SLOW INITIAL β-LACTAM INFUSION WITH HIGH-DOSE PARACETAMOL TO IMPROVE THE OUTCOMES OF CHILDHOOD BACTERIAL MENINGITIS, ESPECIALLY OF PNEUMOCOCCAL MENINGITIS, IN ANGOLA

Prospective, Randomized, and Double-Blind Clinical Study

"INFU/PARA-BOLU/PLACE"

International standard randomized controlled trial number (to be registered)

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* The author names and order will likely change in different publications

Summary of the Trial Protocol

The main *purpose* of this trial is to test if mortality of childhood bacterial meningitis (BM) can be reduced by slow, continuous infusion of cefotaxime initially, instead of the traditional bolus administration *qid,* combined with high-dose paracetamol orally, when both treatments are executed for the first 4 days. The series will be collected at Hospital Pediátrico David Bernardino, Luanda, Angola.

The *recruitment* of patients begins, the conditions permitting, in early 2012. The *criteria for patient participation* is a child at the age of 2 months to 15 years who presents with the symptoms and signs suggestive of BM, for whom a lumbar puncture is performed, and the cerebrospinal fluid (CSF) is cloudy, positive by Gram staining or latex agglutination, or shows at least 50 leukocytes per mm^3.

Introduction

Although large-scale vaccinations have virtually eliminated severe *Haemophilus influenzae* type b (Hib) infections from children in many parts of the world – albeit less so in the less privileged regions[1] –, BM remains a major issue globally. Hib[2] and pneumococcal[3] conjugate vaccines can potentially prevent meningitis, but neither vaccine is much used in countries with limited resources.[1,4] New (and expensive) antimicrobials have not improved the prognosis. Various other approaches[5-9] are too costly to be used for most children with BM. High prevalence of HIV infection in countries adds to the gloomy prognosis of BM. Today, pneumococcal meningitis,[4,10] the most deleterious type of childhood (and adulthood) BM, is of even greater relevance than before.

Dexamethasone

Thanks to some favorable biochemical effects in damping the host's inflammatory response,[11,12] adjuvant dexamethasone has gained much attention, until the first sufficiently powered randomized trials proved it rather useless in childhood BM.[13,14] In adult patients, though not in all studies,[15] dexamethasone has shown a salutary effect.[16,17] Importantly, a large meta-analysis[18] which used the individual patient data from 2029 subjects (of whom 833 children) from five trials confirmed the

negative results; dexamethasone did not reduce death or neurological or audiological disability in children. The much-cited Cochrane analysis,[19] in which dexamethasone is recommended in "high-income countries", is of minor relevance, because it totally neglected the single most important prognostic factor, the child's presenting status.[20,21] With this handicap, the conclusions became genuinely skewed.

Of special concern are the data accumulating from a series of animal experiments and human autopsy studies which suggest that dexamethasone, not only being useless, likely harms the child with BM. In pneumococcal meningitis of rabbits, a single dose of corticosteroids potentiates neuronal toxicity in the dentate gyrus of hippocampus (a structure critical for memory function) rich in corticoid receptors.[22] In an infant rat model, dexamethasone increases hippocampal cell injury, reduces learning capacity,[23] and does not prevent hearing loss better than saline.[24] As up to 90% of children with BM present with high serum cortisol levels,[25] adding exogenous steroids, and thus potentially increasing the vulnerability of neurons possessing a high concentration of corticosteroid receptors,[26] may be deleterious. This risk could, at most, be taken if the clinical benefits of dexamethasone would have been shown in a sufficiently-powered, randomized clinical study. This has not yet happened in childhood BM.

Glycerol

The potential of glycerol (glycerine, 1, 2, 3-propanetriol), a naturally occurring trivalent alcohol and an essential compound of the human cell-membrane, was studied in a large (N 654), prospective, randomized, four-arm, double-blind study in six countries of Latin America.[14] The causative agent was identified in 74 % of cases, Hib, pneumococci, and meningococci being the three most common bacteria. Severe neurological sequelae (SeNeSe) were reduced by glycerol (OR 0.31; 95% CI 0.13-0.76; P=0.010), slightly less by the dexamethasone-glycerol combination (OR 0.39; 95% CI 0.17-0.93, P=0.033), whereas dexamethasone failed to reach significance.

When neurological sequelae and death (which may form a *continuum*)[27,28] were examined together, again, glycerol proved effective (OR 0.44; 95% CI 0.25-0.76; P=0.003), the dexamethasone-glycerol combination did worse (OR 0.55; 95% CI 0.32-0.93; P=0.027), and the dexamethasone-only group did not reach significance. Aetiology did not affect the outcomes, nor did the timing between dexamethasone (or glycerol), and the institution of antimicrobial - not even in Hib meningitis. [14]

Although neither adjuvant (or their combination) prevented hearing loss,[21] glycerol protected the children from SeNeSe so effectively[14] that we deem it unethical not to use it in childhood BM. Therefore, in this trial, oral glycerol is administered routinely to all participants. Glycerol likely works by more than one mechanism, but essential is the quick increase in plasma osmolality.[29] This improves rheology and contributes to improved cerebral circulation and brain oxygenation. Osmotic diuresis is of less importance, because urine output does not increase with the doses (6 ml/kg/day) used here.[14,29]

A recent study on adult meningitis patients in Malawi did not support the use of glycerol.[30] However, glycerol in that trial was administered probably in too large quantities, and – most importantly – too long (4 days).[31] Glycerol *must* be discontinued after 48 hours; otherwise its effects will reverse.[32,33] Of note is the finding from our own study in Angola:[34] all children received glycerol, and SeNeSe developed less frequently (15%) than had been the case earlier (24%) in the same hospital. Convulsions were not associated with the use of glycerol. These findings fully agreed with those deriving from children in Latin America.[14]

Non-steroidal anti-inflammatory drugs

Paracetamol (acetaminophen, *N*-acetyl-*p*-aminophenol), disputably considered a *non-steroidal anti-inflammatory drug* (NSAID), is used widely as an antipyretic, analgesic, and anti-inflammatory drug. Paracetamol is the most widely used antipyretic worldwide, because it is effective, safe, inexpensive, and available in different forms (syrup, tablet, effervescent, suppository and intravenous injection). It is suitable for all ages, and the effect is dose-dependent. There are only a few contraindications to its use (infrequent allergy). Hepatotoxicity has been described in adults, but in children, it is exceedingly rare.[35] A placebo-controlled trial confirmed the safety in infants and children.[36] In *Plasmodium falciparum* malaria – an important disease to be distinguished from meningitis in the tropics – paracetamol ostensibly prolongs parasite clearance time,[37] but this finding only reflects delayed parasite development.[38] Interestingly, paracetamol lowers antibody responses in childhood vaccinations.[39]

Potential of NSAID's to improve the prognosis of bacteremic infections

NSAIDs relieve the host's inflammatory response[40] (demonstrated e.g. by lowering cytokine concentrations). The mechanisms are not well understood, but NSAIDs dampen inflammatory

reactions other than those mediated by inhibition of arachidonic acid metabolism.[41] There are, however, differences between paracetamol and the other NSAIDs. While most NSAID's inhibit cyclooxygenase enzyme (COX) in periphery, paracetamol inhibits also COX3[42] which is not seen outside the central nervous system. Furthermore, the COX enzymes are highly active only when appropriately oxidized, and since paracetamol reduces these forms, the concentration of pro-inflammatory chemicals are reduced, too.[43]

An important observation was made in a retrospective analysis of 809 adult patients with bacteremia in Finland:[44] Whatever the causative agent of bacteremia - pneumococci, staphylococci or Gram negative agents -, patients having received paracetamol survived significantly better than those treated with other NSAIDs (a positive trend was observed for ibuprofen). Among the 220 patients with"rapidly fatal underlying disease" – classification for gram-negative bacteremia[45] – the case fatality rate among the paracetamol-recipients was 30% *vs.* 60% the non-recipients (OR 0.4; $CI_{95\%}$ 0.18-0.67, P=0.001).[46] A similar effect was seen in practically all subgroups.[46,47] Interestingly, ibuprofen – a classical NSAID – did not improve survival in a randomized, placebo-controlled sepsis trial.[48]

Slow infusion of β-lactams

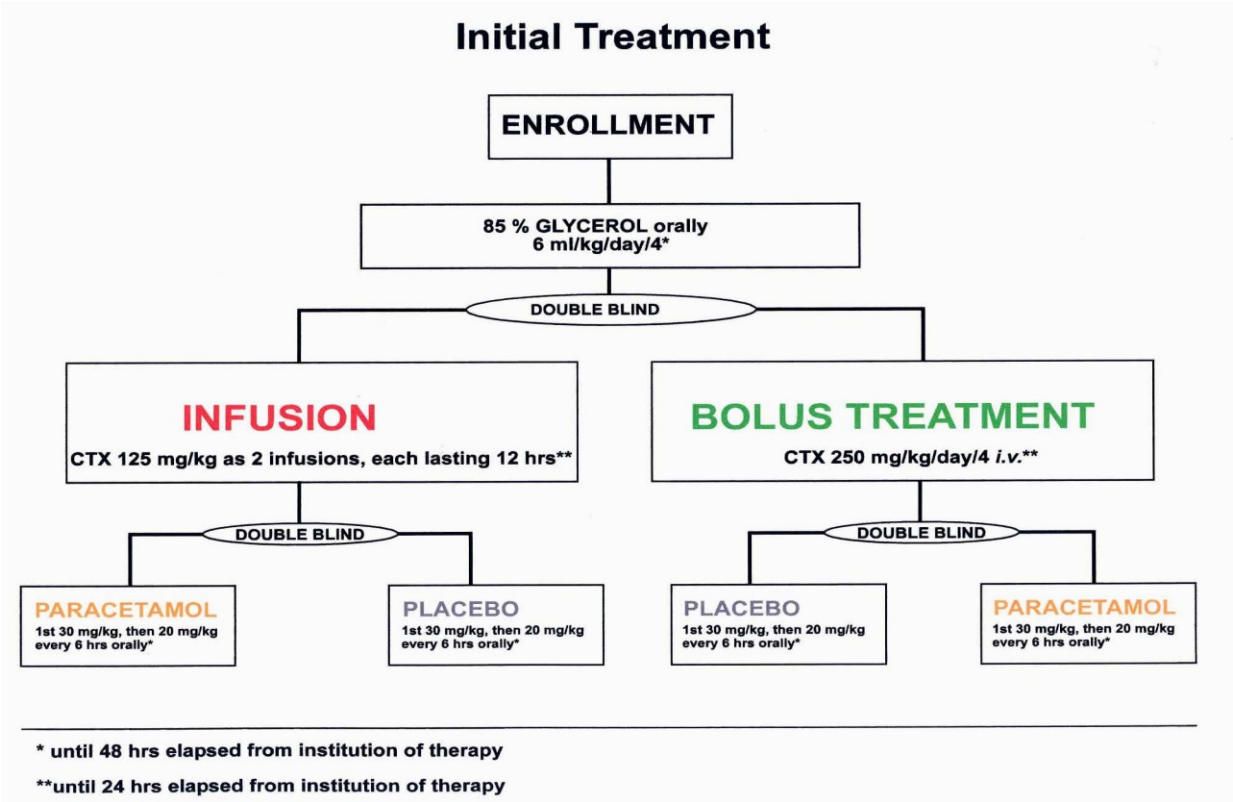
β-lactam antimicrobials are "time-dependent" agents whose effectiveness correlates with the time that plasma concentration exceeds the minimal inhibitory concentration (MIC).[49] Now for some years, questions have been raised[50,51] if β-lactams are used sub-optimally when administered intermittently as boluses every 4-6 hours. This strategy triggers massive bacteriolysis and release of toxic cell wall components into the blood stream to which the host responds with a fierce inflammatory reaction. The great majority of patients are not sufficiently ill to be harmed by this inflammation; for them, the way of administration is not an issue. In contrast, the situation is profoundly different in life-threatening conditions, such as BM and severe sepsis,.

Low-dose β-lactams kill growing bacteria effectively also without major degradation,[52] and this finding has been applied to the clinical practice. The evidence for the salutary effects of continuous β-lactam infusion has not overwhelming, but a number of pharmacokinetic and other studies favor this approach.[53-68] Importantly, lower clinical effectiveness has never been reported.[65,67] As the β-lactam infusion is safe, achieves sufficient tissue levels and sustains necessary serum concentrations long,[68] allows a reduced daily dose, is cost-effective,[58] and may be

more active against resistant organisms and might slow the development of resistance,[62,66,68] sufficiently-powered clinical studies are ethically well justified.

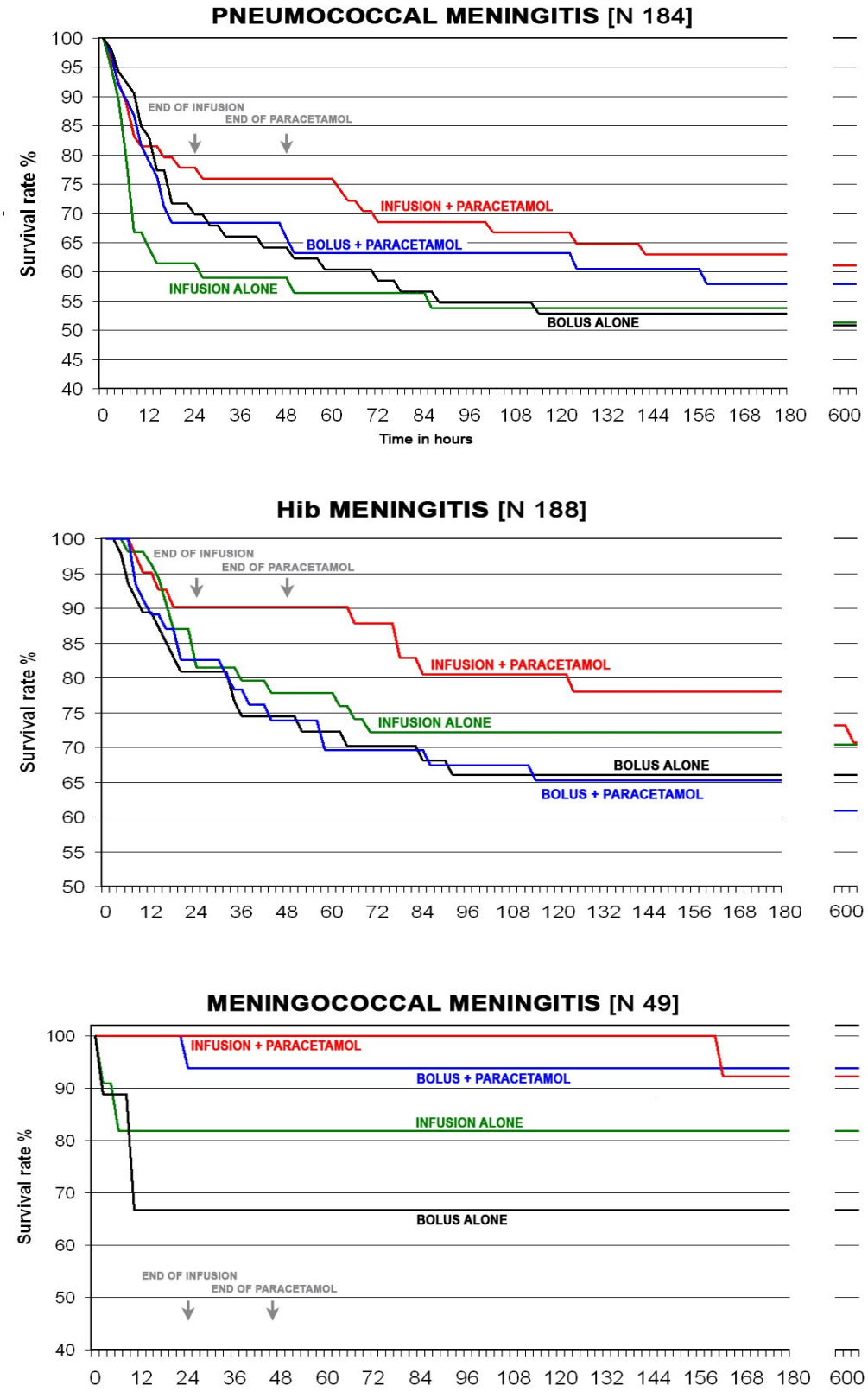
Encouraging results from Angola

In 2005-2008, we carried out a randomized, prospective, double-blind study (2 x 2 factorial design) on childhood bacterial meningitis in Luanda, Angola.[34] All patients at age 2 months to 15 years received oral glycerol and i.v. cefotaxime, but for the first 24 hours, this β-lactam was administered intermittently *qid* (50% of patients), or by slow continuous infusion (thereafter *qid).* A further randomization (**Fig 1**) divided the children to receive high-dose paracetamol or placebo orally. No less than 723 children were gathered; most had pneumococcal or Hib meningitis.



The key result was that while cefotaxime infusion or oral paracetamol alone did generally not much affect the outcomes, a significant reduction in initial mortality was achieved when these elements were combined,. The same phenomenon was observed across all etiology groups (**Fig. 2**, "PANEL B" [34]). No treatment since chloramphenicol and ampicillin some 50 years ago has shown similar effect on mortality of childhood BM.

PANEL B



However, this clear effect waned slowly. We had assumed that the deleterious effects of β-lactam (bacteriolysis and, hence, strong inflammation) would mostly be over within a day, but it

looks like we probably discontinued the infusion + paracetamol treatment too early. Whatever the reason, this finding warrants a further study. If we can confirm the positive effect to be longstanding, the finding will benefit all children, also those in the resource-poor settings who have no access to expensive treatment modalities.

Objectives

Principal objective:

To examine if mortality of childhood BM can be reduced by slow continuous infusion of cefotaxime combined with high-dose paracetamol orally for the first 4 days (instead of the traditional *qid* administration of cefotaxime without concomitant paracetamol).

Secondary objectives:

To compare the efficacy of the two treatment modalities in:

1. A potential reduction of the following outcomes:
   - **a**) Severe neurological sequelae (SeNeSe), defined as blindness, quadriplegia/paresis, hydrocephalus requiring a shunt, or severe psychomotor retardation) or death
   - **b**) Deafness (better ear's hearing threshold >80 dB)
   - **c**) Any adverse outcome

2. An improvement on the scale of the Glasgow Outcome Scale

3. The subgroup analyses regarding the etiology, disease severity, and the nutritional status.

Methods

Trial design:

A randomized, double-blind, parallel-group clinical trial with the patients allocated in a 1 : 1 ratio.

Participants:

The patients are enrolled in Hospital Pediátrico David Bernardino, Luanda, Angola.

Eligibility criteria:

The study entry is assessed for all children at age 2 months - 15 years who present at the centre with the symptoms and signs suggestive of BM, and to whom lumbar puncture is performed.

Inclusion criteria:

All patients whose cerebrospinal fluid (CSF) turns out to be cloudy, positive by Gram staining or latex agglutination, or shows at least 50 leukocytes per mm^3, will be enrolled in the study.

Exclusion criteria:

1. Trauma, or relevant underlying illness such as intracranial shunt, previous neurological abnormality (cerebral palsy, Down's syndrome, meningitis)

2. Previous hearing impairment (if known)

3. Immunosuppression, except HIV infection

4. More than one parenteral dose of a pretreatment antimicrobial. Children with oral antimicrobials are included, this information being marked in the FOLLOW-UP sheet.

5. Active tuberculosis (if tuberculotic meningitis is diagnosed during trial, it will be included in intention-to-treat (ITT) analysis)

6. Known hepatic disease.

ITT vs. PP datasets

The patients fulfilling the inclusion criteria and showing no exclusion criterion comprise in the ITT dataset. The per-protocol (PP) analysis includes those with one or more of the following criteria:

1. Positive CSF culture.

2. Positive PCR from CSF.

3. Symptoms and signs compatible with BM, and positive blood culture.

4. Symptoms and signs compatible with BM, and at least 2 of the following criteria: CSF pleocytosis ≥100 cells/mm^3 (predominantly polymorphs), a positive Gram-stain result, positive latex agglutination test, or serum CRP ≥40 mg/L[14]

Study interventions

All patients will receive *cefotaxime* in a dose of 250 mg/kg/24 hours[69] for 7 days,[34] except in salmonella meningitis for which the duration is ≥14 days (because of proneness to relapse).[70] Cefotaxime is chosen because it is a β-lactam that covers most relevant agents, is one of the recommended third-generation cephalosporins,[71] is pharmacodynamically suitable for infusion (recommended also by manufacturer), and was used in our previous trial in Angola.[34] It is also effective against penicillin-resistant pneumococci.

The general course of 7 days of antimicrobial should not be extended, because even this duration is unnecessarily long to sterilize CSF which occurs with cefotaxime in 1-2 days.[71] Long persisting neck stiffness, fever, subdural effusion etc.[72] do *not* warrant prolongation of antimicrobial therapy; these events call for anti-inflammatory, not antibacterial medication.

Experimental intervention:

The administration of *cefotaxime* during the first 4 days as continuous intravenous infusion, each single infusion lasting for 12 hours (to prevent degradation of the agent), combined with high-dose *paracetamol* orally; the first dose is 30 mg/kg, then 20 mg/kg every 6 hours for 4 full days.

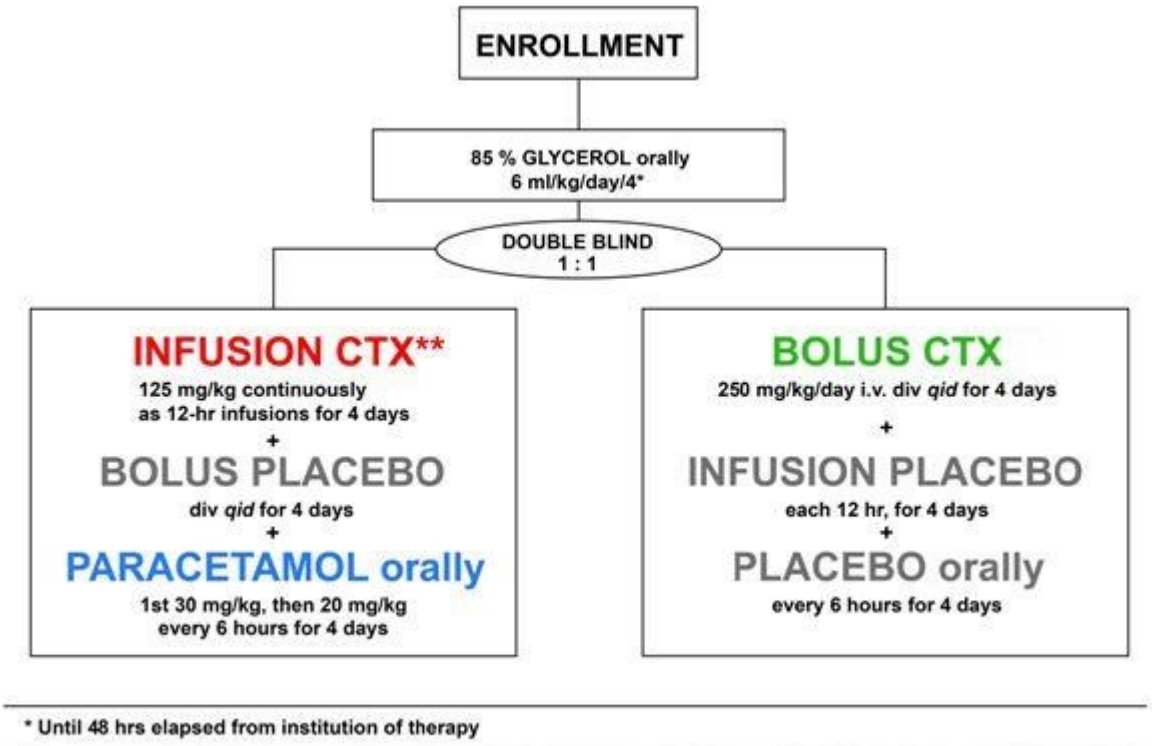
The total amount of paracetamol is 90 mg/kg per day during hours 0-24, and 80 mg/kg per day during hours 25 - 96 (4 days). Thereafter, paracetamol is discontinued. When the effervescent tablet is dissolved in 50 ml of water, the solution contains 10 mg/ml of paracetamol (child of 10 kg needs 30 ml of the ready-to-use solution). Paracetamol/placebo is given at the same time with glycerol. Which agent is given first, is not considered important.

NB ! <u>During the first 4 days</u>, *no other antipyretic* should be used, unless fever continues high and/or pain is a problem. To lower high fever, physical means should primarily be used. If medication is deemed absolutely necessary, oral *ibuprofen* with a dose of 15 mg/kg every 12 hours is the drug of choice, but the course should be kept as short as possible. All details should be marked in the follow-up sheet. After 4 days, paracetamol can be used openly to any child with temperature exceeding 39 C.

Control intervention:

The control intervention consists of cefotaxime administered traditionally with intermittent *i.v.* boluses and the placebo of paracetamol orally, both repeated every 6 hours *(qid)* for 4 days.

The allocation and masking of treatments is depicted in **Figure 3**:



Outcomes

The *primary outcome* is mortality on day 7 from the institution of treatment. All patients should stay in hospital ≥7 days. This time frame is twice longer than the duration of the modified treatment.

The *secondary outcomes* are the following:

1. Mortality on days 14, 21, and 28 from the institution of treatment.

The other secondary outcomes are examined on days 7, 14, 21, and 28.

2. SeNeSe or death

3. Profound hearing loss (defined as the better ear's threshold >80 dB)

4. Status on the modified Glasgow Outcome Scale[73] (see Appendix)

5. Death or any neurological sequelae (SeNeSe, hemi- or monoparesis, ataxia, or psychomotor retardation of any degree), or any hearing impairment. Hearing is deemed impaired if the better ear fails to detect a threshold of 40 dB. The cut-off levels for moderate and severe hearing impairment are 60 dB and 80 dB, respectively.

6. A change in hearing threshold compared to the first test result

Sample size

Assuming in confirmed meningitis a 13% decrease (from 27% to 14%, based on our experience from Angola) in mortality,[34] and accepting a 5% error after adjustment for multiple testing in one-tailed test with a power of 80%, at least 165 patients are required in both arms (CTX-BOLUSES + ORAL PLACEBO *vs.* CTX-INFUSION + ORAL PARACETAMOL). Because several confounding factors, such as dissimilar age, severity on admission, malnutrition, malaria, are to be included in the adjusted efficacy calculations, we intend to enrol 400 patients.

It is possible that one treatment will be significantly better than the other. Therefore, an external Data Safety Monitoring Board (DSMB) obtains the 7-day results after each 100 patients have been evaluated. If an indisputable significance between treatments will be found, DSMB shall interrupt enrolment for ethical reasons.

Randomization (Fig. 3, p. 11)

Sequence generation

A randomization sequence is accomplished by uninvolved persons for 500 patients by means of a computer generated list of random numbers in blocks of 20. The patients are allocated 1:1 to one of the two alternative treatments. The code is kept in a sealed envelope, a copy being sent to DSMB for the interim analyses. For emergency purposes, the key for opening the code is kept sealed also in Helsinki.

Allocation concealment

Numbered and sealed envelopes, each disclosing the specific treatment, are kept in a box in the institution.

Allocation implementation

Once a patient is included into the study by the attending physician, an auxiliary person, who does not otherwise participate in the study, takes the next sealed envelope, prepares cefotaxime and the placebo as ordered by the card, and gives both preparations for 96 hours (4 days). The assignment of any given patient into one of the treatment groups is not known beforehand by the auxiliary person who prepares the antimicrobial(s) and paracetamol/placebo(s).

Blinding (masking)

To mask the experimental *vs.* control interventions, all children receive *both* an infusion *and* a bolus treatment for the entire 4-day course (see page 11). Since the ready-to-use cefotaxime is slightly yellowish liquid, yellow i.v. lines[Becton-Dickinson GmbH, Art.No. 300326], black 50 ml syringes[B Braun, Ref No 8728828F], are used with a foil covering on the 3-way stopcock's [B Braun Smallbore T-Port Extension Set, Ref No 471954] short end which leads to the skin-penetrating needle (for boluses). This setup allows the use of the same one line for the antimicrobial and placebo administrations, each always given as infusion or boluses.

Placebo preparations

Since black syringes and yellow i.v. lines are used, *saline* is an appropriate placebo preparation for cefotaxime, no matter whether administered as infusion or boluses. Since paracetamol *effervescent tablets* are used, regular *drinking water* serves as its placebo. Once bubbles have disappeared, the practically tasteless solution looks like plain water. Each tablet (Panadol®) contains 500 mg of paracetamol. Dissolved in 50 ml of water, the solution contains 10 mg/ml of paracetamol (child of 10 kg needs 30 ml of the ready-to-use solution). Paracetamol/placebo(s) is given at the same time with glycerol.

Statistical methods, analysis plan

Comparability of the study groups prior to therapy will be checked by Student's t-test, whereas chi-square test is applied to the qualitative variables.

Primary (crude, unadjusted) analyses

The primary endpoint (mortality on day 7), and the secondary endpoints are examined by using Fisher's exact test (because of directed hypothesis). The extent of the potential decrease in mortality by the experimental intervention is measured with logistic regression, and the results are expressed as risk ratios (RR) with 95% confidence intervals, both for the ITT and PP datasets.

The time of death from the institution of therapy is registered, and a survival analysis between groups is done. Kaplan-Meier analysis assesses mortality, whereas Fisher's exact and sign tests are used when analyzing the time of death.

All data are analyzed with StatView (version 5.1), and the trial will be registered in the International Standard Randomized Controlled Trial Number Register (ISRCTN).

Adjusted efficacy analyses

Multiple logistic regression is used when testing the influence of various known (severity of disease, age, malnutrition, malaria, etc.) and likely unknown variables in the crude efficacy ratio. If a confounding variable is detected – *e.g.*, once included in analysis, the crude efficacy ratio changes ≥ 10% –, the adjusted efficacy ratios are calculated for each endpoint by combining all confounding variables with the treatment variables. Should some data be missing (which would drop the case from logistic regression), Bayesian multivariate analysis is used.

Subgroup analyses

Subgroup analyses, for both crude (unadjusted) and adjusted efficacy, are needed because of potential heterogeneity in the treatment effect due to dissimilar patient and etiological characteristics. Provided the series is large enough, the subgroup analyses will likely cover

a) Severity of disease, using different gradings of the Glasgow Coma Scale

b) The causative agents: *S. pneumoniae, H. influenzae, N. meningitidis,* and other agents

c) The nutritional status, using the z-score grading of "normal" weight/age (+1 to -1), "malnourished" (below -1), and "severely malnourished" (below -3)[74]

d) The child's HIV status

e) Time of death

f) Different categories identified by the indices of inflammation or sequential CRP determinations

g) Sickle-cell disease

Sequential analysis

The statistician of study group, permanently located in Finland, will get regularly the core result data and analyse the mortality in the sense of sequential analysis.[75]

Supplementary analysis

Since a very similar study will be carried out in Santo Domingo, Dominican Republic, the data will be examined also combined, provided the results are in the same direction. Were this the case, the statistical power of the results would increase considerably.

Other medications and management

Glycerol

Because 85% glycerol *proved* so beneficial in Latin-America,[14] its omission would raise ethical questions. Therefore, it is given to all patients in a quantity of 6.0 g (6.0 ml) per kg/day divided in 4 equal daily doses *ad* 25 ml per dose. If it induces vomiting (rare), a nasogastric tube is inserted, and the same dose is repeated immediately. Glycerol is given for 2 days [8 doses 1.5 g/kg (1.5 ml/kg) ad 25 g (25 ml) per dose]. Some authors recommend giving glycerol chilly. An old report[76] tells how best to disguise the slightly sweet taste: "Orange juice immediately before and after glycerol leaves virtually nothing but the taste of orange."

Dexamethasone

For reasons explained before,[14,18,21] dexamethasone is not used in this study. Notably, the Ethics Committee in Luanda did not approve its use in our previous meningitis study in Angola.[34]

Convulsions

Seizures are treated as usual in each center. Paraldehyde is often used with a dose of 0.2 ml/kg intramuscularly; the dose can be repeated at least once. In Malawi, intranasal lorazepam 100 µg/kg has proved very useful.[77]

Malaria

In many tropical regions malaria is a major disease to be distinguished form BM. It is diagnosed and treated as is the practice in the institution.

HIV infection

All efforts will be done to materialize HIV-testing for all participants, and the test results should be marked in the FOLLOW-UP sheet. HIV infection is treated according to the lines of each institution.

Fluid therapy

Most children with meningitis have alterations in their fluid and electrolyte homeostasis, which may lead to death, if not corrected in time. Capillary leak because of sepsis and shock add to the problems.

More children suffer from fluid depletion than overload.[78,79] In spite of overwhelming reasons for hypovolemia, many children are still deemed to have the Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH),[80,81] because hyponatremia, hypernatriuria (U-Na >20 mmol/l), and high plasma arginine-vasopressin (ADH) are found in more than 50% of children with BM. Thus, 'SIADH' is considered the cause of free-water retention, hypo-osmolality and hyponatremia. Then, death is explained by fluid overload, hyponatremia and oliguria, which worsened the intracranial pressure. With this reasoning, fluid restriction to two-third of normal maintenance was previously recommended.[82]

However, clinical evidence has not supported fluid restriction,[83] because, actually, an increased ADH level is probably a very appropriate response to hypovolemia; the ADH levels return to normal when fluids are administered rather freely.[84] Elevated plasma ADH represents a compensatory mechanism to overcome raised intracranial pressure and to maintain adequate cerebral blood flow.[85] This in turn depends on the main arterial pressure, which is adversely affected by hypovolemia. Therefore, restriction of fluids can be dangerous, and might enhance cerebral ischemia. In experimental meningitis, fluid restriction did not relieve brain oedema,[86] but lowered the blood pressure, cerebral blood flow, and increased the CSF lactate concentration (suggesting increasing hypoxia).[87] Prospective, randomized clinical study in India showed that, instead of being beneficial, fluid restriction was harmful;[88] children with reduced extracellular volume (10 ml/kg or more) within first 48 hrs had significantly lower intact survival. This experience is further corroborated by another randomized trial from Papua-New Guinea.[27]

Fluid restriction affects cerebral edema minimally (if at all) and, if pursued to excess, may induce hypotension and cerebral hypoxia, and then, further increase intracranial pressure. Normal maintenance fluids with isotonic crystalloids are justified. Widely used 50% Darrow or Ringer fluid, with added glucose (5%), are appropriate fluids for this purpose. If the patient is hypovolemic (dry mouth, tachypnea, sunken eyes, or shocked), fluid replacement will be rapid according to WHO shock and severe dehydration protocols.

Monitoring of the hydration status, intravascular volume, electrolytes, and osmolality are the guides for fluid management, with the aim of maintaining normovolemia, iso-osmolality and normal blood pressure - and thereby adequate cerebral perfusion. Glycerol probably adds to these positive effects.[29] Monitoring of serum glucose 3-4 times a day is mandatory, resources permitting, for unconscious patients, because severe hypoglycemia is one of the insidious risks during the acute phase of meningitis. Monitoring of the hydration status, intravascular volume, electrolytes, and osmolality are the guides for the fluid management, aiming at maintaining the normovolemia, iso-osmolality and normal blood pressure – and thereby adequate cerebral perfusion.

Blood transfusion

A 10 cc/kg of transfusion of packed red blood cell (in two parts, if deemed necessary) will be administered to all children with an admission hemoglobin of <5 g/dL. If the child is in a poor condition, a transfusion may be given when the hemoglobin is higher, *e.g.* <6 g/dL.

Data collection and samples taken during hospital stay

Data collection

All data will be collected with the 3 forms (APPENDICES) which were modified from those we used previously.[14,34] Hence, comparable data on the history of patient, presenting status, and the course and outcomes of illness will be obtained. At discharge, the forms are e-mailed to the Study Coordinator, the original data being kept at the centre. The results from the check-up are sent later.

Disease severity

The severity of disease is graded by the *Glasgow Coma Scale* (adjusted for age), the *Blantyre Coma*[89] and the *Bayesian Luanda* and the Simple *Luanda Scales* (APPENDICES).[90]

Audiology

Special attention is paid to measure hearing at presentation, and on days 7, 14, 21, and 28. The child's cooperation permitting, traditional pure tone *audiometry* is preferred, but this is rarely possible. Hence, *brain stem evoked response audiometry* (BERA, ABR, BSA) is the main method used in this study. The equipment (Madsen Octavus,™ Windows XP/2000 compatible) will be provided.

Otitis media or other benign reason for reduced hearing should be excluded with pneumatic otoscopy or tympanometry. If impairment is likely/confirmed, the child will be retested a few months later. All test documents are sent to an audiology expert who is kept blinded from other patient details. Three threshold levels, 40 dB (mild impairment), 60 dB (moderate impairment), and 80 dB (severe impairment, social deafness) are used. The data are given for the better ear and both ears separately.

Samples

CSF

A CSF sample is taken on admission, and if needed, preferably after 12 *or* 24 hours (precisely) from the institution of antimicrobial. The sample should be cultured immediately on fresh blood and sugar agar plates. Good-quality plates ready should be kept on site, and by letting the first CSF drops to fall directly onto the plates.

Conditions permitting, a CSF sample (≥1 ml) for further analyses should be kept at -20 °C. Because the agent may later be identified by PCR, a CSF sample should always be collected also on a *filter paper strip*[91] (circles throughout moistened with CSF). The strips, provided by the study, are left to dry in room air, placed in an envelope and sent to Finland by regular mail. Resources permitting, the isolated bacterial strain is lyophilized. All samples must be clearly marked with the name, date, and the time of the day, using deep freeze-resisting ink.

Routine biochemistry and cytology are done as routinely. Resources permitting, inflammatory mediators, mycobacteria and viruses are investigated (details in Sub-study protocols).

Serum, urine, and saliva

A 4-5 ml sample of blood is collected on admission for basic hematological and biochemical determinations (such as hemoglobin, blood-leukocyte and platelet counts, glucose concentration, electrolytes), CRP and/or serum procalcitonin with other inflammatory mediators, malaria parasites, and testing for HIV and sickle-cell disease. A few drops of serum (or blood) should be collected on *filter strips.* The same procedure applies to saliva samples, too, because those render possible examining the inflammatory mediators. Urine analysis and tuberculin test by the Mantoux technique are done as is the routine of the institution.

Check-up samples during medications

Besides potential second CSF sample at 12 *or* 24 hours, monitoring of *blood glucose* 2-4 times per 24 hours is highly desirable especially for patients with lessened consciousness. Severe hypoglycaemia is an under-recognized risk in the acute phase of meningitis. For easy measuring, a handy gadget (Contour,™ Bayer) is provided.

The only check-up blood sample, appr. 3 ml, is taken on day 4 (±1) from the institution of therapy. From this specimen, plasma *hemoglobin,* CRP and/or procalcitonin are measured. A serum (or blood) sample should also be collected on filter *strips* for later determination of a set of other inflammatory mediators. Urine and saliva samples are an option.

Serial *serum CRP* measurements are very useful in monitoring the course of illness. Ideally, CRP is measured (from a finger-prick) every 24 hours, 5 times in total (days 1-5), beginning on admission. At least CRP should be measured on admission and on day 4 from the institution of therapy.

Follow-up visits

All randomized patients should stay in hospital for at least 7 days to be included in the survival dataset. Thereafter, the participants will be discharged according to their clinical condition.

A control visit on day 21 (±2 days) from the institution of therapy, unless the child is still in hospital, is of paramount importance. And especially so is the case if any hearing, neurological, or other abnormality was found before. Special attention is paid to all potential short- or long-term sequelae, whatever their nature. The follow-up sheet is filled, using also the *Modified Glasgow Outcome Scale.*

Launch and duration of study, registration

The study is launched in early 2012, once the ethics committee has approved the protocol. One can expect the enrolment to last approximately three years. The enrolment ends once 400 patients have been gathered, or five years have elapsed. The study will be registered in an international register.

Persons in charge, publication politics, and the study group meetings

Drs *Tuula Pelkonen* and *Manuel Leite Cruzeiro* are the Principal Co-investigators, headed by Prof *Luis Bernardino.* These persons have the right to make all decisions, such as to change the antimicrobial in case of resistance to cefotaxime and, in emergency, to open the code. Dr *Irmeli Roine* is the General Study Coordinator, whereas Prof *Heikki Peltola* is the Director and Scientific Advisor. Dr *Matti Kataja* is the statistician, whereas Prof *Anne Pitkäranta* is the oto-audiological

consultant. All data will be published as collaborative papers at a national and international level. - Resources permitting, meetings of the Study Group are organized annually.

Ethical issues

Informed consent

The protocol and the informed consent form should be approved by the relevant ethics committee. The Helsinki and Tokyo Declarations will be followed. Before a child enters the study, the attending physician describes the study to the legal guardian, asks him/her to read the Informed Consent, and addresses all potential questions. If the guardian agrees the study, he/she should sign the form. Only children with a signed consent enter the study. If the guardian is illiterate, the text is read to him/her. Then the guardian may express his/her acceptance with a finger-mark or by drawing a cross in the consent form. If participation is refused, the child is treated as is the routine of hospital.

Data Safety Monitoring Board, DSMB

DSMB comprises 3 experienced scientists, Professor *Markku Koskenvuo* (epidemiologist, University of Helsinki), Docent *Marjo Renko* (pediatric infectious disease specialist, University of Oulu), and Docent *Terho Heikkinen* (pediatric infectious disease specialist, University of Turku). As the Board's responsibility is to follow-up the study from the scientific and ethical points of view, it has an access to the treatment code at any time. Dr *Roine* keeps the study group up-to-dated of the trial's status.

Not being involved in the treatment, Dr *Kataja* (statistician) is the only person in the study group who is familiar with the treatment of each patient. By sequential analysis, conditions permitting, he checks the situation every weekend, or at least, after each 100 patients have entered the study. If a crude significance appears between groups, he immediately contacts DSMB to discuss if the trial should be terminated because of ethical reasons.

The Ethics Committee has to be informed biannually about the progress of the study, and can reunite always when considered necessary

Jan 21, 2012

Heikki Peltola, MD, Professor

References

1. Peltola H. Worldwide of *Haemophilus influenzae* type b disease at the beginning of the 21st century; global analysis of the disease burdren 25 years after the use of polysacharide vaccine and a decade after the advent of conjugates. Clin Microbiol Rev 2000;13:302-17.
2. Mulholland EK, Hilton S, Adegbola RQA, et al. Randomised trial with *Haemophilus influenzae* type-b tetanus protein conjugate vaccine in prevention of pneumonia and meningitis in Gambian infants. Lancet 1997;349:1191-7.
3. Black SB, Shinefield H, Ling S, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. Pediatr Infect Dis J 2002;21:810-5.
4. Peltola H. Burden of meningitis and other severe bacterial infections of children in Africa: implications for prevention. Clin Infect Dis 2001;32:64-75.
5. Matthay MA. Severe sepsis - a new treatment with both anticoagulant and antiinflammatory properties. N Engl J Med 2001;344:759-62.
6. Warren BL, Eid A, Singer P, et al. High-dose antithrombin III in severe sepsis. A randomized controlled trial. JAMA 2001;286:1869-78.
7. Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699-709.
8. Manns BJ, Lee H, Doig CJ, Johnson D, Donaldson C. An economic evaluation of activated protein C treatment for severe sepsis. N Engl J Meed 2002;347:993-1000.
9. Levin M, Quint PA, Golsdstein B, et al. Recombinant bactericidal/permeability-increasing protein (rBPI21) as adjunctive treatment for children with severe meningococcal sepsis: a randomised trial. Lancet 2000;356:961-7.
10. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. Lancet 2009;374:893-902.
11. Lebel MH, Freij BJ, Syrogiannopoulos GA, et al. Dexamethasone therapy for bacterial meningitis: Results of two double-blind, placebo-controlled trials. N Engl J Med 1988; 319: 964-71.
12. Odio C, Faingezicht I, Paris M, et al. The beneficial effect of early dexamethasone administration in infants and children with bacterial meningitis. N Engl J Med 1991;324:1525-31.
13. Molyneyx EM, Walsh AL, Forsyth H, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. Lancet 2002;360:211-8.
14. Peltola H, Roine I, Fernández J, et al. Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2007;45:1277-86.
15. Scarborough M, Gordon SB, Whitty CJM, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. N Engl J Med 2007;357:2441-50.
16. de Gans J, van de Beek D, European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. N Engl J Med 2002;347:1549-56.
17. Mai NTH, Chau TTH, Thwaites G, et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. N Engl J Med 2007;357:2431-40.
18. van de Beek D, Farrar JJ, de Gans J, et al. Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. Lancet Neurol 2010;9:254-63.
19. van de Beek D, de Gans J, McIntyre P, Prasad K. Corticosteroids in acute bacterial meningitis. Cochrane Database Syst Rev 2007(1). Art No CD004405. DOI: 10.1002/14651858.CD004405.pub2.
20. Roine I, Peltola H, Fernández J, et al. Influence of admission findings on death and neurological outcome from childhood bacterial meningitis. Clin Infect Dis 2008;46:1248-52.
21. Peltola H, Roine I, Fernández J, et al. Hearing impairment in childhood bacterial meningitis is little relieved by dexamethasone or glycerol. Pediatrics 2010;125:e1-e8.
22. Zysk B, Brück W, Gerber J, et al. Anti-inflammatory treatment influences neuronal apoptotic cell death in the dentate gyrus in experimental pneumococcal meningitis. J Neuropath Exp Neurol 1996;55:722-8.
23. Leib S, Heimgartner C, Bifrare Y-D, et al. Dexamethasone aggravates hippocampal apoptosis and learning deificiency in pneumococcal meningitis in infant rats. Pediatr Res 2003;54:353-7.
24. Coimbra RS, Loquet G. Leinb SL. Limited efficacy of adjuvant therapy with dexamethasone in preventing hearing los in experimental pneumococcal meningitis in the infant rat. Pediatr Res 2007;62:291-4.
25. Singhi SC, Bansal A. Serum cortisol levels in chilren with acute bacterial and aseptic meningitis. Pediatr Crit Care Med 2006;7:74-8.

26. Nau R, Soto A, Brück W. Apoptosis of neurons in the dentate gyrus in humans suffering from bacterial meningitis. J Neuropathol Exp Neurol 1999;58:265-74.
27. Duke T, Mokela D, Frank D, et al. Management of meningitis in children with oral fluid restriction or intravenous fluid at maintenance volumes: a randomized trial. Ann Trop Pediatr 2002;22:145-57.
28. Principi N, Esposito S. Dexamethasone in acute bacterial meningitis. Lancet 2002;360:1610.
29. Singhi S, Järvinen A, Peltola H. Increase in serum osmolality is possible mechanism for the beneficial effects of glycerol in childhood bacterial meningitis. Pediatr Infect Dis J 2008;27:892-6.
30. Ajdukiewicz KMB, Cartwright KE, Scarborough M, et al. Glycerol adjuvant therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomised controlled trial. Lancet Infect Dis 2011;11:293-300
31. Peltola H, Singhi S, Roine I. Don't hurry with the condemnation of glycerol in bacterial meningitis! Manuscript submitted
32. Rottenberg DA, Hurwitz BJ, Posner JB. The effect of oral glycerol on intraventricular pressure in man. Neurology 1977;27:600-8.
33. Nau R, Prins F-J, Kolenda H, Prange HW. Temporary reversal of serum to cerebrospinal fluid glycerol concentration gradient after intravenous infusion of glycerol. Eur J Clin Pharmacol 1992;42:181-5.
34. Pelkonen T, Roine I, ML, Pitkäranta A, Kataja M, Peltola H. Slow initial β-lactam infusion and oral paracetamol to treaat childhood bacterial meningitis: a randomised, controlled trial. Lancet Infect Dis 2011;11:613-21.
35. Penna A, Buchanan N. Paracetamol poisoning in children and hepatotoxicity. Br J Clin Pharmac 1991;32:143-9.
36. Kramer MS, Naimark LE, Roberts-Bräuer R, McDougall Am Leduc DG. Risks and benefits of paracetamol antipyresis in young children with fever of presumed viral origin. Lancet 1991;337:591-4.
37. Brandts CH, Ndjavé M, Graninger W, Kremsner PG. Effect of paracetamol on parasite clearance time in *Plasmodium falciparum* malaria. Lancet 1997;350:704-9.
38. Udomsangpetch R, Pipitaporn B, Silamut K, et al. Febrile temperatures induce cytoadherence of ring-stage *Plasmodium falciparum*-infected erythrocytes. PNAS 2002; 99:11825-9.
39. Prymula R, Siegrist CA, Chlibek R, et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. Lancet 2009;374:1339-50.
40. van der Flier M, Geelen SPM, Kimpen JLL, Hoepelman IM, Tuomanen EI. Reprogramming the host response in bacterial meningitis: how best to improve outcome? Clin Microbiol Rev 2003;16:415-29.
41. Abramson S, Korchak H, Ludewig R, et al. Modes of action of aspirin-like drugs. Proc Natl Acad Sci 1985;82:7227-31.
42. Piletta P, Pporchet HC, Dayer P. Central analgesic effect of acetaminophen but not of aspirin. Clin Pharmacol Ther 1991;49:350-4.
43. Aronoff DM Aronoff DM, Oates JA, Boutaud O. New insights into the mechanism of action of acetaminophen: Its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. Clin Pharmacol Ther 2006; 79: 9–19.
44. Kuikka A. Factors associated with the outcome of bacteraemia during twenty years (1976-1996) with special reference to bacteraemias due to *Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa.* Academic dissertation, University of Helsinki, Helsinki 1999 (83 p).
45. McCabe WR, Jackson GG. Gram-negative bacteraemia. Arch Intern Med 1962;110:847-64.
46. Kuikka A, Sivonen A, Emelianova A, Valtonen VV. Prognostic factors associate with improved outcome of *Escherichia coli* bacteraemia in a Finnish university hospital. Eur J Clin Micro Infect Dis 1997;16:125-34.
47. Kuikka A, Valtonen VV. Factors associated with improved outcome of *Pseudomonas aeruginosa* bacteraemia in a Finnish university hospital. Eur J Clin Micro Infect Dis 1998;17:701-8.
48. Bernard GR, Wheeler AP, Russell JA, Schein R, Summer WR, Steinberg KP, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. N Engl J Med 1997; 336: 912–8.
49. Vogelman B, Gudmundsson S, Leggett J, Ebert SC, Craig WA. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J Infect Dis 1988;158:831-7.
50. Craig WA, Ebert SC. Continuous infusion of beta-lactam antimicrobials. Antimicrob Agents Chemother 1992;36:2577-83.
51. Craig WA. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. Diagn Microbiol Infect Dis 1995;22:89-96.
52. Spreer A, Lugert R, Stoltefaut V, Hoecht A, Eiffert H, Nau R. Short-term rifampicin pretreatment reduces inflammation and neuronal cell death in a rabbit model of bacterial meningitis. Crit Care Med 2009; 37: 2253–8.
53. Roosendaal R, Bakker-Woudenberg IAJM, van den Berghe-van Raffe M, Michel MF. Continuous versus intermittent administration of ceftazidime in experimental *Klebsiella pneumoniae* pneumonia in normal and leukopenic rats. Antimicrob Agents Chemother 1986;30:403-8.
54. Thauvin C, Elliopoulos GM, Willey S, Wennerstein C, Moellering RC Jr. Continuous-infusion ampicillin therapy of enterococccal endocarditis in rats. Antimicrob Agents Chemother 1987; 31: 139-43.

55. Daenen S, de Vries-Hospers H. Cure of *Pseudomonas aeruginosa* infection in neutropenic patients by continuous infusion of ceftazidime. Lancet 1988;2: 937.
56. Guggenbichler JP, Allerberger F, Dietze O, Klima G. Die Behandlung der eitrigen Meningitis im Kindesalter. Pädiatrie und Pädologie 1989; 24:3-19.
57. Visser LG, Arnouts P, van Furth R, Mattie H, van den Broek PJ. Clinical pharmacokinetics of continuous intravenous administration of penicillins. Clin Infect Dis 1993;17:491-5.
58. Hitt CM, Nightingale CH, Quintiliani R, Nicolau DP. Cost comparison of single daily i.v. doses of ceftriaxone versus continuous infusion of cefotaxime. Am J Health Syst Pharm 1997; 54: 1614–8.
59. Klepser ME, Patel KB, Nicolau DP, Quintiliani R, Nightingale CH. Comparison of bactericidal activities of intermittent and continuous infusion dosing of vancomycin against methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecalis*. Pharmacotherapy 1998;18:1069–74.
60. Lipman J, Gomersall CD, Gin T, Joynt GM, Young RJ. Continuous infusion ceftazidime in intensive care: a randomized controlled trial. J Antimicrob Chemother 1999; 43: 309–11.
61.. Robaux MA, Dubé L, Cailllon J, et al. In vivo efficacy of continuous infusion versus intermittent dosing of ceftazidime alone or in combination with amikacin relative to human kinetic profiles in a *Pseudomonas aerugionsa* rabbit endocarditis model. J Antimicrob Chemother 2001;47:617-22.
62.. Nicolau DP, McNabb J, Lacy MK, Quintiliani R, Nightingale CH. Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia. Int J Antimicrob Agents 2001;17: 497–504.
63. Bernard E, Breilh D, Bru J-P, et al. Is there a rationale for the continuous infusion of cefepime? A multidisciplinary approach. Clin Micrbiol Infect 2003;9:339.
64. Kasiakou SK, Sermaides GJ, Michalopoulos A, Soteriades ES, Falagas ME. Continuous versus intermittent intravenous administration of antibiotics: a meta-analysis of randomised controlled trials. Lancet Infect Dis 2005; 5: 581–9.
65. Roberts JA, Paratz J, Paratz E, Krueger WA, Lipmn J. Continuous infusion for □-lactam antibiotics in severe infections: e review of its roole. Int J Antibicorb Ag 2007;30:11-8.
66. van Zanten AR, Oudijk M, Nohlmans-Paulssen MK, van der Meer YG, Girbes AR, Polderman KH. Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: pharmacokinetics/pharmacodynamics, bacterial susceptibility and clinical efficacy. Br J Clin Pharmacol 2007; 63: 100–9.
67. Roberts JA, Boots R, Rickard CM, Thomas P, Quinn J, Roberts DM, et al. Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? A randomized controlled pilot study. J Antimicrob Chemother 2007; 59: 285–91.
68. Roberts JA, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Piperacillin penetration into tissue of critically ill patients with sepsis--bolus versus continuous administration? Crit Care Med 2009;37:926–33.
69. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004;39:1267-84.
70. Chotpitayasunondh T. Bacterial meningitis in children: etiology and clinical features, an 11-year review of 618 cases. Southwest Asian J Trop Med Publ Health 1994; 25: 107-15.
71. Peltola H, Anttila M, Renkonen O-V, The Finnish Study Group. Randomised comparison of chloramphenicol, ampicillin, cefotaxime and ceftriaxone for childhood bacterial meningitis. Lancet 1989;1:1281–7.
72. Anttila M. Clinical criteria for estimating recovery from childhood bacterial meningitis. Acta Paediatr 1994;83:63-8.
73. Wilson JTL, Pettigrew LEI, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelineds for their use. J Neurotrauma 1998;15:573-85.
74. Roine I, Weisstaub G, Peltola H, the LatAm Meningitis Study Group. Influence of malnutrition on the course of childhood bacterial meningitis. Pediatr Infect Dis J 2010;29:122-5.
75. Documenta Geigy, 6th Edition, Basel 1962 pp 195
76. Johnson V, Carlson AJ, Johnson A. Studies on the physiological action of glycerol on the animal organism. Am J Physiol 1933;103:517-34 [The paper includes some human data, too.]
77. Ahmad S, Ellis JC, Kamwendo H, Molyneux E. Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open randomised trial. Lancet 2006;367:1591-7.
78. Kanakriyeh M, Carvajal HF, Vallone AM. Initial fluid therapy for children with meningitis with consideration of the syndrome of inappropriate anti-diuretic hormone. Clin Pediatr 1987;6(3):126-30.
79. Floret D. Hydration and meningitis. (French). Arch Pediatr 1999;6(2):199-202.
80. Feigin RD, Kaplan S. Inappropriate secretion of antidiuretic hormone in children with bacterial meningitis. Am J Clin Nutr 1977;30:1482-4.
81. Kaplan S, Feigin RD. The syndrome of inappropriate secretion of antidiuretic hormone in children with bacterial meningitis. J Pediatr 1978;92:758-61.
82. Smith A. Fluid management during bacterial meningitis. Rep Pediatr Infect Dis 1993;3:10-11.
83. Moller K, Larsen FS, Bie P, Skinhoj P. The syndrome of inappropriate secretion of anti-diuretic hormone and fluid restriction in meningitis - how strong is the evidence? Scand J Infect Dis 2001;33(1):13-26).

84. Powell KR, Sugarman LI, Eskenazi AE et al. Normalization of plasma arginine-vasopressin concentrations with children with meningitis are given maintenance plus replacement fluid therapy. J Pediatr 1990; 117: 515-22.
85. Kumar V, Singhi P, Singhi S. Changes in body water compartments in children with acute meningitis. Pediatr Infect Dis J 1994; 13: 299-305.
86. Täuber 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: 473-6.
87. Tureen JM, Täuber MG, Sande MA. Effect of hydration status on cerebral blood flow and cerebrospinal fluid lactic acidosis in rabbits with experimental meningitis. J Clin Invest 1992;89:947-53.
88. Singhi SC, Singhi PD, Srinivas B, et al. Fluid restriction does not improve the outcome of acute meningitis. Pediatr Infect Dis J 1995;14:495-503.
89. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: A study of 131 comatose Malawian children. Q J Med. 1989;71:441-459.
90. Pelkonen T, Roine I, Monteiro L, et al. Accuracy of five simple prognostic scales in childhood bacterial meningitis. Submitted.
91. Peltola H, Roine I, Leinonen M, et al. Diagnosis of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b meningitis by identifying DNA from cerebrospinal fluid-impregnated filter paper strips. Pediatr Infect Dis J 2010;29:111-4.

APPENDIX 1

GLASGOW COMA SCALE

	Infants and children <2 yrs		Older children
Eye opening			
	Spontaneous	**4**	Spontaneous
	To verbal stimuli	**3**	To verbal stimuli
	To pain only	**2**	To pain only
	No response	**1**	No response
Verbal response	Coos and babbles	**5**	Oriented, appropriate
	Irritable, cries	**4**	Confused
	Cries to pain	**3**	Inappropriate words
	Moarns to pain	**2**	Incomprehensible words or nonspecific sounds
	No response	**1**	No response
Motor response	Moves spontaneously	**6**	Obeys commands and purposefully
	Withdraws to touch	**5**	Localizes painful stimulus
	Withdraws in response to pain	**4**	Withdraws in response to pain
	Decorticate posturing* in response to pain	**3**	Flexion in response to pain
	Decerebrate posturing** in response to pain	**2**	Extension in response to pain

No response	**1**	No response

* abnormal flexion ** abnormal extension

APPENDIX 2

BLANTYRE COMA SCALE FOR YOUNG CHILDREN [scores from 0 to 5][89]

Best motor response	
Localizes painful stimulus*	**2**
Withdraws limb from painful stimulus**	**1**
No response, or inappropriate response	**0**
Best verbal response	
Cries appropriately with painful stimulus* or, if verbal, speaks	**2**
Moan or abnormal cry with painful stimulus	**1**
No vocal response to painful stimulus	**0**
Eye movement	
Watches or follows (e.g. mother's face)	**1**
Fails to watch or follow	**0**

* Presssure with blunt end of pencil on sternum or supraorbital ridge

** Pressure with horizontal pencil on nailed, or finger, or toe

APPENDIX 3 a

BAYESIAN LUANDA SCALE [scores from 0 to 5][90]

Variable

Electricity at home

Yes	☐
No	☐

Days of illness

≤3	☐
4-7	☐
≥8	☐

Convulsion at home

No	☐
Yes, focal	☐
Yes, generalized	☐

Consciousness

Normal	☐
Altered	☐
Coma	☐

Dyspnoea

None or slight	☐
Moderate	☐
Grave	☐

Blood glucose on admission, mg/dL (lowest value)

-40	☐

41-100	□
101-120	□
121-	□

APPENDIX 3 b

SIMPLE LUANDA SCALE [scores from 0 to 10][90]

Electricity at home

Yes	**0**
No	**2**
Unknown	**1**

Days of illness

≤3	**0**
4-7	**1**
≥8	**3**

Convulsion on admission

No	**0**
Yes, focal	**1**
Yes, generalized	**2**
Unknown	**1**

Consciousness

Normal	**0**
Altered	**5**
Coma	**10**
Unknown	**1**

Dyspnoea

None or slight	**0**
Moderate	**1**
Grave	**2**

Unknown **1**

APPENDIX 4

MODIFIED GLASGOW *OUTCOME* SCALE [scores from 5 to 1][73]

Death **1**

Vegetative state **2**
Unable to interact with the environment

Severe disability **3**
Unable to live independently (if grown), but can follow commands

IN SMALL (appr. <2 yrs) CHILDREN: Better ear's hearing >80 dB, blindness, quadriplegia/paresis, severe psychomotor retardation (does not sit or walk, speak, or establish contact, or requires institutionalization)

Moderate disability **4**
Capable of living independently (if grown), but unable to go to school

IN SMALL (appr. <2 yrs) CHILDREN: Better ear's hearing 61-80 dB, hemiparesis, mild-to-moderate psychomotor retardation

Mild or no disability **5**
Able to go to school

IN SMALL (appr. <2 yrs) CHILDREN: Better ear's hearing 41-60 dB, ataxia, monoparesis

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APPENDIX 5

INFU/PARA - BOLU/PLACE follow-up sheets in Portuguese (separate sheets):

5a: Admission

5b: The Glasgow & Blantyre & Bayesian Luanda Scores

5c: Treatment

5d: Laboratory results, and the Clinical follow-up

5e: Assessment of the clinical course

5f: Assessment and follow-up of sequelae

APPENDIX 6

Informed Consent Form (in Portuguese)