



WHO/CHD/98.6
WHO/EMC/BAC/98.2

Antimicrobial and support therapy for bacterial meningitis in children. Report of the meeting of 18-20 June 1997, Geneva, Switzerland

World Health Organization
Emerging and other Communicable Diseases,
Surveillance and Control

This document has been downloaded from the WHO/EMC Web site. The original cover pages and lists of participants are not included. See <http://www.who.int/emc> for more information.

© World Health Organization

This document is not a formal publication of the World Health Organization (WHO), and all rights are reserved by the Organization. The document may, however, be freely reviewed, abstracted, reproduced and translated, in part or in whole, but not for sale nor for use in conjunction with commercial purposes.

The views expressed in documents by named authors are solely the responsibility of those authors. The mention of specific companies or specific manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned.

| CONTENTS | Page |
|--|-------------|
| 1. Introduction | 1 |
| 1.1. Purpose of the meeting | 1 |
| 1.2. Bacterial meningitis in developing countries | 1 |
| 2. Antimicrobial therapy | 2 |
| 2.1. Empiric antimicrobial therapy for bacterial meningitis | 2 |
| 2.2. Strategies for countries with penicillin and/or chloramphenicol resistance | 3 |
| 2.3. Prospects for affordability of third generation cephalosporins in developing countries | 3 |
| 2.4. Summary of discussions on antimicrobial therapy | 4 |
| 3. Chloramphenicol – A review of recent pharmacokinetic and efficacy data | 5 |
| 3.1. Pharmacokinetic of chloramphenicol administered by IV/oral routes | 5 |
| 3.2. Chloramphenicol use in malnourished children | 5 |
| 3.3. Chloramphenicol use in young infants | 6 |
| 3.4. Clinical efficacy of oily chloramphenicol compared with ceftriaxone in bacterial meningitis | 6 |
| 3.5. Summary of discussions on chloramphenicol | 7 |
| 4. Dexamethasone therapy in meningitis | 8 |
| 4.1. Review of available information | 8 |
| 4.2. Summary of the discussions on dexamethasone therapy | 9 |
| 5. Fluid requirements in meningitis management | 10 |
| 5.1. The basis of fluid restriction and current views | 10 |
| 5.2. Developing country perspective – the Chandigarh studies | 11 |
| 5.3. Summary of discussion of fluid therapy in meningitis | 12 |
| 6. Recommendations | 13 |
| 6.1. Antimicrobial therapy for meningitis | 13 |
| 6.2. Use of chloramphenicol | 13 |
| 6.3. The role of dexamethasone | 14 |
| 6.4. Fluid therapy in meningitis | 14 |
| 6.5. CSF testing for diagnostic and surveillance purposes | 14 |
| 6.6. Recommendations for future research | 15 |

ANTIMICROBIAL AND SUPPORT THERAPY FOR BACTERIAL MENINGITIS IN CHILDREN

**Report of the meeting of June 18-20, 1997
held at World Health Organization, Geneva**

1. INTRODUCTION

WHO and UNICEF have developed an integrated approach to address the major life-threatening illnesses of children known as Integrated Management of Childhood Illness (IMCI). Lessons learned from disease-specific programmes have been applied to promote co-ordination and integration of the activities to improve the prevention and management of childhood illness. Apart from five major killer diseases of children under five years (acute respiratory infections - mostly pneumonia, diarrhoea, measles, malaria and malnutrition) bacterial meningitis is an important cause of childhood morbidity and mortality [1].

1.1 Purpose of the meeting

Various differences exist in the management of meningitis from one place to another. It was decided, therefore, to convene a meeting to review current practices and make recommendations. The agenda of the meeting and the list of participants are included in Annexes 1 and 2. Four issues regarding the management of bacterial meningitis in children in developing countries were considered by the meeting:

- the choice of antimicrobial therapy for bacterial meningitis and the implications of antimicrobial resistance,
- the pharmacokinetics and current use of chloramphenicol,
- the role of dexamethasone in bacterial meningitis, and
- fluid management in bacterial meningitis.

1.2 Bacterial meningitis in developing countries

The incidence of bacterial meningitis is higher in developing countries than developed countries [1-10] and is particularly high in children under one year of age. Case fatality rates (CFR) for bacterial meningitis range from 4.5% in developed countries to 15-50% in developing countries [2,11,12]. A further 15-20% of survivors sustain neurologic sequelae [13,14]. *H. influenzae*, *S. pneumoniae* and *N. meningitidis* are the common bacteria causing meningitis in under five year old children [14-19]. Delay in presentation contributes to the higher morbidity and mortality [20]. Pre-treatment with antibiotics varies [13,14,21-28] and good data are not available to show the effect of prior antimicrobial use on mortality and morbidity. There is great variability in the quality of laboratory diagnoses and there is a lack of good microbiological data from developing countries as compared to developed countries [29-33]. There is a need for development of simple tests to diagnose bacterial meningitis, particularly in developing countries [34].

2. ANTIMICROBIAL THERAPY

2.1 Empiric antimicrobial therapy for bacterial meningitis

Current international recommendations for empiric therapy according to the age, immunocompetence and country status are given in Table 1.

Table 1. Empiric therapy for bacterial meningitis in developed and developing countries

| Patient group | Likely etiology | Antimicrobial choice | |
|---|--|--|---------------------------------|
| | | Developed countries | Developing countries |
| Immunocompetent children: age < 3 months | Developed countries | Ampicillin plus cefotaxime or ceftriaxone | Ampicillin plus gentamicin |
| | Group B <i>Streptococcus</i> <i>E. coli</i> <i>L. monocytogenes</i> * | | |
| | Developing countries <i>S. pneumoniae</i> <i>E. coli</i> | | |
| Immunocompetent children: age ≥ 3 months - 18 years | <i>H. influenzae</i> <i>S. pneumoniae</i> <i>N. meningitidis</i> | Cefotaxime or ceftriaxone** | Ampicillin plus chloramphenicol |
| Immunodeficient | <i>L. monocytogenes</i> Gram negative organisms | Ampicillin plus ceftazidime | |
| Neurosurgical problems and head trauma | <i>S. aureus</i> Gram negative organisms <i>S. pneumoniae</i> | Vancomycin plus third generation cephalosporin | |

Source: [21,35,36]

* In infants age 1-3 months *Staphylococcus aureus*, *H. influenzae*, *N. meningitidis* and *Salmonella* species also occur in developing countries

** For resistant *S. pneumoniae* the American Academy of Pediatrics recommends vancomycin plus cefotaxime or ceftriaxone as empiric therapy

2.2 Strategies for countries with penicillin and or chloramphenicol resistance

Available data suggest that resistance to chloramphenicol is not yet a major problem in *H. influenzae* disease. Data from 11 developing countries showed that only 1.6% of *H. influenzae* were resistant to chloramphenicol [37,38], but that pneumococcal resistance was in the range of 5-10% [39-40]. Available information suggests that: pneumococcal resistance increases with increased use of antimicrobials [41-44]; there is more resistance in urban areas [45,46]; and HIV is a risk factor for invasive penicillin-resistant pneumococcal disease [41,44,47,48]. Penicillin-resistant pneumococcal meningitis has been associated with higher CFR and more serious sequelae in survivors [40,49]. In South Africa, bacterial meningitis patients with penicillin-resistant pneumococcal disease also did not respond to chloramphenicol due to higher associated chloramphenicol minimum bactericidal concentrations, not evident on *in vitro* disk testing [40]. The increasing prevalence of penicillin-resistant pneumococci strains world-wide raises concern [50-55]. Data from developing countries are limited.

Penicillin-resistant pneumococcal meningitis responds very well to third generation cephalosporins (cefotaxime or ceftriaxone) [56]. In some parts of the world, however, invasive pneumococcal disease with cefotaxime / ceftriaxone resistant pneumococci is being reported [53,56,57]. In such children a combination of cefotaxime or ceftriaxone and vancomycin or rifampicin is recommended [56-59]. A new antimicrobial drug cefpirome (fourth generation cephalosporin) is also promising [60], but needs to be studied in a clinical trial of bacterial meningitis. Oral and injectable quinolones have been used successfully in meningococcal meningitis, but their effect in *H. influenzae* and *S. pneumoniae* meningitis needs to be studied. A few studies have shown short course ceftriaxone (4-8 days) therapy to be efficacious for bacterial meningitis [61-64]; this needs to be studied further.

2.3 Prospects for affordability of third generation cephalosporins in developing countries

Some issues related to process and product patents for pharmaceuticals were discussed. Minimum patents for pharmaceuticals are generally for a period of 20 years. Sometimes pharmaceutical companies make the patented drugs available at lower costs because they want to enhance their public image, penetrate the market, limit waste, avail themselves of tax benefits and sometimes just for philanthropic reasons. Cost lowering can be stimulated by global action on the part of international agencies like WHO and UNICEF, market competition within the industry, and national actions regarding taxes / duties, group purchases, price regulation and local production. The first third generation cephalosporin antimicrobial to come off patent would be ceftriaxone in 1999. Pharmaceutical costs come down considerably when the medicine comes off patent and if a number of pharmaceutical companies start manufacturing the same generic medicine.

2.4 Summary of discussions on antimicrobial therapy

Discussion evolved around: treatment guidelines, the definition of failure of therapy (whether death or development of sequelae); the importance of information on the level of consciousness of patients at the time of admission; prevalence of penicillin-resistant organisms; and the pharmacokinetic levels of chloramphenicol in CSF and serum after injectable oily preparation. It was emphasised that penicillin resistance should only be tested by using oxacillin discs and not ampicillin discs.

Another focus of discussion was the level of penicillin resistance that should warrant a change in empiric therapy to third-generation cephalosporins as the first-line drug in a developing countries. No consensus on a figure could be reached and the term 'significant resistance' (to be defined in individual countries) was agreed upon.

The group reached the following conclusions (see also section 6):

- In the light of antimicrobial resistance data, cefotaxime or ceftriaxone alone or with ampicillin should be the preferred treatment in definite bacterial meningitis in young infants (< 3 months of age). Suspected cases of bacterial meningitis in young infants (< 3 months of age) should be treated as sepsis, with (ampicillin or penicillin) + aminoglycoside until meningitis is confirmed. If third-generation cephalosporins are not available ampicillin + (gentamicin or chloramphenicol) may be used.
- In children over 3 months, initial treatment with chloramphenicol + (penicillin or ampicillin) is suitable if there is no significant pneumococcal penicillin resistance. If significant resistance has been observed then cefotaxime or ceftriaxone should be used.
- Non-availability of ceftriaxone or cefotaxime should never lead to delay in initiating therapy in bacterial meningitis.
- There is a need to evaluate the availability and cost of third-generation cephalosporin therapy for hospitalized patients in developing countries.
- It was proposed that clinical efficacy and safety of shorter duration regimens of third-generation cephalosporin therapy for bacterial meningitis should be studied, i.e., five days versus seven days or five days versus ten days of cefotaxime or ceftriaxone.
- The group felt that meningitis should be diagnosed by lumbar puncture, unless there was a contraindication. Further research or the development of simplified systems of testing CSF (e.g. by dip stick) was also suggested.

3. CHLORAMPHENICOL - A REVIEW OF RECENT PHARMACOKINETIC AND EFFICACY DATA

3.1 Pharmacokinetics of chloramphenicol administered by IV/oral routes

Pharmacokinetic data on intravenous administration of chloramphenicol succinate show that the serum half-life is in the range of 0.34-2.2 hours with a mean varying from 0.4 [65] to 0.7 hours [66]. This short half-life is due to rapid renal elimination which, on average, results in renal loss of 30% of the infused drug [65]. When chloramphenicol is infused simultaneously with ampicillin, both of these weak acids compete for secretion by the renal tubular epithelium. This results in the area of the serum concentration time curve of chloramphenicol succinate being greater, making more drug bioavailable to the patient [67]. The chloramphenicol succinate which is not secreted by the kidney is converted to active drug by a hepatic esterase. Thus, good liver function is needed to convert the pro-drug chloramphenicol succinate into the active antibiotic [68].

After oral administration of 20-25mg/kg dose, the absolute bioavailability of chloramphenicol palmitate (the oral dosage form for children) is increased. This results from the large absorptive area present in the gastrointestinal tract [69, 70]. After oral administration of chloramphenicol palmitate to infants and children, the drug must be hydrolyzed by pancreatic lipase; this permits absorption of the active antibiotic [71].

CSF chloramphenicol concentrations are higher after oral administration (because of the large area under the serum concentration curve) in comparison to intravenous administration. With both routes, early in the course of the disease, the CSF concentration approximates 50% of the simultaneous serum concentrations [72,73]. As the inflammation in the meninges resolves, the CSF concentration decreases to being 38% (by day 10) of the simultaneous serum concentration. After an initial period of administration of intravenous chloramphenicol succinate, when chloramphenicol palmitate was used in children, reasonable serum levels were sustained. There was wide patient-to-patient variability in serum concentrations seen with both oral chloramphenicol palmitate and parenteral chloramphenicol succinate.

3.2 Chloramphenicol use in malnourished children

Pharmacokinetic data from a study conducted in Pakistan of oral chloramphenicol palmitate use in 14 severely malnourished and 14 well nourished children suffering from pneumonia was presented. Each child was given 25 mg/kg every six hours for five days. Therapeutic levels (10µg/l) were achieved in 10 malnourished and 12 well-nourished children at some time during 5 days of therapy. Toxic levels (25µg/l) were seen in one malnourished and two well nourished children. There was wide variability in the serum levels. In general, the mean serum levels were lower in malnourished than well-nourished children, although there were no significant differences between the two groups. One malnourished and three well-nourished

children needed a change of therapy. Of the three well nourished children, one had developed toxic levels and another did not achieve therapeutic level.

Pharmacokinetic data from two different studies in The Gambia, one conducted in 1990 on 36 patients and another in 1994 on 16 patients showed similar results. There was a great deal of variability in serum levels, and in general the sick malnourished children achieved lower serum levels than the well nourished children.

It was concluded that sick malnourished children should be treated with injectable chloramphenicol. It was also concluded that 75 mg/kg/day should be recommended instead of 100 mg/kg/day in all childhood illnesses, due to concern regarding toxic levels.

3.3 Chloramphenicol use in young infants

Combined pharmacokinetic data from 20 Gambian and 10 Filipino children given intramuscular chloramphenicol and 20 Filipino children given oral chloramphenicol were presented. All children were less than 3 months old. There was wide variability in the serum levels obtained in Filipino children who received oral chloramphenicol. Children who received intramuscular chloramphenicol were able to achieve therapeutic levels.

It was concluded that oral chloramphenicol should not be used in young infants less than 3 months of age, and if necessary they should be treated with injectable chloramphenicol.

3.4 Clinical efficacy of oily chloramphenicol compared with ceftriaxone in bacterial meningitis

Oily chloramphenicol has been used in the treatment of bacterial meningitis in Africa, in doses ranging from 50 to 100 mg/kg IM in a single dose (divided in two injections, one in each buttock), up to a maximum of 3 grams [74-79]. The dose was in some cases repeated once after 24 or 48 hours. These studies did not report any adverse reactions to these doses but haematological investigations were not undertaken. Oily chloramphenicol has been successfully used to treat mostly epidemic meningococcal meningitis, but it has also been used for treatment of meningitis due to other causes. Data were presented from a double blind trial of two intramuscular injections of either oily chloramphenicol (100 mg/kg) or ceftriaxone (75 mg/kg) 24 hours apart for the treatment of bacterial meningitis in 2-35 months old children. Three hundred children from one hospital each in Mali and Niger were enrolled. The CFR at 72 hours was 18.5% in the ceftriaxone and 21.7% in the chloramphenicol group. This difference in CFR was only significant for presence of *S. pneumoniae* meningitis. Eighty percent (60/74) of all deaths occurred within 72 hours of admission. Logistic regression modelling identified only convulsions, presence of *S. pneumoniae* and assignment to chloramphenicol as independent risk factors for mortality. Although the study protocol did not include antimicrobial use after the second day of admission, treating physicians treated 35% of cases with other antimicrobials for 7-10 days. Ceftriaxone had better clinical efficacy as compared to oily chloramphenicol in bacterial meningitis due to *S. pneumoniae*. There is a need for safe, efficient, simple to administer and affordable treatment for bacterial meningitis

in developing countries.

3.5 Summary of discussions on chloramphenicol

- Therapeutic levels are achieved reasonably well with injectable chloramphenicol. Absorption of oral chloramphenicol is good but achieved serum levels are variable.
- There is some evidence that while therapeutic levels are achieved with oral chloramphenicol use in well nourished children, lower levels are achieved in sick malnourished children. It is recommended that sick malnourished children should be treated with injectable chloramphenicol.
- If young infants have to be treated with chloramphenicol, injectable chloramphenicol should be used.
- The pharmacokinetics of oily chloramphenicol should be explored, with a view to assessing its potential use in meningitis other than epidemic bacterial meningitis. One study in a small number of patients has reported a rapid rise of serum concentration after one injection of oily chloramphenicol [79].
- The Committee on Infectious Diseases of the American Academy of Pediatrics indicates that a dose of 75-100 mg/kg/24 hours can be used in children with bacterial meningitis [80]. Chloramphenicol has been clinically used successfully at a dose of 75mg/kg/24 hours in pneumonia [81], bacterial meningitis [69,82] and typhoid fever [83-85]. Concerns have been raised, however, about chloramphenicol toxicity when using 100mg/kg/24 hours dose in children [86-89]. Pharmacokinetic data shows that chloramphenicol can be used in three divided doses daily [65,86,90]. However, there were reservations in the group about using 75 mg/kg/24 hours in three divided doses for treatment of bacterial meningitis.
- For bacterial meningitis, injectable chloramphenicol should be used in 100 mg/kg/24 hours divided in four equally divided doses. However, if necessary, injectable chloramphenicol can be changed to oral form after 3-4 days of initial therapy in children aged three months and above. It was recommended that for other serious infections (e.g. very severe pneumonia, failure of therapy with benzyl penicillin in severe pneumonia or enteric fever) chloramphenicol should be used in 75 mg/kg/24 hours in three equally divided doses..
- It is important to be aware of interactions between and chloramphenicol and other drugs. Phenobarbitone reduces chloramphenicol levels when both drugs are used together [91-93]; and phenytoin and chloramphenicol levels are both increased if both drugs are used in combination [91,94,95].

4. DEXAMETHASONE THERAPY IN MENINGITIS

4.1 Review of available information

Review of the pathophysiology of dexamethasone use in experimental models and in humans shows that the use of the drug regulates down the effect of the inflammatory cascade and reduces brain water content [96-98]. This effect was more evident when dexamethasone was given prior to antibiotics. Different recommendations have been made regarding use of dexamethasone as an adjunctive therapy in bacterial meningitis in developed countries. The American Academy of Pediatrics recommended that dexamethasone be used in *H. influenzae* [99] and be considered in *S. pneumoniae* and in *N. meningitidis* meningitis. Tunkel and Scheld concluded after a meta-analysis in 1995 that only high risk and neurologically impaired children with bacterial meningitis should be given steroids [21]. Quagliarello and Scheld in 1997 advised steroids for all children above 2 months of age with bacterial meningitis, especially if not vaccinated against *H. influenzae* b (Hib) [3].

Review of the studies on the use of adjunctive steroid therapy in bacterial meningitis in developed countries suggests a reduction in hearing deficit and neurological deficit following the addition of dexamethasone [100-103]. The best results were obtained when dexamethasone was given before antimicrobial therapy [103,104]. Two-day steroid therapy appeared as effective as four-day therapy [103,105] and the incidence of side effects was very small. However, the results for *S. pneumoniae* meningitis were retrospective and fewer in number [100,102]. One multi-centre trial of dexamethasone adjunctive therapy did not find any significant difference between dexamethasone and placebo with antimicrobials [106]. A meta-analysis of adjunctive steroid therapy studies in bacterial meningitis criticized the methodologies of many studies, and concluded that the data did not show any benefit of steroid therapy [107].

Review of the few studies of adjunctive steroid therapy from developing countries [13,14,104,108-110] shows that the studies were not comparable. The study criteria varied widely; some studies were retrospective, not all were controlled or double-blind, different antimicrobial regimens were used and the ages of patients were not comparable. Most studies enrolled small numbers. One (Recife, Brazil) included retrospective data [110]. In two studies (Recife and Islamabad, Pakistan) the steroid/non steroid groups were not strictly comparable [13,110]. Conclusions differed; studies from Recife [110] and Maputo, Mozambique [14] showed improved outcome in the dexamethasone groups in certain age groups and the Cairo, Egypt study in pneumococcal infections only [108]. In Islamabad, the dexamethasone group had an increased risk of sequelae (especially hearing deficit) and worsened mortality [13]. The Islamabad study was a placebo-controlled double-blind, and included children 2 months to 12 years who were treated with ampicillin and chloramphenicol [13]. This result could be due to late presentation of patients (average 5.7 days of fever) and use of antibiotics (48%) prior to hospital presentation [13]. The condition

of a child at admission is clearly important to the outcome. Problems of these developing country studies included: variable definitions for coma; CSF results in which no bacteria were isolated; different nutritional status assessment; different age ranges; small study numbers; and lack of internal consistency in some studies.

Several concerns have been raised with the adjunctive use of steroids, such as gastrointestinal bleeding [111], secondary fever [100,112,113], and difficulties in the clinical assessment of bacteriological cure due to quicker defervescence and penetration of antimicrobials through the blood brain barrier, particularly in penicillin-resistant pneumococcal meningitis [114]. From Denmark a failure rate of 4% was reported in penicillin sensitive cases receiving dexamethasone [115], and from San Diego three failures in children were reported, one who relapsed, one with TB meningitis and one with a brain abscess [116]. Children with bacterial meningitis may be in septic shock and the role of steroids in septic shock [117] and viral infections [23] is unclear. Its use appears to increase the severity of cerebral malaria [118]. CSF sterilization by ampicillin and gentamicin in the presence of steroids also needs clarification [109,110]. Not much is known about the use of dexamethasone in malnourished patients or those with HIV infection or serious illness.

Another major problem was that 65-70% of the children in the developed country studies had *H. influenzae* bacterial meningitis (excluding one retrospective study of pneumococcal infections from Dallas) [100-106], whereas in developing countries the causative organisms for bacterial meningitis were different [13,14,108-110] (Table 2).

Table 2. Comparison of bacterial meningitis etiology in developing and developed countries

| | Developing country studies | Developed country studies |
|------------------------|----------------------------|---------------------------|
| <i>H. influenzae</i> b | 30% | 65% |
| <i>S. pneumoniae</i> | 23% | 13% |
| <i>N. meningitidis</i> | 28% | 18% |
| Other organisms | 19% | 4% |

Source: [13,14,100-106,108-110]

It was concluded that there was insufficient evidence either for or against the use of steroids in bacterial meningitis for children in developing countries, and that additional studies were needed.

4.2 Summary of the discussions on dexamethasone therapy

- The existing data did not provide sufficient evidence for recommending routine use of dexamethasone in all children with bacterial meningitis in developing countries. It should not be used in new-borns, suspected cerebral malaria or viral encephalitis or in areas with high penicillin-resistant pneumococcal invasive disease.
- A large enough randomized controlled trial (probably multi-centre) or comparable trials at several sites are needed to provide sufficient evidence of the usefulness of

steroids. The group recommended that randomization should be done by age groups 2-11 months, one to five years, and more than five years. The antibiotic of choice should be ceftriaxone for seven days and injectable dexamethasone should be given five minutes before antibiotic therapy in a dose of 0.4 mg/kg every 12 hours for two days. Severe viral infections should be excluded. The sample size should be sufficiently large. A lumbar puncture at 24 hours post-treatment initiation in a subset of at least 20 patients should be done to confirm clearance of bacteria and drug levels.

5. FLUID REQUIREMENTS IN MENINGITIS MANAGEMENT

5.1 The basis of fluid restriction and current views

Fluid restriction in meningitis is widely recommended in current textbooks [119]. The composition and amount of body fluids is tightly regulated [120] and determinants of actual status are intake and excretion. Loss of body fluids can occur through sweat, stool, and vomiting. The organ mainly involved however, is the kidney. The excretion of water and salts is regulated by three hormonal mechanisms: the renin-angiotensin-aldosterone mechanism, the atrial natriuretic hormone, and the antidiuretic hormone (ADH, arginine vasopressin). The ability of the kidney to respond to these mechanisms might be compromised through damage to the parenchyma or hypoperfusion. ADH is secreted by the pituitary gland and results in retention of water. Appropriate secretion of ADH is a result of hypovolemia and leads to the retention of water. An abnormal mechanism has been described in some diseases that leads to the inappropriate secretion of ADH (SIADH), and therefore inappropriate retention of water.

Characteristics of SIADH are hyponatraemia with hypo-osmolality of serum, continued renal sodium excretion, hyperosmolality of urine, absence of clinical volume depletion, normal renal function and normal adrenal function [121]. Several studies over the past 30 years have suggested that SIADH plays a role in bacterial meningitis, and adversely affects the outcome of children with meningitis. Table 3 summarizes studies of fluid and electrolyte balance in children and experimental animals.

Questions arise whether reported high levels of ADH in combination with hyponatraemia describe:

- appropriate ADH secretion to maintain cerebral perfusion in the presence of cerebral oedema,
- appropriate ADH secretion to compensate for hypovolaemia possibly due to decreased fluid intake in a sick child or in the presence of renal sodium loss, or
- inappropriate ADH secretion due to brain damage and which might contribute to further brain damage.

Table 3. Studies of fluid and electrolyte balance in meningitis

| Study | Finding | Number Studied | Interpretation |
|------------------------------|---|-------------------|---|
| Reynolds 1972 [122] | low serum, high urinary sodium | 1 | SIADH |
| Feigin 1977 [123] | 58% hyponatraemic, 86% increased ADH | 124 | SIADH |
| Kaplan and Feigin 1978 [124] | ADH higher than in controls | 17 | SIADH |
| Garcia 1981 [125] | ADH increased in CSF | 14 | contributing to brain oedema |
| Shann 1985 [126] | 50% hyponatraemic | 20 | SIADH, fluid requirement 50 ml/kg/day |
| Kanakriyeh 1987 [127] | 32% hyponatraemic, but only 7% SIADH | 85 | fluid restriction not recommended |
| Powell 1990 [128] | ADH lower after fluid loading | 13 (7 more fluid) | hypovolaemia leads to appropriate ADH secretion |
| Padilla 1991 [129] | urine ADH high in bacterial meningitis | ? <18 | clinically none with SIADH |
| Täuber 1993 [130] | no effect of fluid regime on oedema | ??? rabbits | high fluid does not contribute to oedema |
| Singhi 1995 [131] | increased poor outcome with fluid restriction | 50 | fluid restriction not indicated |

5.2 Developing country perspective - the Chandigarh studies

Two studies have been conducted in Chandigarh, India [131,132]. The first study described changes in body water compartments in children with acute meningitis [132]. Thirty children were studied, together with age matched controls. Children with meningitis had significantly higher extracellular water level (311 ml/kg compared with 271 ml/kg in controls). The excess in extracellular water was higher in the more severely ill children. Children who developed complications or sequelae had a higher extracellular water than those who did not. Inappropriate secretion of ADH was diagnosed in 14/30 children.

In the second study, 50 children were randomised to receive either maintenance fluids or restricted fluid intake to 65-70% of normal maintenance levels [131]. Children on reduced intake showed a significant decrease in total body water,

whereas those on normal maintenance remained unchanged. Children with a reduction of extracellular water of over 10 ml/kg had a significantly lower intact survival than those with less or no reduction.

It was concluded that fluid restriction worsened the outcome of acute meningitis. After the introduction of a liberal fluid regime in Chandigarh, it was reported that the mortality rate of meningitis dropped from 16% to 6%.

5.3 Summary of discussion of fluid therapy in meningitis

There was agreement that there was limited evidence that fluid restriction was useful in the treatment of meningitis. In view of the current recommendations, further trials were considered necessary. The Chandigarh study showed a trend, but more conclusive information is needed. There was discussion whether an increase in fluid to 125% of maintenance may also be harmful, as there might be a U-shaped relation between fluid intake and mortality, with increased mortality on both sides (with too little or too much fluid). Another issue discussed was the composition of the fluids, whether one-fifth normal saline was more appropriate than normal saline, and whether fluid should be given by intravenous infusion or by the oral route. It was concluded that trials are needed to determine the optimal fluid regime in meningitis and that consideration should be given to the route of administration and the composition of the fluids used.

6. RECOMMENDATIONS

6.1 Antimicrobial therapy for bacterial meningitis

General considerations:

- Cephalosporin resistance is rare, especially in developing countries. Where cephalosporin resistance is a problem, there are few options e.g., ceftriaxone or cefotaxime + vancomycin or rifampicin. New drugs such as meropenem, ceftiofime or trovafloxacin may have a role but at present these are very expensive and not in common use.

In infants less than 3 months:

- For definite neonatal bacterial meningitis (confirmed by CSF examination) cefotaxime (or ceftriaxone) alone or with ampicillin is the preferred treatment. If this is not available ampicillin + (gentamicin or chloramphenicol) may be used.
- Suspected cases should be treated as sepsis with (ampicillin or penicillin) + aminoglycoside until meningitis is confirmed.

In children 3 months and over

- Treatment of bacterial meningitis (confirmed by CSF examination) with chloramphenicol + (ampicillin or penicillin) is appropriate if there is no significant penicillin resistance. Penicillin-resistant pneumococci are now found in many parts of the world with increasing frequency, and this treatment is unsatisfactory for meningitis caused by penicillin-resistant pneumococci, even at intermediate levels of resistance. Where resistance data for pneumococcal meningitis is not available, an effort should be made to collect such data.
- In areas where penicillin-resistant pneumococci are common, initial therapy should be with cefotaxime or ceftriaxone.
- Where immediate CSF examination is not possible or the CSF report is not immediately available, suspected cases of bacterial meningitis should be treated with the recommended antimicrobial drugs.

6.2 Use of chloramphenicol

- Oral chloramphenicol palmitate is not recommended in neonates or malnourished children because of unreliable absorption and the tendency to accumulate the drug to toxic levels. If chloramphenicol is to be administered to malnourished children or neonates, it should be administered in the succinate form, intramuscularly or intravenously.
- For bacterial meningitis injectable chloramphenicol should be used in 100 mg/kg/24 hours in four equally divided doses. For serious infections (e.g., very severe pneumonia, failure of therapy with benzyl penicillin in severe pneumonia or enteric fever) other than bacterial meningitis chloramphenicol

should be used in 75 mg/kg/24 hours in three equally divided doses.

6.3 The role of dexamethasone

- There is insufficient evidence to support recommendations for the routine use of steroids for all children with bacterial meningitis treated with penicillin and chloramphenicol in developing countries.
- There is some evidence that dexamethasone may be helpful in cases of *H. influenzae* type b meningitis but opinion is divided on this. If it is to be used, a two-day regimen of dexamethasone is as likely to be effective as a four-day regimen, and it must be given before the antibiotics. There is no basis for restricting the use of dexamethasone to more severe cases.
- The role of steroids in cephalosporin (cefotaxime or ceftriaxone) treated bacterial meningitis in developing countries should be further studied.

6.4 Fluid therapy in meningitis

- Bacterial meningitis is associated with increased total body water, low serum sodium and high ADH levels in more severe cases. The high ADH levels probably represent compensatory mechanisms to maintain cerebral perfusion. The current recommendation to restrict fluids in children with bacterial meningitis is based on the presumption that the raised ADH levels are inappropriate and harmful.
- There is no clear evidence that fluid restriction is beneficial. Animal studies of experimental meningitis and a human study from India suggests that fluid restriction may be harmful but the evidence is inconclusive.
- Fluid restriction in the first 48 hours of meningitis management should be compared with full maintenance fluid in randomized trials.

6.5 CSF testing for diagnostic and surveillance purposes

- Wherever possible meningitis should be diagnosed by lumbar puncture. If a child is clinically unstable this may be deferred until the child's condition has improved sufficiently.
- All CSF specimens should be subjected to microscopy for cell count and Gram stain. Wherever possible, culture and susceptibility testing of CSF should be established and utilized.
- Simplified systems for testing CSF samples in developing countries should be explored by WHO.
- Latex agglutination test may be made available at reasonable cost, so that where culture facilities are not available they could be used to identify the causative organism.
- The WHO Division of Emergency and other Communicable Diseases is to be commended for its project to increase the coverage of CSF culture facilities for *N. meningitidis* in meningitis belt countries. This should be extended to include *H. influenzae* b and *S. pneumoniae* in addition to *N. meningitidis* and basic susceptibility testing should be included.

6.6 Recommendations for future research

- Clinical efficacy and safety of treatment regimens employing antibiotics (e.g., ceftriaxone, cefotaxime and conventional therapy) for periods of seven days or less should be evaluated in clinical trials.
- The role of dexamethasone in the management of bacterial meningitis in children should be formally evaluated in a multi-centre or several linked randomized trials in developing countries. These studies could be combined with studies comparing shorter duration of ceftriaxone therapy in a factorial design.
- Fluid restriction in the first 48 hours of meningitis management should be compared with full maintenance fluid in randomized trials.
- The pharmacokinetics of oily chloramphenicol should be explored with a view to providing guidance on the extension of its use to non-epidemic meningitis, in settings where penicillin-resistant pneumococci are not common.

● REFERENCES

1. Murray CJ and Lopez AD. Global Burden of Disease and Injury Series Vol II. Global Health Statistics. World Health Organization, Geneva, 1996:285.
2. Baraff LJ, Lee SI and Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatr Infect Dis J* 1993; 12:389-94.
3. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. *N Engl J Med*. 1997 6;336: 708 16.
4. Tefuarini N, Vince JD. Purulent meningitis in children: outcome using a standard management regimen with chloramphenicol. *Ann of Trop Paediatr* 1992;12;375-383.
5. Cadoz M, Denis F, Diop Mar I. Etude epidemiologique des cas de meningitis purulentes hospitalises a Dakar pendant la decennie 1970 - 1979. *Bull World Health Organ* 1981;59: 575 - 584.
6. Bhushan V, Chintu C. The changing pattern of pyogenic meningitis in Lusaka. *East Afr Med J* 1979;56:548-556.
7. Mar ID, Denis F, Cadoz M. Epidemiologic features of pneumococcal meningitis in Africa. Clinical and serotypical aspects. *Pathol Biol Paris*. 1979;27: 543-8.
8. Wright PF. Approaches to prevent acute bacterial meningitis in developing countries. *Bull World Health Organ*. 1989; 67: 479-86.
9. Carroll KJ, Carroll C. A prospective investigation of the long-term auditory-neurological sequelae associated with bacterial meningitis: a study from Vanuatu. *J Trop-Med Hyg*. 1994 ; 97: 145-50.
10. Bijlmer HA; van Alphen L. A prospective, population-based study of Haemophilus influenzae type b meningitis in The Gambia and the possible consequences. *J Infect Dis*. 1992; 165 (Suppl 1): S29-32.
11. Salih MAM, El Hag Al, Ahmed H, Bushara M, Yasim I, Omer MIA, Hofvander Y, Olcen P. Endemic bacterial meningitis in Sudanese children: aetiology, clinical findings, treatment and short-term outcome. *Ann Trop Paediatr* 1990; 10:203-10.
12. Salih MAM, Khaleefa OH, Bushara M, Taha ZB, Musa ZA, Kamil I, Hofvander Y, Olcen P. Long term sequelae of childhood acute bacterial meningitis in a developing country. *Scand J Infect Dis* 1991; 23:175-82.
13. Qazi SA, Khan MA, Mughal N, Ahmad M, Joomro B, Sakata Y, Kuriya N, Matsuishi T, Abbas KA and Yamashita F. Dexamethasone and bacterial meningitis in Pakistan. *Arch Dis Child* 1996; 75:482-488.
14. Ciana G, Parmar N, Antonio C, Pivetta S, Tamburlini G and Cuttini M. Effectiveness of adjunctive treatment with steroids in reducing short-term mortality in a high-risk population of children with bacterial meningitis. *J Trop Ped* 1995; 41:164-8.
15. Wanyoike MN, Waiyaki PG, McLiegeyo SO, Wafula EM. Bacteriology and sensitivity

- patterns of pyogenic meningitis at Kenyatta National Hospital, Nairobi Kenya. *East Afr Med J* 1995;72:658-60.
16. Wenger JD, Hightower AW, Facklam RR, Gaventa S, Broome CV and the Bacterial Meningitis Study Group. Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. *J Infect Dis* 1990; 162:1316.
 17. Wald ER, Kaplan SL, Mason EO, Sabo D, Ross L, Arditi M, Wiedermann BL, Barson W, Kim KS, Yogev R and Hofkosh D. Dexamethasone therapy for children with bacterial meningitis. *Pediatrics* 1995; 95:21-31.
 18. Wright PF. Approaches to prevention of acute bacterial meningitis in developing countries. *Bull World Health Organ* 1989; 67:470-86.
 19. Funkhouser A, Steinhoff M C and Ward J. Haemophilus influenzae disease and immunization in developing countries. *Rev Infect Dis* 1991; 13(Suppl. 6):S542-54.
 20. Radetsky M. Duration of symptoms and outcome in bacterial meningitis: an analysis of causation and the implication of a delay in diagnosis. *Pediat Infect Dis J* 1992; 11:694-8.
 21. Tunkel AR, Scheld WM. Acute bacterial meningitis. *Lancet* 1995; 346:1675-80.
 22. Swinger G, Delpont S, Hussey G. An audit of the use of antibiotics in presumed viral meningitis in children. *Ped Infect Dis J* 1994; 87:137-8.
 23. Ahmed AA, Salih MAM, Ahmed HS. Post-endemic acute bacterial meningitis in Sudanese children. *East Afr Med J* 1996; 73:527-532.
 24. Valmari P, Peltola H, Ruuskanen O and Korvenranta H. Childhood bacterial meningitis: initial symptoms and signs related to age, and reason for consulting a physician. *Europ J Paediat* 1987; 46:515.
 25. Research Committee of the BSSI. Bacterial meningitis: causes for concern. *J Infect* 1995; 30:89-94.
 26. Dabernat H, Scheimberg A and Astruc J. Analysis of oral antibiotic treatment that failed to prevent the development of haemophilus influenzae meningitis: consequences on mortality. *J Antimicrob Chemother* 1996; 38:679-89.
 27. Schaad UB, Suter S, Gianella-Borradori A, et al. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. *N Engl J Med* 1990; 322:141-7.
 28. Zaki M, Daoud AS, EL Saleh Q, West P. Childhood bacterial meningitis in Kuwait. *Journal of Tropical Medicine and Hygiene* 1990; 93: 7-11.
 29. Kumar P and Verna IC. Antibiotic therapy for bacterial meningitis in children in developing countries. *Bull World Health Organ* 1993; 71:183-88.
 30. Girgis NI, Abu El Ella AH, Farid Z, Haberberger RL, Galal FS and Woody JN.

- Intramuscular Ceftriaxone versus Ampicillin-Chloramphenicol in childhood bacterial meningitis. *Scand J Infect Dis* 1988; 20:613-17.
31. Schaad UB. Treatment of bacterial meningitis. *Eur J Clin Microbiol* 1986; 5:492-97.
 32. Spanos A, Harrell F E and Durack DT. Differential diagnosis of acute meningitis. An analysis of the predictive value of initial observations. *JAMA* 1989; 262:2700-7.
 33. Waagner DC, Kennedy WA, Hoyt MJ, McCracken GH. Lack of adverse effects of Dexamethasone therapy in aseptic meningitis. *Pediatr Infect Dis J* 1990; 9:922.
 34. Moosa AA, Quortum HA and Ibrahim MD. Rapid diagnosis of bacterial meningitis with reagent strips. *Lancet* 1995; 345:1290-1291.
 35. Quagliarello V and Scheld WM. Treatment of bacterial meningitis. *N Engl J Med* 1997; 336:708-16.
 36. Molyneux E. Managing meningitis and severe malaria. *Child Health Dialogue* 1996: Issue 3-4; 6-8.
 37. Wenberg GA, Spitzer ED, Murray PR, Gafoor A, Montgomery J, Tupasi TE, et al. Antimicrobial susceptibility patterns of Haemophilus isolates from children in eleven developing nations. *Bull World Health Organ* 1990;68:179-184.
 38. Hussey G, Hitchcock J, Hanslo D, Coetzee G, Van Schalkwyk E, Pitout J and Schaaf H. Serotypes and antimicrobial susceptibility of Haemophilus influenzae. *J Antimicrob Chemother* 1994; 34:1031-6.
 39. Hussey G, Hitchcock J, Hanslo D, Schaaf S, Klugman K, Coetzee G. Epidemiology, antimicrobial resistance patterns and serotype distribution of Streptococcus pneumoniae infections in Cape Town children. Annual Research Day, Department of Paediatrics and Child Health, University of Cape Town, 1996.
 40. Friedland IR and Klugman KP. Failure of chloramphenicol therapy in penicillin-resistant pneumococcal meningitis. *Lancet* 1992; 339; 405-8.
 41. Kristinsson KG. Effect of antimicrobial use and other risk factors on antimicrobial resistance in pneumococci. *Microb Drug Resist.* 1997; 3: 117- 23.
 42. Baquero F, Martinez-Beltran J, Loza E. Review of antibiotic-resistance patterns of *Streptococcus pneumoniae* in Europe. *J Antimicrob Chemother* 1991;28:31-38.
 43. Hammond ML, Norriss MS. Antibiotic resistance among respiratory pathogens in preschool children. *Med J Aust.* 1995;163: 239-42.
 44. Crewe-Brown J, Karsteadt AS, Saunders GL, Khoosal M, Jones N, Klugman KP. *Streptococcus pneumoniae* bacteremia and HIV infection: alteration in penicillin-susceptibility and sergroups/serotypes. *Clin Infect Dis* 1997;25:1165-72.
 45. Mastro TD, Nomani NK, Ishaq Z, Ghafoor A, Shaukat NF, Esko E, Leinonen M, Henrichsen J, Breiman RF, Schwartz B, et al. Use of nasopharyngeal isolates of

- Streptococcus pneumoniae* and *Haemophilus influenzae* from children in Pakistan for surveillance for antimicrobial resistance. *Pediatr Infect Dis J*. 1993; 12: 824-30.
46. Elhanan G, Raz R, Pitlik SD, Sharir R, Konisberger H, Samra Z, Kennes Y, Drucker M, Leibovici L Bacteraemia in a community and a university hospital. *J Antimicrob Chemother*. 1995; 36: 681 -95.
 47. Frankel RE, Virata M, Hardalo C, Altice FL, Friedland G. Invasive pneumococcal disease: clinical features, serotypes, and antimicrobial resistance patterns in cases involving patients with and without human immunodeficiency virus infection. *Clin Infect Dis*. 1996; 23: 577- 84.
 48. Roca V, Perez Cecilia E, Santillana T, Romero J, Picazo JJ Comparative study of pneumococcal bacteremia in patients with and without HIV infection . *Rev Clin Esp*. 1993;192: 21- 4.
 49. Carey I, Glauser MP, Bille J. Pneumococcal bacteremia: what is new? *Schweiz Med Wochenschr*. 1995 May 13; 125: 952-8.
 50. Hoffman J, Cetron MS, Farley MM, Baughman WS, Facklam, Elliot J A et al. The prevalence of *Streptococcus pneumoniae* in Atlanta. *N Engl J Med* 1995;31:3255-9.
 51. Enting RH, Spanjaard L, van de Beek D, Hensen EF, de Gans J and Dankert J. Antimicrobial susceptibility of *Haemophilus influenzae*, *Neisseria meningitis* and *Streptococcus pneumonia* isolates causing meningitis in The Netherlands, 1993-1994. *J Antimicrob Chemother* 1996; 38:777-86.
 52. Klugman KP. Pneumococcal resistance to antibiotics. *Clin Microb Rev* 1990; 3:171-196.
 53. Castaneda E, Leal AL, Castillo O, De La Hoz F, Vela MC, Arango M, Trujillo H, Levy A, Gama ME, Calle M, Valencia ML, Parra W, Agudelo N, Mejia GI, Jaramillo S, Montoya F, Porras H, Sanchez A, Saa D, Di Fabio JL, Homma A. Distribution of capsular types and penicillin resistance of strains of *Streptococcus pneumoniae* causing systemic infections in Argentinian children under 5 years of age. *Streptococcus pneumoniae* Working Group. *Microb Drug Resist*. 1997; 3: 147 -52.
 54. Rossi A, Ruvinsky R, Regueira M, Corso A, Pace J, Gentile A, Di Fabio JL. Distribution of capsular types and antimicrobial susceptibility of invasive isolates of *Streptococcus pneumoniae* in Colombian children. Pneumococcal Study Group in Colombia. *Microb Drug Resist*. 1997;3:135 -40.
 55. Tarasi A, Sterk Kuzmanovic N, Sieradzki K, Schoenwald S, Austrian R, Tomasz A. Penicillin resistant and multidrug resistant *Streptococcus pneumoniae* in a pediatric hospital in Zagreb, Croatia. *Microb Drug Resist*. 1995;1:169 -76.
 56. Bradley JS, Scheld WM. The challenge of penicillin resistant *Streptococcus pneumoniae* meningitis: current antibiotic therapy in the 1990s. *Clin Infect Dis*. 1997; 24 (Suppl 2): S213 -21.
 57. Klugman KP, Friedland IR, Bradley JS. Bactericidal activity against cephalosporin resistant *Streptococcus pneumoniae* in cerebrospinal fluid of children with acute bacterial meningitis. *Antimicrob Agents Chemother*. 1995; 39: 1988- 92.

58. American Academy of Pediatrics Committee on Infectious Diseases. Therapy for children with invasive pneumococcal infections. *Pediatrics*. 1997; 99: 289- 99.
59. McGowan JE Jr, Metchock BG. Penicillin resistant pneumococci an emerging threat to successful therapy. *J Hosp Infect*. 1995; 30 (Suppl): 472 -82.
60. Fitoussi F, Doit C, Sandin A, Pechinot A, Kazmierczack A, Geslin P, Bingen E. Killing activity of cefpirome against penicillin resistant *Streptococcus pneumoniae* isolates from patients with meningitis in a pharmacodynamic model simulating the cerebrospinal fluid concentration profile. *Antimicrob Agents Chemother*. 1995; 39: 2560-3.
61. Peltola H , Anttila M , Renkonen OV. Randomised comparison of chloramphenicol, ampicillin, cefotaxime, and ceftriaxone for childhood bacterial meningitis. Finnish Study Group. *Lancet* 1989; 1: 1281-7.
62. Kavaliotis J , Manios SG , Kansouzidou A , Danielidis V. Treatment of childhood bacterial meningitis with ceftriaxone once daily: open, prospective, randomized, comparative study of short-course versus standard-length therapy. *Chemotherapy*. 1989; 35: 296-303.
63. Martin E , Hohl P , Gugli T, Kayser FH, Fernex M. Short course single daily ceftriaxone monotherapy for acute bacterial meningitis in children: results of a Swiss multicenter study. Part I: Clinical results. *Infection*. 1990; 18: 70-7.
64. Isaacs RD , Howden CW , Lang WR , Ellis Pegler RB. Short course chemotherapy for meningococcal meningitis. *Aust N Z J Med*. 1988;18: 731-2.
65. Sack, CM, Koup, JR, Opheim, KE, Neeley, N. and Smith, AL. Chloramphenicol succinate kinetics in infants and young children. *Ped Pharm* 1982;2:93-103.
66. Kauffman, RE, Niceli, JN, Strebel, L, Buckley, JA, Done, AK, Dajani, AS. Relative bioavailability of intravenous chloramphenicol succinate and oral chloramphenicol palmitate in infants and children. *J Pediatrics* 1981;99:963-67.
67. Smith, AL. Chloramphenicol. *In* S. Yaffe and J. Aranda (eds), *Pediatric Pharmacology*. W.B. Saunders Company, Philadelphia, 1992: 276-298.
68. Slaughter, RL, Pieper, JA, Cerra, FB, Brodsky, B, and Koup, JR. Chloramphenicol sodium succinate kinetics in critically ill patients. *Clin Pharm* 1980;28:69-77.
69. Tuomanen EI, Powell KR, Marks MI, Laferriere CI, Altmiller DH, Sack CM, Smith AL. Oral chloramphenicol in the treatment of *Haemophilus influenzae* meningitis. *J Pediatr* 1981;99:968-74.
70. Pickering LK, Hoecker JL, Kramer WG, Kohl S and Cleary TG. Clinical pharmacology of two chloramphenicol preparations in children: sodium succinate (iv) and palmitate (oral) esters *J Pediatr* 1980;96:757-61.
71. Dickenson, CJ, Reed, MD, Stern, RC, Aronoff, SC, Yamashita, TS, and Blumer, JL. The effect of exocrine pancreatic function on chloramphenicol pharmacokinetics in patients with cystic fibrosis. *Ped Res* 23:388-92, 1988.

72. Yogev R, Kolling WM, Williams T. Pharmacokinetic comparison of intravenous and oral chloramphenicol in patients with *Haemophilus influenzae* meningitis. *Pediatrics* 1981; 67:656-60.
73. Van Nieketk, CH, Steyn, DL, Davis, WG, and Heese, HDH. Chloramphenicol levels in cerebrospinal fluid in meningitis. *S Afr Med J* 58:159-160, 1980.
74. Wali SS, MacFarlane JT, Weir WRC et al. Single injection treatment of meningococcal meningitis. Long acting chloramphenicol. *Trans Royal Soc Trop Med Hyg*, 1979; 73:698-701.
75. Pécoul B, Varaine F, Keita M et al. Long-acting chloramphenicol versus intravenous ampicillin for treatment of bacterial meningitis. *The Lancet* 1991;338:862-66.
76. Puddicombe JB. A field trial of a single intramuscular injection of long-acting chloramphenicol in the treatment of meningococcal meningitis. *Trans R Soc Trop Med Hyg* 1984;78:399-402.
77. Saliou P, Ouedraogo L, Muslin D et Rey M. L'injection unique de chloramphénicol dans le traitement de la méningite cérébrospinale en Afrique Tropicale. *Méd Trop*, 1977; 37:189-193.
78. Varaine, F. Essai clinique comparant la ceftriaxone et le chloramphénicol huileux dans le traitement des méningites bactériennes chez les enfants de 2 à 35 mois au Mali et au Niger. Rapport Epicentre, avril. 1997.
79. Rey M, Ouedraogo L, Saliou P, Perino L. Traitement minute de la meningite cerebrospinale epidemique par injection intra-musculaire unique de chloramphenicol (suspension huileuse). *Med Mal Infect* 1976;6:120-4.
80. American Academy of Pediatrics (AAP). Report of the Committee on Infectious Diseases. Red Book 24th Edition. Elk Grove Village, American Academy of Pediatrics. 1997.
81. Mulholland EK, Falade AG, Corrah PT, Omosigho C, N'Jai P, Giadom B, Adegbola RA, Tschappler H, Todd J, Greenwood B. A randomized trial of chloramphenicol Vs trimethoprim-sulphamethoxazole for the treatment of malnourished children with community acquired pneumonia. *Pediatr Infect Dis J*. 1995;14:959-65.
82. Chartrand SA, Marks MI, Scribner RK, Johnston JT, Frederick DF. Moxalactam therapy of *Haemophilus influenzae* type b meningitis in children. *J Pediatr* 1984;104: 454-9.
83. Bhutta ZA, Naqvi SH, Durrani S, Suria A. Chloramphenicol therapy of typhoid fever. *J Pak Med Assoc* 1991;41:26-30.
84. Bhutta ZA, Niazi SK, Suria A. Chloramphenicol clearance in typhoid fever: implications for therapy. *Indian J Pediatr* 1992;59:213-9.
85. Dutta P, Rasaily R, Saha MR, Mitra U, Manna B, Chakraborty S, Mukherjee A. Randomized clinical trial of furazolidone for typhoid fever in children. *Scand J*

- Gastroenterol 1993;28:168-72.
86. Shann F, Linnemann V, Mackenzie A, Barker J, Gratten M, Crinis N. Absorption of chloramphenicol sodium succinate after intramuscular administration in children. *N Engl J Med* 1985;313:410-4.
 87. Schreiner M, Schaible D, Fleisher G. Intramuscular chloramphenicol in children [letter]. *N Engl J Med* 1986;314: 451.
 88. Yodat Y. Toxic effects of chloramphenicol. *Israel J Med Sci* 1969;5:1184-87.
 89. Ekblad H, Ruuskanen O, Lindberg R, Iisalo E. The monitoring of serum chloramphenicol levels in children with severe infections. *J Antimicrob Chemother* 1985; 15:489-94.
 90. Erikson M, Paazlow L, Balme P and Mariam TW. Chloramphenicol pharmacokinetics in Ethiopian children of differing nutritional status. *Eur J Clin Pharmacol* 1983;24:817-23.
 91. Kransinski K, Kusmiesz H, Nelson JD. Pharmacologic interactions among chloramphenicol, phenytoin and phenobarbital. *Pediatr Infect Dis* 1982; 1:232-35.
 92. Nahata MC, Powell DA. Chloramphenicol serum concentration falls during chloramphenicol succinate dosing. *Clin Pharmacol Ther* 1983; 33:308-13.
 93. Bloxham RA, Durbin GM, Johnson T, Winterborn MH. Chloramphenicol and phenobarbitone - a drug interaction. *Arch Dis Child* 1979; 54:76-77.
 94. Rose JQ, Choi HK, Schentag JJ, Kinkel WR, Jusko WJ. Intoxication caused by interaction of chloramphenicol and phenytoin. *JAMA* 1977; 237:2630-31.
 95. Koup JR, Gibaldi M, McNamara P, Hilligoss DM, Colburn WA, Bruck E. Interaction of chloramphenicol with phenytoin and phenobarbital. *Clin Pharmacol Ther* 1978; 24:571-75.
 96. Mustafa MM, Ramilo O, Saez Llorens X, Olsen KD, Magness RR, McCracken GH Jr Cerebrospinal fluid prostaglandins, interleukin 1 beta, and tumor necrosis factor in bacterial meningitis. Clinical and laboratory correlations in placebo treated and dexamethasone treated patients. *Am J Dis Child*. 1990; 144: 883- 7 .
 97. Mustafa MM, Ramilo O, Saez Llorens X, Mertsola J, Magness RR, McCracken GH Jr. Prostaglandins E2 and I2, interleukin 1 beta, and tumor necrosis factor in cerebrospinal fluid in infants and children with bacterial meningitis. *Pediatr Infect Dis J*. 1989;8:921-2.
 98. Lauritsen A, Oberg B. Adjunctive corticosteroid therapy in bacterial meningitis. *Scand J Infect Dis*. 1995; 27: 431- 4 .
 99. American Academy of Pediatrics. Report of the Committee on Infectious Diseases of AAP: Dexamethasone therapy for bacterial meningitis in infants and children. 23rd Edition Elk Grove Village, American Academy of Pediatrics. 1994: 558-559.
 100. Lebel MH, Freyi BJ, Syrogiannopoulos GA, Chrane DR, Hoyt MJ, Stewart SM et al.

- Dexamethasone therapy for bacterial meningitis: results of two double-blind, placebo-controlled trials. *N Engl J Med* 1988; 319:964-71.
101. Lebel MH, Hoyt MJ, Waagner DC, Rollins NK, Finitzo T, McCracken GH Jr. Magnetic resonance imaging and dexamethasone therapy for bacterial meningitis. *Am J Dis Child* 1989; 143:301-6.
 102. Kennedy WA, Hoyt MJ, McCracken GH Jr. The role of corticosteroid therapy in children with pneumococcal meningitis. *Am J Dis Child*. 1991;145:1374-8.
 103. Schaad UB, Lips U, Gnehm HE, Blumberg A, Heinzer I, Wedgewood J. Dexamethasone therapy for bacterial meningitis in children. *Lancet* 1993; 342:457-61.
 104. Odio CM, Faingezicht I, Paris M, Nassar M, Baltodano A, Rogers J, Sáez Llorens X, Olsen KD and McCracken GH. The beneficial effects of early Dexamethasone administration in infants and children with bacterial meningitis. *N Engl J Med* 1991; 324:1525-31.
 105. Syrogiannopoulos GA, Lourida AN, Theodoridou MC, Pappas IG, Babilis GC, Economidis JJ, Zoumboulakis DJ, Beratis NG, Matsaniotis NS Dexamethasone therapy for bacterial meningitis in children: 2 versus 4 day regimen. *J Infect Dis*. 1994; 169: 853-8.
 106. Wald ER, Kaplan SL, Mason EO Jr, Sabo D, Ross L, Arditi M, Wiedermann BL, Barson W, Kim KS, Yogov R, et al. Dexamethasone therapy for children with bacterial meningitis. Meningitis Study Group. *Pediatrics*. 1995; 95: 21-8.
 107. Prasad K and Haines T. Dexamethasone treatment for acute bacterial meningitis: how strong is the evidence for routine use? *J Neurol Neurosurg Psych* 1995; 59:31-37.
 108. Girgis NI, Farid Z, Mikhail I A, Farrag I, Sultan Y and Kilpatrick ME. Dexamethasone treatment for bacterial meningitis in children and adults. *Pediatr Infect Dis J* 1989; 8:848-51.
 109. Kanra GY, Ozen H, Secmeer G, Ceyhan M, Ecevit Z and E Belgin Z. Beneficial effects of dexamethasone in children with pneumococcal meningitis. *Pediatr Infect Dis J* 1995; 14:490-4.
 110. Macaluso A, Pivetta S, Schindler Maggi R, Tamburlini G and Cattaneo A. Dexamethasone adjunctive therapy for bacterial meningitis in children: a retrospective study in Brazil. *Ann Trop Paed* 1996; 16:193-98.
 111. Ioannidis J, Samarel M, Lau J, Drapkin M. Risk of gastrointestinal bleeding from dexamethasone in children with bacterial meningitis (Letter). *Lancet* 1994;343:792.
 112. Pichard E, Gillis D, Aker M, Engelhard D. Rebound fever in bacterial meningitis: role of dexamethasone dosage. *Isr J Med Sci*. 1994 ; 30: 408-11.
 113. Esterle TM, Edwards KM. Concerns of secondary fever in *Streptococcus pneumoniae* meningitis in an era of increasing antibiotic resistance. *Arch Pediatr Adolesc Med*. 1996; 150: 552-4.
 114. Paris MM, Hickey SM, Uscher MI, Shelton S, Olsen KD, McCracken GH Jr. Effect of

- dexamethasone on therapy of experimental penicillin and cephalosporin resistant pneumococcal meningitis. *Antimicrob Agents Chemother* 1994;38:1320-4.
115. Nielsen PE, Thelle T and Tvede M. Recrudescence and relapse of meningococcal meningitis and septicaemia. *Acta Paediatr* 1995;84:342-5.
 116. Bradley JS. Dexamethasone therapy in meningitis: potentially misleading anti-inflammatory effects in central nervous system infections. *Pediatr Infect Dis J* 1994; 13:823-6.
 117. Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA et al. A controlled trial of high dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987;317:653-8.
 118. Warrell DA, Loreesuwan S, Warrell MJ, Kasensarn P, Intaraprasert P, Bunnag D, Harinasuta T. Dexamethasone proves deleterious in cerebral malaria: a double blind trial in 100 comatose patients. *N Eng J Med* 1982;306:313-9.
 119. Feigin RD. Acute bacterial meningitis beyond the neonatal period. In: Behrman RE, Vaughan VC, Nelson WE, editors. *Nelson Textbook of Pediatrics*. 13th ed. Philadelphia: W.B. Saunders, 1987:569-573.
 120. Robson AM. The pathophysiology of body fluids. In: Behrman Re, Vaughan VC, Nelson WE, editors. *Nelson Textbook of Pediatrics*. 13th ed. Philadelphia: W.B. Saunders, 1987:172-191.
 121. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 1967; 42:790-806.
 122. Reynolds DW, Dweck HS, Cassady G. Inappropriate antidiuretic hormone secretion in a neonate with meningitis. *Am J Dis Child* 1972; 123:251-253.
 123. Feigin RD, Kaplan SL. Inappropriate secretion of antidiuretic hormone in children with bacterial meningitis. *Am J Clin Nutr* 1977; 30:1482-1484.
 124. Kaplan SL, Feigin RD. The syndrome of inappropriate secretion of antidiuretic hormone in children with bacterial meningitis. *J Pediatrics* 1978; 92:758-761.
 125. Garcia H, Kaplan SL, Feigin RD. Cerebrospinal fluid concentration of arginine vasopressin in children with bacterial meningitis. *J Pediatrics* 1981; 98:67-70.
 126. Shann F, Germer S. Hyponatremia associated with pneumonia or bacterial meningitis. *Arch Dis Child* 1985; 60:963-966.
 127. Kanakriyah M, Carvajal HF, Vallone AM. Initial fluid therapy for children with meningitis with consideration of the syndrome of inappropriate antidiuretic hormone. *Clinical Pediatrics* 1987; 26:126-130.
 128. Powell KR, Sugarman LI, Eskanazi AE, Woodin KA, McCormick Klea. Normalization of plasma arginine vasopressin concentration when children with meningitis are given maintenance plus replacement fluid therapy. *J Pediatr* 1990; 117:515-522.

129. Padilla G, Ervin MG, Ross MG, Leak RD. Vasopressin Levels in Infants During the Course of Aseptic and Bacterial Meningitis. *Am J Dis Child* 1991; 145:991-993.
130. Tauber MG, Sande E, Fournier MA, Tureen JH, Sande MA. Fluid administration, brain edema, and cerebrospinal fluid lactate and glucose concentrations in experimental escherichia coli meningitis. *J Infect Dis* 1993; 168:473-476.
131. Singhi SC, Singhi B, Srinivas B, Narakesri HP, Ganguli NK, Sialy Rea. Fluid restriction does not improve the outcome of acute meningitis. *Pediatr Infect Dis J* 1995; 14:495-503.
132. Kumar V, Singhi P, Singhi S. Changes in body water compartments in children with acute meningitis. *Pediatr Infect Dis J* 1994; 13:299-305.

AGENDA

1. Antibiotic therapy

- | | | | |
|--------|-----|--|---------------|
| Hussey | 1.1 | Empiric antibiotic therapy in developing countries | Dr G. |
| | 1.2 | Strategies for countries with penicillin and/or chloramphenicol resistance | Dr K. Klugman |
| | 1.3 | Ceftriaxone vs oily chloramphenicol in bacterial meningitis | Dr F. Varaine |
| | 1.4 | Prospects for availability of third generation cephalosporins | WHO |

2. Chloramphenicol - A review of current usage and recent pharmacokinetic data

- | | | |
|-----|---|-----------------------------------|
| 2.1 | Chloramphenicol, IM, IV or oral? | Dr A.L. Smith |
| 2.2 | Review of chloramphenicol/malnutrition data | Dr S. Qazi |
| 2.3 | Chloramphenicol in neonates | Dr Martin Weber/ S. Gatchalian |

3. Dexamethasone therapy

- | | | |
|-----|--|------------------|
| 3.1 | Does it have a role in developing countries? | Dr E. Molyneux |
| 3.2 | The argument in favour | Dr G. Tamburlini |
| 3.3 | The argument against | Dr G. Hussey |
| 3.4 | What recommendations should WHO make? | |

4. Supportive therapy - fluid requirements

- | | | |
|-----|--|--------------|
| 4.1 | Fluid restriction - the basis of fluid restriction and current views | Dr M. Weber |
| 4.2 | Plans for a study to address the issue | Dr T. Duke |
| 4.3 | Developing country perspective - the Chandigarh study | Dr S. Singhi |

5. Conclusions

- | | | |
|-----|--|------------------|
| 5.1 | Recommendations from previous two days | Dr K. Mulholland |
| 5.2 | Free discussion | |