ORIGINAL ARTICLE

Chloramphenicol or ceftriaxone, or both, as treatment for meningitis in developing countries?

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Aims: To determine in children with meningitis whether there is any difference in mortality and neurological sequelae using chloramphenicol as first line treatment, with a change to ceftriaxone if chloramphenicol resistance is shown in vitro, compared to using ceftriaxone as first line treatment, with a change to chloramphenicol if there is no evidence of in vitro resistance.

Methods: An observational study with a retrospective control group nested within a randomised trial of fluid management for bacterial meningitis where clinical care was standardised. Chloramphenicol is standard treatment for bacterial meningitis in Papua New Guinea. In the first 150 cases we used chloramphenicol and only changed treatment to ceftriaxone if chloramphenicol resistance for cerebrospinal fluid isolates was proved. After finding 20% of *Haemophilus influenzae* were resistant to chloramphenicol, and that most affected children had poor outcomes, we changed to an alternative strategy. In the next 196 cases first line treatment was ceftriaxone and treatment was changed to chloramphenicol if the isolated bacteria were found to be susceptible.

Results: When chloramphenicol was used as first line treatment for meningitis followed by ceftriaxone when in vitro resistance was shown, there was invariably a very poor outcome in chloramphenicol resistant disease (71% of children died or had severe neurological complications). Using ceftriaxone as first line treatment was effective in reducing mortality and neurological sequelae from chloramphenicol resistant *Haemophilus influenzae* type (71% v 9%, relative risk 0.13; 95% CI 0.02 to 0.87; p = 0.013). Changing to chloramphenicol if there was no evidence of in vitro resistance was less than half the cost of empirical use of ceftriaxone for a full course for all children with meningitis.

Conclusions: Using a third generation cephalosporin as first line treatment is effective in dealing with the problem of poor outcomes from meningitis due to *Haemophilus influenzae* that is resistant to chloramphenicol, and a strategy of changing to chloramphenicol if in vitro susceptibility is shown will reduce the use of expensive third generation cephalosporins without comprising on clinical outcomes. This highlights the urgent need to reduce the costs of third generation cephalosporins, to improve bacteriological services in developing countries, and to introduce effective and affordable vaccines against *H influenzae* and *Streptococcus pneumoniae*.

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When the rates of resistance to chloramphenicol of cerebrospinal fluid (CSF) isolates of *Steptococcus pneumoniae* or *Haemophilus influenzae* are "high", the World Health Organisation recommends a change in standard treatment of meningitis to a third generation cephalasporin.[1] There are 15 published trials comparing ceftriaxone, cefotaxime, or ceftrazadime to chloramphenicol in childhood bacterial meningitis.[2–16] All but one of these,[16] a study of only 23 patients, were done in the 1980s. Only five of these studies[2 3 9 10 14] have reported their rates of chloramphenicol resistance of CSF isolates: of 247 isolates (61 pneumococci and 186 *H influenzae*), there were only seven resistant strains (2.8%): three *S pneumoniae* (4.9%) and four *H influenzae* (2.2%). There are no major published studies of the relative efficacy of third generation cephalosporins or chloramphenicol on the outcome of meningitis in developing countries in the modern era of high level antibiotic resistance. Over the past decade in many developing countries resistance to chloramphenicol among meningitis pathogens has become a major problem, but the routine use of third generation cephalosporins for meningitis is often unaffordable. A full course of ceftriaxone for meningitis is about six times the cost of a course of chloramphenicol. Unnecessary use of third generation cephalosporins will be associated with further rapid development of antibiotic resistance,[17] and strategies are required to limit their use to those patients who really need them.

In Papua New Guinea chloramphenicol has been standard treatment for meningitis for three decades,[18] and there are very limited stocks of third generation cephalosporins. Previously, intermediate resistance to penicillin by *S pneumoniae* isolates from patients with pneumonia and meningitis in Papua New Guinea had been described,[19] but there had been no reports of chloramphenicol resistant *H influenza* and no reports of clinical failure with chloramphenicol for common meningitis bacteria. In 1998 in Goroka and Port Moresby, chloramphenicol resistance among *H influenzae* was found to contribute substantially to meningitis mortality and morbidity. We have reviewed our experience with a strategy for the efficient use of ceftriaxone in this setting.

METHODS
Antibiotic protocols
From August 1997 to October 2000 a controlled trial of fluid management in meningitis was performed in three hospitals in Papua New Guinea.[20] Between August 1997 and September 1999, for the first 150 cases enrolled in the trial, chloramphenicol (25 mg/kg every six hours) was used as first line antibiotic treatment. As third generation cephalosporins were in very limited supply we changed to ceftriaxone only if resistance was found on cultured CSF isolate. This inevitably

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Abbreviations: CSF, cerebrospinal fluid; Hib, *Haemophilus influenzae* type b

Table 1 Baseline comparison of the children treated initially with chloramphenicol or ceftriaxone

Characteristics	Chloramphenicol	Ceftriaxone	p value
Number enrolled	150	196	
Median (IQR) age in months	7 (4–12)	6 (4–11)	0.19
Male sex	86 (57%)	99 (51%)	0.27
Number (%) malnourished (<80% expected weight for age)	47 (31%)	47 (24%)	0.13
Antibiotic treatment in previous week	78 (52%)	93 (47%)	0.37
Mean (SD) days of symptoms	7.0	5.6	0.01§
Convulsions prior to presentation	102 (68%)	129 (66%)	0.61
Spasticity	35 (23%)	49 (25%)	0.75
Focal motor deficit	23 (15%)	31 (16%)	0.92
Bulging fontanelle	48 (32%)	90 (46%)	0.03§
Apnoeas	14 (9%)	14 (7%)	0.47
Cyanosis	34 (23%)	24 (12%)	0.009§
Sunken eyes or poor skin turgor	19 (13%)	23 (12%)	0.79
Hyponatraemia (Na$^+$ <130)	26 (17%)	35 (18%)	0.9
Hypoglycaemia (<3 mmol/l)	30 (20%)	39 (20%)	0.99
Median (IQR) CSF WCC per mm^3	414 (131–1070)	698 (180–1682)	0.02§
Streptococcus pneumoniae	44 (29%)*	82 (42%)	
Haemophilus influenzae type b	47 (31%)*	65 (33%)	
Non-type b *H influenzae*	1	4	
Enteric Gram negative bacilli	5	3†	
Other Gram positive bacilli	5	6†	
Neisseria meningitidis	1	1	
No bacteria identified but definite meningitis	45	30	
Likely *Mycobacterium tuberculosis*‡	4	5	
Cryptococcus neoformans	0	1	

*Two children in the chloramphenicol group had both *H influenzae* type b and *S pneumoniae* cultured from CSF.
†One case where both *Proteus mirabilis* and streptococci were cultured from CSF.
‡Diagnosis of *Mycobacteriam tuberculosis* based on chronicity of symptoms, CSF lymphocytosis, reactive Mantoux test, and miliary or other suggestive pattern on chest radiograph.
§Not significant after Bonferroni correction for multiple comparisons (p>0.05).

meant that children with chloramphenicol resistant meningitis had a period of less than adequate treatment prior to confirming resistance. In September 1989 we found persistently high rates of chloramphenicol resistance among *Haemophilus influenzae* type b (Hib) isolates from cases in Goroka and Port Moresby.[21] These cases were associated with excessive case fatality and serious neurological sequelae (table 2). Poor outcomes occurred even though children with chloramphenicol resistant meningitis received adequate treatment with a third generation cephalosporin from the time antibiotic resistance information was available; typically 2–3 days after hospital admission. This finding of poor outcomes led to a change in the antibiotic protocol. For the next 196 cases we used ceftriaxone (50 mg/kg every 12 hours) as first line treatment, but to save this antibiotic we changed to chloramphenicol if susceptibility was shown. If the isolated bacteria were resistant in vitro to chloramphenicol, ceftriaxone was continued for a total of 14 days. If no bacteria were grown after 72 hours of CSF culture, the antibiotic treatment was changed to chloramphenicol.

Had we empirically given a full 10–14 day course of ceftriaxone to all children with bacterial meningitis we would have rapidly depleted our limited stocks of the drug. We hypothesised that there would be little difference in outcome of meningitis for children treated with ceftriaxone or chloramphenicol, as long as there was in vitro susceptibility to chloramphenicol.

Entry criteria, supportive care, and outcome assessment
Children were eligible for study entry if they fulfilled the following requirements: (1) age >1 month, <12 years; (2) clinical signs of meningitis; and (3) cloudy or turbid CSF, with moderate or large leucocytes, and moderate or large protein on dipstick testing[22] (Multistix 10 SG, Bayer Australia Ltd, Sydney, Australia). Children were screened for meningitis and the following data were recorded: history of convulsions, ability to feed, axillary temperature, respiratory rate, and presence of neck stiffness, bulging fontanelle, apnoea, cyanosis, spasticity or hypertonicity, focal neurological signs, and papil-

loedema. A lumbar puncture was not done or was delayed if there was papilloedema, apnoea, clinical signs of coning, or coagulopathy. The following tests were done on CSF: Gram stain and microscopy, latex agglutination antigen testing for *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, bacterial culture as previously described,[23] and Zeil-Nielson stain for acid fast bacilli. Serotyping and antibiotic sensitivity testing were done on all bacterial isolates.

All children were managed with a standardised protocol of supportive care[20] and antibiotic treatment. Corticosteroids are not part of standard treatment for meningitis in Papua New Guinea and were not used in this study. We prospectively defined outcomes. An adverse outcome was defined as death or severe neurological sequelae: a severe motor deficit (severe spasticity, hemiplegia, severe hypotonia), and at least one of: a major sensory deficit (inability to fix and follow in an age appropriate way, or no response to sound), persistent convulsions, or coma. A good outcome was neurologically intact survival or survival with at worst mild to moderate disability (such as an isolated monoparesis or cranial nerve palsy). The outcomes were assessed at 14 days and 3 months after starting treatment.

Data analysis
Data were entered into an Excel spreadsheet and analysed with Stata 7.0 (Stata Corporation, Texas). We have analysed the outcome data according to whether chloramphenicol or ceftriaxone was used as first line treatment, for all cases of meningitis, those due to *Haemophilus influenzae*, and those due to chlorampenicol resistant bacteria. Outcomes were analysed using Fisher's exact text and presented as relative risk and 95% confidence intervals (95% CI). We estimated the power of our analysis using Stata 7.0 (sampsi command). For comparison of baseline characteristics of the two groups, Student's *t* test was used for comparison of means of continuous variables with normal distribution; the Mann-Whitney U test to compare variables with marked skewness of distribution, and the χ^2 test or Fisher's exact test for comparison of proportions.

Table 2 Outcomes from meningitis in children where chloramphenicol or ceftriaxone were given as first line treatment

	Chloramphenicol		Ceftriaxone	
	No.	No. with adverse outcome (%) (died/severe sequelae)	No.	No. with adverse outcome (%) (died/severe sequelae)
Meningitis (all cases)	150	48 (32%) (31/17)	196	53 (27.0%) (29/23)
Hib meningitis (culture or antigen positive)	45	12 (26.7%) (4/8)	65	12 (18.5%) (5/7)
Hib meningitis (culture positive)	36	10 (27.8%) (3/7)	54	10 (18.5%) (4/6)
Chloramphenicol sensitive Hib meningitis	29	5 (17.2%) (0/5)	43	9 (20.9%) (3/6)
Chloramphenicol resistant Hib meningitis	7	5 (71.4%) (3/2)	11	1 (9.1%) (1/0)

RESULTS

A total of 346 children were enrolled; 150 treated initially with chloramphenicol and 196 treated initially with ceftriaxone. Table 1 outlines the baseline clinical and laboratory characteristics of the children. Twenty one per cent of culture positive Hib isolates were chloramphenicol resistant; this translated to just 5.6% of all laboratory confirmed cases of meningitis. There was only one child in each treatment group who had a chlorampenicol resistant *S pneumoniae*, and both had good outcomes after treatment with ceftriaxone. In the first 150 cases we changed to ceftriaxone in eight (seven Hib and one pneumococcus), and in the next 196 cases we continued ceftriaxone for a full course in 12 (11 Hib and one pneumococcus).

Table 2 outlines the outcomes for children treated with the two antibiotic strategies. With the change from first line treatment with chloramphenicol to ceftriaxone, there was a 16% reduction (32% v 27%) in severe adverse outcomes for all meningitis (relative risk 0.84: 95% CI 0.60 to 1.17). This difference was not statistically significant (Fisher's exact test, p = 0.34); however, the estimated power of the analysis (to find an absolute difference of 5% from the baseline adverse outcome of 32% was low: 0.14. There was a 31% reduction (relative risk 0.69: 95% CI 0.34 to 1.40, p = 0.35) in severe adverse outcome in cases of culture or antigen positive Hib meningitis. In the subgroup of children with chloramphenicol resistant Hib isolates, there was a significantly better outcome in those treated empirically with ceftriaxone (relative risk of an adverse outcome 0.13; 95% CI 0.02 to 0.87; Fischer's exact test, p = 0.013).

On average the cost per patient of the second antibiotic strategy was two and a half times greater than using chloramphenicol as the only treatment, but less than half the estimated cost of using ceftriaxone for a full course for all cases.

DISCUSSION

Using ceftriaxone as first line treatment and changing to chloramphenicol in cases of in vitro susceptibility was effective in reducing adverse outcomes from bacterial meningitis, compared to using chloramphenicol as first line treatment and later change to ceftriaxone if the bacteria isolated were proven to be resistant. This is not altogether surprising as delays in effective treatment of two or three days in bacterial meningitis may have serious consequences, although previous evidence for a detrimental effect of prehospital delay is not strong. The median duration of symptoms prior to presentation in the children in this study was just over six days, and we found longer duration of symptoms was associated with higher probability of adverse outcomes.[20]

Our study was a retrospective before-and-after comparison, and there are several potential sources of bias that require scrutiny. If case management of meningitis had improved over the two and a half years when the study was conducted, this would bias the data in favour of ceftriaxone. This may have been a factor, however the supportive management protocols

were fixed from the beginning of the study, so it is likely that such an effect was minimal. The risk factors for an adverse outcome in the 346 children overall were longer duration of symptoms, spasticity, sunken eyes or reduced skin turgor, malnutrition (weight <80% expected for age), and hypoglycaemia.[20] Children who were initially treated with chloramphenicol had a significantly longer duration of symptoms prior to presentation (7.0 v 5.6 days), and a higher proportion of them were cyanosed at presentation, which may be expected to have biased the results towards a higher adverse event rate for those children treated with chloramphenicol. On the other hand the ceftriaxone group had higher CSF white cell counts, a higher proportion of *S pneumoniae*, and fewer cases of aseptic meningitis, which may be associated with a higher rate of adverse outcomes.[24 25] These, and other potential biases could only be overcome by a randomised trial. We did not find an overall statistically significant difference in adverse outcomes for all children with meningitis using ceftriaxone compared with using chloramphenicol, although we have inadequate power for a definitive conclusion. To detect a 20% relative difference in mortality or severe sequelae (32% reduced to 25.6%), a sample size of 1630 patients would be required.

Of the 15 previous studies comparing chloramphenicol and third generation cephalosporins, one reported a higher incidence of mild to moderate motor sequelae with chloramphenicol at discharge but not at four months after diagnosis,[10] one a higher incidence of transient ataxia and prolonged fever in the ceftriaxone group,[2] two others more prolonged fever in the chloramphenicol groups,[3 16] two reported a faster rate of CSF sterilisation with ceftriaxone, and two studies reported cases of recurrence that occurred in patients on chloramphenicol[15] and ceftriaxone.[8] There were no differences found in long term or severe neurological sequelae or mortality, although the power of these studies was low. Our study found little difference in outcome of meningitis for children treated with ceftriaxone or chloramphenicol, as long as there was in vitro susceptibility to chloramphenicol. A beneficial effect of ceftriaxone over chloramphenicol will be dependent on the proportion of resistant cases within the meningitis population. The much lower rates of resistance in earlier studies and their small sample sizes will account for why so few of the earlier studies found a difference in major outcomes. The treatment strategy we used can only be applied to settings where antibiotic susceptibility testing can be done. Unfortunately in Papua New Guinea, like many developing countries, this is only possible at a few of the major hospitals. Lack of diagnostic facilities at first and second level referral hospitals is a problem in many developing countries, and has major implications for introduction of treatments considered "standard" in industrialised countries. The scant data from previous comparison trials also highlights a major deficit in understanding the extent of antibiotic resistance in less developed countries.

In most developing countries, to change standard treatment to empirical use of ceftriaxone for all cases of meningitis would be two edged sword. It would save the lives of many

children but add substantially to the cost of meningitis treatment, and uncontrolled use of third generation cephalosporins may risk more rapid development of antibiotic resistance. In hospitals without bacteriology services antibiotic resistance may only manifest as an increasing proportion of clinical failure and unexplained deaths.[26] The emergence of cephalosporin resistance in developing countries, now a real problem in some industrialised countries, would be a disaster, and every effort should be made to prolong the effective lifespan of both chloramphenicol and ceftriaxone for serious illnesses by evidence based approaches to antibiotic prescribing. If standard treatment policies cannot be implemented because of non-availability or high costs of drugs, this can undermine confidence in the programme. However, to continue to use chloramphenicol as first line treatment in the setting of high resistance or to use ceftriaxone only in children who are not showing clinical improvment after 2–3 days (one possible strategy where bacteriology facilities are absent) will be associated with a very high case fatality or severe brain injury, as we experienced among the first 150 cases. These highlight the importance of lowering the cost of third generation cephalosporins and developing minimal bacteriological facilities in hospitals in developing countries to include CSF isolate susceptibility testing, so that cephalosporins can be available, but their use limited as much as possible, to patients who really need them. There is also a need to improve referral mechanisms for children with meningitis to hospitals where bacteriological facilities are available.

In settings where pneumococcal resistance to chloramphenicol is low, introduction of conjugate Hib vaccine[27] would almost eliminate the need to use third generation cephalosporins for bacterial meningitis, and chloramphenicol could again be effective standard treatment. Unfortunately, in the past 18 months in Papua New Guinea, *S pneumoniae* meningitis that is resistant to chloramphenicol is emerging. Pneumococcal resistance has been present for years in many other developing countries,[28–30] many of which are now also reporting high rates of Hib resistance and the emergence of cephsalosporin resistance.[24 31] It is clear that affordable pneumococcal vaccine strategies and Hib vaccine are the only long term solutions to the excessive mortality and suffering caused by bacterial meningitis worldwide. Until then it is essential that third generation cephalosporins are made available and bacteriology services developed.

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