REPORT ON THE COMPARATIVE EFFECTIVENESS AND SAFETY OF CHLORAMPHENICOL INJECTION

Executive summary

This review was undertaken to examine the evidence for retaining chloramphenicol as first line therapy on the Model List for the treatment of bacterial meningitis and for the use of oily chloramphenicol injection in meningococcal meningitis epidemics.

The available randomized controlled trial evidence suggests that third generation cephalosporins are as effective as standard treatment regimens that include chloramphenicol for the treatment of bacterial meningitis. Once or twice daily dosing schedules with ceftriaxone are more convenient than the four times daily schedules required for chloramphenicol and ampicillin regimens. There is also some evidence to suggest that shorter courses of treatment may be possible with ceftriaxone. Many of the trials were conducted in the 1980s and 1990s. It difficult to apply the results of these studies to current routine practice, where the effectiveness of chloramphenicol may be markedly reduced with increasing evidence on the emergence of chloramphenicol resistant strains of Haemophilus influenzae. Over time, the prices of third generation of cephalosporins have also come down, so the price differentials are smaller. In some settings, treatment with ceftriaxone may be cheaper than for chloramphenicol. Concerns about the adverse effects of chloramphenicol have not been borne out in the clinical trials. There were no reports of the severe haematological side effects that have led to limited use of chloramphenicol in developed country settings. In the trials available, ceftriaxone was often associated with more adverse effects than conventional therapy, particularly more diarrhoea. The haematological side effects of chloramphenicol remain a concern, but the balance of benefits versus harms favours use of chloramphenicol in severe life threatening infections.

Ceftriaxone has also been shown to be as effective as oily chloramphenicol injection for meningococcal meningitis epidemics.

It is proposed that chloramphenicol be retained on the Model List for use in severe life threatening infections but not recommended as first line treatment for bacterial meningitis or for meningococcal meningitis epidemics. It is proposed that ceftriaxone be moved from the Complementary to the Core List. In settings where substantial cost differentials between third generation cephalosporins and chloramphenicol remain, chloramphenicol offers an alternative treatment, but may not be effective in all cases.

Proposal

The WHO Model Formulary (2004)[1] lists chloramphenicol for the treatment of life threatening infections caused by Haemophilus Influenzae (H. Influenzae) and Typhoid fever caused by Salmonella typhi (S. typhi).

It is proposed that chloramphenicol no longer be listed as a first line agent for either bacterial meningitis or typhoid fever as its effectiveness against both these infections has been markedly reduced due to the emergence of chloramphenicol resistant strains of both bacteria in the past decade and a half. Concerns about the potential side effect profile of chloramphenicol have reduced the use of chloramphenicol in developed countries and these concerns may also make it a less desirable treatment option in resource poor settings.

Introduction

In developing countries, the WHO's treatment recommendation for bacterial meningitis (BM) has been chloramphenicol combined with ampicillin (or penicillin).[2] The Pocket Book of Hospital Care for Children (WHO 2005, p 50)[3] suggests that first line treatment for BM is ampicillin and gentamicin or a third generation cephalosporin (ceftriaxone or cefotaxime). Suggested alternative antibiotics are penicillin and gentamicin. Chloramphenical is noted as an alternative but should not be used in premature or low birth weight neonates. However, over the past decade and a half, chloramphenicol resistant Haemophilus Influenzae (CRHI) has been noted to be increasing at an alarming rate in many developing countries.[4-7] Initial treatment for BM must be rapidly effective, otherwise the outcome for the individual is likely to be very poor, with the risk of death or long term neurological sequelae.[5] The incidence of chloramphenicol resistant Salmonella typhi is now also high in most developing countries and exceedingly high in many.[8-10]

Chloramphenicol has long enjoyed a price advantage over once daily third generation cephalosporins in the developing world. However this is no longer always the case and in some developing countries, the latter has been noted to be cheaper.[11]

Most of the studies comparing the effectiveness of chloramphenicol and a third generation cephalosporin were performed more than 15 years ago, the two most recent studies between 10 and 15 years ago. These were all performed prior to the advent of significant CRHI in developing countries. The studies conducted concluded that chloramphenicol and third generation cephalosporins were equally effective, and equally safe, at that time. The advent of significant CRHI in developing countries has diminished the usefulness of those particular studies, many of which were performed in the developed world and designed to show the benefits of third generation cephalosporins. Until recently, the cost advantage of chloramphenicol in developing countries has been substantial; this is no longer the case. While the potential side effects of chloramphenicol are serious, side effects are not an issue for either drug when compared with the sequelae of inadequate treatment of BM.

This report will summarise the available clinical data regarding the effectiveness of chloramphenicol in the treatment of BM in developing countries. Data will also be presented on:

(i) the rate of rise of CRHI in developing countries in the past decade and a half

(ii) side effect profiles of chloramphenicol and third generation cephalosporins

(iii) the usefulness of the various forms of injectable chloramphenicol

(iv) cost differential between chloramphenicol and third generation cephalosporins in developing countries.

Literature review

Studies for this review were identified by searching the Cochrane Data Base of Systemic Reviews and randomised controlled trials, searches of the PubMed and Medline databases using the search terms “Chloramphenicol” “Bacterial Meningitis” “Children” “Comparisons of Treatment” and "Adverse effects".

Early literature searches identified a recent Cochrane review[12] and a comprehensive published review of the topic[2], so the focus of subsequent searches was to identify any recent studies that would update these reviews (studies conducted from 2000-2007). The literature search on adverse effects covered the time period 1990-2007. In addition, the bibliographies of identified reviews and studies were scanned to identify additional studies to inform this report.

Current listing of chloramphenicol

Chloramphenicol is listed in the WHO Model List (2005) in several formulations:

(i) capsule 250 mg;

(ii) oral suspension (as palmitate) 150 mg per 5 ml;

(iii) powder for injection (as sodium succinate) 1 gram in a vial, and

(iv) oily suspension for injection (as sodium succinate) 0.5 gram in 2 ml ampoules

The recommended doses in adults and children are:

By mouth or by IV injection: 50mg/kg/day in 4 divided doses up to 100mg/kg/day in severe infections such as meningitis, septicaemia, and epiglottitis (caused by Haemophilus Influenzae). Infants under 2 weeks are administered 25mg/kg daily in 4 divided doses; infants 2 weeks to 1 year are given 50mg/kg/day in 4 divided doses.

By IM injection (of oily injection for epidemics of meningococcal meningitis): adults: 3G as a single dose, repeated after 48 hours if necessary; infants: 1-8 weeks 250mg as a single dose; infants 2-11 months 500mg as a single dose; children 1-2 years 1 gram as a single dose; 3-5 years 1.5 gram as a single dose; 6-9 years 2 gram as a single dose; 10-14 years 2.5 gram as a single dose; over 15 years as for adult; dose repeated after 48 hours if necessary.

The WHO Model Formulary (2004)[1] notes that the oily suspension should be reserved for use in situations of catastrophic epidemics of meningococcal meningitis occurring mainly in sub-Saharan Africa, during which the medical services are overwhelmed by the epidemic and in which the overwhelming scale of the epidemic precludes any other form of antimicrobial.

Chloramphenicol has been included on the Model List for 30 years, it has long been associated with potentially serious adverse effects. Its inclusion in the first Model List (1977) was accompanied by a note that its adverse effects diminish the benefit/risk ratio. The side effects can be categorised into dose-related and not dose-related events[9]:

Dose related adverse effects

Haematologic
- Bone marrow suppression
- Haemolytic anemia

Cardiac
- Cardiovascular collapse (grey baby syndrome)

Neurologic
- Optic neuritis
- Peripheral neuritis
- Encephalopathy
- Headache
- Mental confusion, depression

Other
- Hypersensitivity reactions
- Nausea, vomiting, diarrhoea
- Pseudomembranous colitis
- Glossitis, stomatitis
- Ototoxicity (topical otic formulations)

Not dose related

Haematologic
- Idiosyncratic aplastic anaemia

These adverse effects have led to dramatic reductions in the use of chloramphenicol in developed country settings. Use of chloramphenicol has been replaced by other antibiotics with a better side effect profile, although it remains a useful agent. In resource poor settings, its use has continued because of its availability and low cost.

Efficacy of chloramphenicol

Bacterial meningitis (BM) is thought to cause 170,000 childhood deaths a year[2], almost all of these deaths occurring in developing countries. It is estimated that between 25% and 50% of survivors have severe neurological sequelae.[2]

Prasad et al[12] conducted a Cochrane review that identified 18 random controlled trials (RCTs) conducted between 1983 and 1996 comparing the effectiveness and safety of the third generation cephalosporins and treatment with penicillin/ampicillin-chloramphenicol in patients with community-acquired acute bacterial meningitis. Ceftriaxone was used in 15 studies, cefotaxime in two and ceftazidime in one. The control treatments used in the studies were ampicillin plus chloramphenicol (n=9), ampicillin plus chloramphenicol plus gentamicin

(n=3), benzylpenicillin plus chloramphenicol (n=2), ampicillin alone (n=2) and benzylpenicillin alone (n=2). 15 of the studies were conducted in children, 9 of the studies undertaken in developing country settings. These authors concluded that the review showed no clinically important difference between ceftriaxone or cefotaxime and conventional antibiotics in the treatment of BM (no statistically significant differences in the risk of death, risk of deafness or risk of treatment failure). There was a significantly decreased risk of culture positivity of CSF after 10-48 hours and a statistically significant increase in the risk of diarrhoea in the groups treated with the third generation cephalosporins. However, the authors noted that the studies were done decades ago and may not apply to current routine practice.

Chloramphenicol, with or without the addition of penicillin or ampicillin, has long been the mainstay of treatment of BM in developing countries.[2] The most compelling evidence on the use of the combination therapy is primarily derived from a trial by Peltola et al[13], conducted in 1989, which compared ceftriaxone, cefotaxime, ampicillin-chloramphenicol and chloramphenicol therapies separately. It concluded that chloramphenicol should never be used alone and that ceftriaxone, cefotaxime and ampicillin showed similar efficacy.

The review by Fuller et al[2] identified 15 studies that compared chloramphenicol and third generation cephalosporins (ceftriaxone 9 studies, cefotaxime 5 studies, ceftazidime 1 study) for the treatment of BM in children. The identified studies largely overlapped with those identified in the Cochrane review. However, Fuller et al included a 1997 study by Ngu et al[14], which was stated to be not randomized in Prasad et al, while the Prasad review included a study by Tuncer et al[15], which compared ceftriaxone and penicillin alone, however it did not satisfy the inclusion criteria for Fuller et al. Overall, the conclusions of the two reviews were the same, i.e. that treatment outcomes were similar for both treatment groups (see Annex 1 for a summary of the clinical trial evidence).

There were no more recent RCTs identified that compared the use of third generation cephalosporins and chloramphenicol in BM. Both reviews highlighted the problems of resistance to chloramphenicol and the implications of this on the application of the results of their reviews to current practice.

Until 1990, chloramphenicol-resistant Haemophilus Influenzae (CRHI) was rare, with a 1990 study finding it in only one of 11 developing countries.[16] However, during the last 15 years there has been a dramatic rise in bacterial resistance to chloramphenicol.[4-7] In Kenya, the incidence of resistance to chloramphenicol has been reported to have increased from 8% in 1994 to 80% in 2000[4], although based on small numbers of isolates. In this study, the death rate was only 9% when the Haemophilus Influenzae (HI) was sensitive to chloramphenicol, but was 31% when the BM was caused by a CRHI.

Using chloramphenicol alone in BM when the causative bacteria are resistant to it has been shown to lead to an extremely poor outcome with death or severe neurological deficits in survivors.[5] In this Papua New Guinea (PNG) study, the rate of CRHI was 20% (18 of 90 isolates). Prior to observing this rapid rise in the resistance rate, 150 consecutive children were given chloramphenicol as first line treatment for BM. However, of those children who had CRHI, 70% either died or had severe neurological sequelae. This was despite being changed to ceftriaxone as soon as it was found that the HI was chloramphenicol-resistant. The remaining 30% included children with mild or moderate neurological sequelae (e.g. an isolated monoparesis or a cranial nerve palsy, which are themselves of significance). After noting the rapid rise in CRHI, the next 196 children with BM were commenced on ceftriaxone

therapy but then changed to chloramphenicol if the Haemophilus Influenza was sensitive to chloramphenicol. These children did much better with only a 9% poor outcome (death or severe neurological sequelae). In the PNG setting, using cefriaxone initially was 2.5 times more expensive than initiating treatment with chloramphenicol, but changing when the sensitivities were known meant the cost was less than half the cost of giving a full course of IV therapy with ceftriaxone, or only slightly more than a course of chloramphenicol alone.

Oily chloramphenicol in meningococcal meningitis epidemics

Greenwood[17] notes that in West Africa, meningococcus remains sensitive to both penicillin and chloramphenicol so that single injection treatment with oily chloramphenicol remains an effective treatment. Because of possible threats to ongoing supplies of the product, Nathan et al[18] investigated ceftriaxone as an alternative drug for use in meningococcal meningitis epidemics. Drugs requiring multiple injections daily are impractical in such circumstances. Only drugs with simple treatment regimens will provide alternatives. The long half life of ceftriaxone (8 hours in blood, 14 hours in the CSF) makes it a suitable candidate.

This study by Nathan et al[18] was conducted as a non-inferiority study to compare the efficacy of single-dose treatment of ceftriaxone and oily chloramphenicol for epidemic meningococcal meningitis. Using an intention-to-treat analysis, the authors reported treatment failure rates at 72 h of 9% for both drug groups. Case fatality rates and clinical failure rates were equivalent in both treatment groups (6% ceftriaxone *vs* 5% chloramphenicol). The results were also similar for both treatment groups in those with confirmed meningitis caused by *Neisseria meningitidis*. These authors concluded that single-dose ceftriaxone provides an alternative treatment for epidemic meningococcal meningitis and that its efficacy, ease of use, and low cost favour its use.

Duration of treatment with third generation cephalosporins

There is some evidence that short courses of third generation cephalosporins may be as effective as longer courses of treatment. If so, then this may reduce the comparative cost of a course of therapy with cephalosporins.

Martin et al[19] randomized patients with acute BM to either short course ceftriaxone daily (4, 6 or 7 days) or long course therapy (8, 12, 14 days) depending on whether the patients had contracted Meningococcal, Haemophilus influenzeae type b or Pneumococcal meningitis. Complete clinical recovery was reported in 88% of patients and was as frequent in the short course (91%) as in the longer course treatment groups (89%) and the secondary exclusion group (81%). The secondary exclusion group comprised 27 children who failed to meet all bacteriological and safety criteria for continuation in the protocol.

Singhi et al[20] compared 7 and 10 day treatment courses with ceftriaxone in BM. Consecutive children aged 3 months to 12 years admitted with acute BM were treated for 7 days and then assessed using a clinical scoring system. Those labeled treatment failures were continued for 10 days, those whose clinical scores were below 10 had ceftriaxone therapy stopped. The authors concluded that clinical outcomes in the two groups were similar, and 7 day treatment was associated with less nosocomial infection and shorter hospital stays.

Roine et al[21] conducted a RCT to compare four and seven day ceftriaxone treatment in children with bacterial meningitis. Strict clinical and laboratory criteria were applied to define

rapid initial recovery, after which treatment was stopped at either 4 days or 7 days. At day 7, there were no differences between the groups regarding fever, clinical signs or serum C-reactive protein concentration. At follow-up, 1-3 months after discharge, the 4-day group had fewer neurologic sequelae (0% vs 5%) and less hearing loss (3% vs 9%) although the differences were not statistically significant.

Typhoid fever

Typhoid fever (caused by S. typhi) remains a significant problem and is estimated to have caused 21·6 million illnesses and 216,500 deaths globally in 2000, affecting all ages.[8]

Chloramphenicol no longer has a place as first line treatment of Salmonella typhi (S typhi) as much of it in the developing world is now resistant to chloramphenicol.[9] Multiple resistance (to chloramphenicol, ampicillin and cotrimoxazole) has been reported in up to 90% of cases of Salmonella typhi in Vietnam and almost 70% in Pakistan. It has been suggested that almost all countries now have a significant proportion of multiple resistance of this bacteria. The current drugs of choice are fluoroquinolones and third-generation cephalosporins, but decreased susceptibility to these antimicrobials has also been reported.[8]

Pneumonia

Similarly, chloramphenicol no longer has a place as initial management of pneumonia because of resistance of the causative bacteria to chloramphenicol. In PNG, during 1998 to 2000, a randomized controlled trial involving chloramphenicol showed only 20 of 56 (36%) of the bacteria causing pneumonia in children to be sensitive to chloramphenicol compared with 35 of 53 (66%) which were sensitive to ceftriaxone.[22]

Side effect profile of chloramphenicol

There are three major side effects of chloramphenicol, but all are extremely rare and are generally not considered a significant factor when managing a life-threatening illness. One of these three, bone marrow suppression, is usually reversible when therapy is ceased. The other two warrant mentioning in more detail. They are chloramphenicol induced aplastic anaemia (CIAA) and the grey baby syndrome.

The incidence of CIAA, seen more often with oral administration[9], is thought to be around one in 25,000 to 40,000 individuals exposed to chloramphenicol. This figure, considered the best estimate, comes from a large study published in 1969.[23] All deaths in California during the 18 months from the start of 1963 were reviewed. CIAA was found to be about 13 times the background risk of aplastic anaemia. CIAA could occur after the first, second or even third exposure, even if there was a considerable time lapse between courses[24]. Since then, the use has largely been restricted to severe and life-threatening illness, primarily in developing countries. Death usually followed an overwhelming infection or haemorrhage or both[24].

The grey baby syndrome is a rare condition almost exclusively seen in neonates and very young infants. Toxic blood levels of chloramphenicol secondary to neonatal hepatic enzyme immaturity leads to circulatory collapse and the signs of cardiac shock. The infant is cyanosed, is acidotic, has cold peripheries and has the signs of all of marked hyponia, poor feeding, vomiting, loose stools and a distended abdomen. Because of this, it is recommended that chloramphenicol not been to be given to neonates or to young infants, but if given should

be administered in low doses (25 mg/kg/day in four divided doses) as noted previously.

Less severe side effects are seen with chloramphenicol but some of these (peripheral neuritis, optic neuritis) only occur with prolonged treatment, which is irrelevant to this report and the management of BM. Other side effects such as nausea, vomiting, diarrhoea, headache, fever and skin rashes are reported with chloramphenicol, but these are not unique to chloramphenicol and can be easily managed. Anaphylaxis has been reported when treating typhoid fever with chloramphenicol. Acute psychosis has been reported in adults.[25,26]

Both chloramphenicol and ceftriaxone have insignificant side effects when weighed up against their use for managing a life-threatening illness. The main difference in commonly reported side effects with these drugs has been a higher incidence of mild and reversible diarrhoea with the third generation cephalosporins.[27] Of 62 children treated for bacterial meningitis in one New Zealand study, 18 (29%) had mild and self limiting diarrhoea with ceftriaxone.[28] On the other hand, a delay in CSF sterilization occurs significantly more often with ampicillin/chloramphenicol than with ceftriaxone.[29] The Cochrane review confirmed these findings but found no difference for any of death, treatment failure, deafness, neutropaenia or skin rashes.[12]

Chloramphenicol formulations

Intravenous (IV) chloramphenicol is given as an inactive ester which must be activated by liver enzymes. This inactive form is able to be excreted by the kidneys, meaning the IV form has a lower bioavailability than the oral base.[30] However, the absorption of the oral formulation can be unpredictable, particularly when given to a child with sepsis (as with BM).

Children with sepsis have circulatory shutdown leading to poor gut perfusion which gives variable drug absorption from the gut. This is exacerbated in malnourished children who may have secondary pancreatic lipase deficiency which impairs hydrolysis of chloramphenicol palmitate leading to lessened absorption. Infants less than three months old can have variable absorption owing to gut immaturity. For these reasons, as well as the risk of the grey baby syndrome, initial treatment with oral chloramphenicol is not recommended in this age group.

IV therapy gives more reliable predictability in the initial stages of sepsis (including bacterial meningitis) management and is thus recommended as initial therapy. However an early switch to oral from IV chloramphenicol, after two days of treatment, has been shown to be equally efficacious as continuing IV therapy.[5,30] A switch to oral antibiotics is cost effective in allowing both a shorter hospital stay and a decline in nosocomial infections.[31]

On the other hand, one study has found chloramphenicol concentrations decreased significantly with increasing number of days of treatment and that the decline was steeper with IV administration.[32] The authors suggest that chloramphenicol should be given as a loading dose of 40 mg/kg, followed by 25 mg/kg per dose 8 hourly for 3-4 days and then 6 hourly to compensate. Although logical, this may be logistically difficult.

If an IV line cannot be inserted, IM (intramuscular) chloramphenicol, made up from powder, can be given instead. It has been shown to be as equally effective as IV therapy.[33]

Oily (long acting) chloramphenicol is given IM as a one off dose (or with a second follow up injection). In a study comparing chloramphenicol and ceftriaxone for the treatment of

epidemic meningococcal meningitis both were shown to be equally effective.[18] Both have been shown to be effective in epidemic meningococcal meningitis outbreaks, but in this study ceftriaxone was cheaper at only half the cost (US$ 2-3) for a course. Oily chloramphenicol is not effective for bacterial meningitis caused by other bacteria as shown by a study conducted in 1989-1990 in Mali and Niger, which reported case-fatality rates of 13% (21/161) for Neisseria meningitidis, 36.1% (48/133) for Haemophilus influenzae, and 67% (77/115) for Streptococcus pneumoniae.[34] Oily chloramphenicol may have a place in resource poor countries during a known meningococcal meningitis epidemic, providing it can be sourced more cheaply than can ceftriaxone. However high level resistance of Nissseria meningitides to chloramphicol has been occurring more frequently over the past 20 years.[35]

Drugs interfering with chloramphenicol blood levels

Both phenobarbitone and rifampicin, each of which is used in developing countries, induce hepatic microsomal enzymes and thus can decrease the chloramphenicol serum level by speeding up the metabolism.[24,25] Conversely, the inhibition of the cytochrome P450 hepatic system by chloramphenicol may increase the serum levels of some medications, amongst them being phenytoin, oral contraceptives and some anticoagulants.[24,25]

Cost

Seven days of treatment with chloramphenicol has been shown to be insufficient for a course of therapy for bacterial meningitis; ten days is required.[13] However, seven days of ceftriaxone treatment is sufficient treatment.[36] Therefore, the appropriate cost comparison should be ten days of chloramphenicol versus seven days of ceftriaxone (or another third generation cephalosporin). The MSH International Drug Price Indicator Guide provides the following cost data (Median Buyer prices):

Chloramphenicol 1gram vial (sodium succinate)	Median price $US 0.2552/vial
Ceftriaxone 1 gram vial	Median price $US 0.6448/vial
Chloramphenicol in Oil 250mg/ml 2ml amp	Price per 2ml amp $US 1.35/amp

Using the examples of a 70kg adult and a 20 kg child, and dosing schedules of 100mg/kg/day for chloramphenicol (divided into four doses per day) and for ceftriaxone, 4gram once daily for severe infections in adults and up to 80mg/kg/day for severe infections in children, doses and costs are estimated as follows:

Estimates of comparative costs for chloramphenicol and ceftriaxone in bacterial meningitis

Population	Drug	Dose	Per dose Daily dose	Total dose for course*	Cost ($US)#
Adult (70kg)	Chloramphenicol	25mg/kg/dose 4 times/day	1.75g = 2 vials 8 vials/day	80 vials	$20.42
	Ceftriaxone	4 gram/day	4 grams	28 vials	$18.05
Child (20kg)	Chloramphenicol	25mg/kg/dose 4 times/day	0.5 g = 1 vial 4 vials/day	40 vials	$10.21
	Ceftriaxone	80mg/kg/day	1.6 g = 2 vials	14 vials	$ 9.03

* course duration 10 days for chloramphenicol, 7 days for ceftriaxone
\# using median buyer prices for MSH International Drug Price Indicator Guide

These calculations are based on highest likely doses and there is some evidence that in less

severe cases, courses shorter than 7 days may be satisfactory for ceftriaxone. There is also considerable variability in prices for ceftriaxone, with the high/low ratio of prices of 3.09 (MSH Price Indicator). Therefore the relative costs of chloramphenicol and ceftriaxone will vary with the setting. Based on the examples in the table, ceftriaxone could be the cheaper treatment option.

For epidemics of meningococcal meningitis, and using the maximum doses in the study of Nathan et al[18] (i.e. maximum chloramphenicol oily 3G, maximum ceftriaxone 4G), the comparative costs would be oily chloramphenicol $8.10 ($1.35 x 6 amps) and ceftriaxone $2.58 ($0.6448 x 4 vials). Based on these prices, ceftriaxone is the cheaper option.

Summary of clinical data

The clinical data reviewed suggest there is similar efficacy of chloramphenicol and third generation cephalosporins for the treatment of bacterial meningitis (BM). However, the conclusions are based on studies conducted more than 10 years ago (and in a number of cases more than 20 years ago) when patterns of resistance to antibiotics were substantially different. There is increasing evidence of chloramphenicol-resistant strains of H. influenzae and S. typhi which diminish the relevance of the clinical studies conducted. Given the importance of instituting therapy before drug sensitivity results are available and the considerable risk of death and neurological sequelae if initially treated inappropriately, the role of chloramphenicol as first-line treatment must be questioned. Until recently, there has been a considerable price advantage in favour of chloramphenicol and third generation cephalosporins have been too expensive for use in resource-poor settings. With the dramatic reductions in prices for the cephalosporins, the arguments in favour of chloramphenicol have largely disappeared.

For epidemics of meningococcal meningitis, ceftriaxone has been shown to be equi-effective to oily chloramphenicol injection, and may be cheaper.

Recommendations

Given the increasing evidence on chloramphenicol resistant strains of both Haemophilus influenzae and Salmonella typhi, chloramphenicol should no longer remain in the WHO formulary as recommended first line treatment for infections caused by either of these organisms. Once a day third generation cephalosporins can be provided at a reasonable and often comparable cost to chloramphenicol and are preferred. However, where substantial cost differentials remain, chloramphenicol offers an alternative treatment, but may not be effective in all cases. Where ceftriaxone is expensive, it may be appropriate to institute therapy with cefriaxone and change to cheaper chloramphenicol when sensitivities are determined. While the side effect profile of chloramphenicol is a concern, the benefits far outweigh the potential risks when being used in severe, life-threatening infections.

A routine mass immunization programme against both Haemophilus influenzae and Pneumococcus in all countries should be the long term goal in order to prevent these serious infections. In developed countries these infections have effectively been eradicated as a result of routine immunization programmes.

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Annex 1: Studies of treatment of bacterial meningitis with cephalosporins (adapted from Prasad et al 2004, Fuller et al 2003)

Study Setting No. subjects	Age Range	Cephalosporin Daily dose and dosing schedule	Comparator arms	Outcomes assessed	Results
Studies conducted in adult populations					
Filali 1993 Morocco N = 36	> 16 years Mean 28.9	Ceftriaxone 2 grams IV daily for 2 days	Penicillin G 300,000 IU/kg/day given 4 hourly for 6 days	Death Neurological sequelae Duration of coma Duration of fever Adverse events	No differences in clinical outcomes or adverse events
Girgis 1987 Egypt N = 30	16-30 years	Ceftriaxone 100mg/kg/day IV once daily	Ampicillin 160mg/kg/day given 6 hourly and chloramphenicol 100mg/kg/day given 6 hourly	Death Duration of fever	No differences in clinical outcomes
Narciso 1983 Italy N = 10	Mean 46 years	Ceftriaxone 80-100mg/kg/day IV given 12 hourly	Ampicillin 110mg/kg/day given 8 hourly	Death Duration of coma Duration of fever	No differences in outcomes
Studies conducted in mixed adult and paediatric populations					
Girgis 1988 Egypt N = 100	5 months - 28 years	Ceftriaxone 100mg/kg/day IM to children, IV to adults	Ampicillin 160mg/kg/day given 6 hourly and chloramphenicol 100mg/kg/day given 6 hourly (IM children, IV to adults)	Death Days to become fully alert Duration of fever Adverse events	No differences in clinical outcomes Mild diarrhoea, cramps, nausea reported in both groups
Studies conducted in paediatric populations - ceftriaxone					
Sharma 1996 Nepal N = 23	5 months - 5 years	Ceftriaxone 50mg/kg/day IM as single dose for 7 days	Chloramphenicol 100mg/kg/day given 6 hourly for 14 days and benzylpenicillin 200,000 IU/kg/day 6 hourly for 14 days	Death Duration of fever	Faster defervescence in ceftriaxone group, other outcomes the same
Peltola 1989 Finland N = 197	3 months - 15 years	Ceftriaxone 100mg/kg/day IV once daily for 7 days	Chloramphenicol 100mg/kg/day; qid 7 days Ampicillin 250mg/kg/day; qid 7 days Cefotaxime 150mg/kg/day; qid 7 days	Death Sensorineural deafness Recurrence of disease Duration of consciousness impairment Duration of fever Adverse events	No differences in case fatality or long term outcomes Four recurrences in chloramphenicol group Ceftriaxone - diarrhoea, gall bladder precipitate Diarrhoea in other groups

Study Setting No. subjects	Age Range	Cephalosporin Daily dose and dosing schedule	Comparator arms	Outcomes assessed	Results
Tuncer 1988 Turkey N = 42	1 month - 12 years	Ceftriaxone 80-100mg/kg/day IV once daily, 4 days	Penicillin G 500,000 IU/kg/day IV 4 hourly for 5 days	Death Duration of fever Reoccurrence within 6 months	No differences in clinical outcomes
Ngu 1987 Cameroon N = 60	unclear	Ceftriaxone 100mg/kg/day once daily	Ampicillin and chloramphenicol		Claims of quicker CSF sterilisation and resolution of clinical signs for ceftriaxone group
Barson 1985 USA N = 50	0.2 - 5 years	Ceftriaxone 100mg/kg/day, IV bd dosing	Ampicillin and chloramphenicol	Death Sensorineural deafness Seizures and cranial nerve palsies Adverse events	No differences in outcomes More diarrhoea in ceftriaxone group
Bryan 1985 Brazil N = 36	2 months - 17 years	Ceftriaxone 80mg/kg/day, once daily IV	Ampicillin and chloramphenicol	Death Neurological sequelae Time for CSF sterility Duration of fever Adverse events	No difference in clinical outcomes Ceftriaxone: anaemia, transient moderate neutropenia, diarrhoea
Aronoff 1984 USA N = 19	0.17 - 8.75 years	Ceftriaxone 100mg/kg/day, IV bd dosing	Ampicillin and chloramphenicol	Death Sensorineural deafness Hydrocephalus Blindness	No differences in clinical outcomes
Congeni 1984 USA N = 45	1 day - 15 years	Ceftriaxone 100mg/kg/day, IV bd dosing	Ampicillin 200-400mg/kg/day IV qid dosing and chloramphenicol 75mg/kg/day IV qid dosing	Death Complications and sequelae during treatment Time for CSF sterility Duration of fever Adverse events	No differences in clinical outcomes Ceftriaxone: transient eosinophilia and neutropenia, anaemia, mild diarrhoea Comparator: mild diarrhoea
Delrio 1983 USA N = 78	> 6 weeks most >2 years	Ceftriaxone 100mg/kg/day, IV bd dosing	Ampicillin 200mgkg/day IV qid dosing and chloramphenicol 100mg/kg/day IV qid dosing	Death Sensorineural deafness Other disabilities Duration of fever Adverse events	Higher rates of transient ataxia, prolonged fever and diarrhoea in cefriaxone No differences in other outcomes

Study Setting No. subjects	Age Range	Cephalosporin Daily dose and dosing schedule	Comparator arms	Outcomes assessed	Results
Steele 1983 USA N = 30	14 days - 14 years	Ceftriaxone 100mg/kg/day, IV bd dosing (IM last days of treatment)	Ampicillin 200-400mg/kg/day IV qid dosing and chloramphenicol 100/kg/day IV qid dosing (orally last days of treatment)	Death Sensorineural deafness Other disabilities Duration of fever Adverse events	Faster resolution of fever in ceftrixone group All other outcomes were similar
Studies conducted in paediatric populations - other cephalosporins					
Haffejee 1988 South Africa N = 31	1 month - 9 years	Cefotaxime 100-200mg/kg/day IV bd or tds dosing for 3-5 days, then IM	Penicillin G 0.5-1 million IU IV 6 hourly 3-5 days then IM and chloramphenicol 80-100mg/kg/day orally, tid or qid dosing (sulphadizine used in early part of trial)	Death Sensorineural deafness Other disabilities Duration of fever Adverse events	No differences in clinical outcomes Cefotaxime: diarrhoea, neutropenia, anaemia, thrombocytosis Comparator: as above plus thrombocytopenia
Odio 1986 Costa Rica N = 85	2 months - 10.5 years	Cefotaxime 200mg/kg/day IV qid dosing for at least 10 days	Ampicillin 200mgkg/day IV qid dosing first 5 days and chloramphenicol 100mg/kg/day IV qid dosing first 5 days then oral for at least 10 days	Death Sensory sequelae Inability to perform ADL Developmental abnormalities Duration of fever Other sequelae Adverse events	Higher incidence of mild to moderate motor sequelae in chloramphenicol at discharge but not at 4 months. No differences in other outcomes. Cefotaxime: diarrhoea, thrombocytosis, neutropenia, skin rash, prolonged fever, elevated ALT, elevated BUN, hyperkalaemia Comparator: diarrhoea, fever, neutropenia, elevated ALT
Jacobs 1985 USA N = 50	1 week - 16 years	Cefotaxime 200mg/kg/day IV qid dosing	Ampicillin 200-400mgkg/day IV qid dosing and chloramphenicol 100mg/kg/day IV qid dosing (or gentamicin for neonates)	Death Sensorineural deafness Other sequelae Duration of fever Adverse events	No differences in clinical outcomes Cefotaxime: diarrhoea Comparator: acute tubular necrosis

Study Setting No. subjects	Age Range	Cephalosporin Daily dose and dosing schedule	Comparator arms	Outcomes assessed	Results
Wells 1984 USA N = 30	0.25 - 200 months	Cefotaxime 20mg/kg/day IV qid dosing for 10-14 days	Ampicillin 200-400mgkg/day IV qid dosing 10-14 days and chloramphenicol 100mg/kg/day IV qid dosing 10-14 days (or gentamicin for neonates < 1 month)	Death Sensorineural deafness Other disabilities Adverse events	No differences in clinical outcomes No adverse effects in cefotaxime group; acute tubular necrosis recorded as potential adverse event in comparator arm
Rodriguez 1985 Dominican Republic N = 100	> 1 month most ≤ 3 years	Ceftazidime 150mg/kg/day IV tid dosing	Ampicillin 400mgkg/day IV qid dosing and chloramphenicol 75-100mg/kg/day IV qid dosing 10-14 days (or gentamicin for neonates < 1 month)	Death Other sequelae Duration of fever Days until asymptomatic Adverse events	No statistical comparison of outcomes Ceftazidime: diarrhoea, drug fever, leucopenia/anaemia requiring transfusion

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