treatment). Chloramphenicol remains a valid option where drug cost is a major consideration. An uncertain fraction of all neonatal meningitis is viral in origin.

Meningitis in later infancy

Vaccines have now greatly reduced the incidence of meningitis later in infancy in most developed countries, but antibiotic treatment remains the main line of defence in developing countries. Here as many as 170,000 children currently die every year of meningitis, and between a quarter and a half of all the survivors suffer some permanent neurological disability. Unfortunately *H influenzae* is rapidly becoming resistant to chloramphenicol in many of these countries (resistance is said to have increased from 8% to 80% between 1994 and 2000 in Kenya). Treatment with amoxicillin and an aminoglycoside has long been the stand-by strategy in this situation, but ceftriaxone has recently become both an affordable as well as a simpler alternative now that its patent has expired and its cost has fallen. However death still remains common in those who are already drowsy or semi-conscious by the time treatment is started. The scourge of childhood meningitis in the third world will only be defeated when the resources are found to adopt the strategy that has been adopted in the developed world – vaccination.

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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 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 a 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 my 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. Once cheap, reliable, pulse oximeters become more widely available it may become easier to identify who really needs hospital admission (and perhaps a little supplementary oxygen as well as an antibiotic).

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]

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