Extended Continuous β-Lactam Infusion with Oral Acetaminophen in Childhood Bacterial Meningitis: A Randomized, Double-Blind Clinical Trial

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Summary: A continuous β-Lactam infusion combined with high-dose oral paracetamol did not improve the prognosis of childhood bacterial meningitis in Angola, while compared to conventional treatment. Our results underline the dismal outcomes of bacterial meningitis in these settings.

ABSTRACT

Background

In our previous study in Luanda, Angola, initial continuous β-lactam infusion for 24 hours combined with oral acetaminophen for 48 hours showed promising results as a new treatment for childhood bacterial meningitis. We investigated whether extending this treatment regimen to 4 days would improve the outcomes further.

Methods

We conducted a randomized, double-blind, parallel-group study at the same hospital in Luanda. Children aged 2 months to 15 years presenting to hospital with symptoms and signs of bacterial meningitis were randomized to receive, for the first 4 days, a continuous infusion of cefotaxime (250mg/kg/day) with simultaneous oral acetaminophen (first dose 30 mg/kg, then 20 mg/kg every 6 hours), or cefotaxime conventionally as boluses (62.5 mg/kg, 4 times per day) with placebo orally. All children received also glycerol orally. The primary outcome was mortality by day 7.

Results

In all, 375 patients were included in the study between January 22, 2012 and January 21, 2017. As two children succumbed before treatment initiation, 187 vs. 186 participants remained in the intervention and control groups, respectively. On day 7, 61/187 (32.6%) children in the intervention group *versus* 64/186 (34.4%) in the control group had died (risk ratio 0.95, 95% confidence interval

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[95% CI] 0.71 –1.26; absolute risk difference 1.8%, 95% CI -7.8 – 11.4). At discharge from hospital, the corresponding numbers were 71/187 (38.0%) and 75/186 (40.3%).

Conclusions

Prolonged continuous β-lactam infusion combined with oral acetaminophen did not improve the gloomy outcomes of childhood bacterial meningitis in Angola.

Keywords: bacterial meningitis, continuous infusion, acetaminophen, paracetamol, children

(ClinicalTrials.gov, NCT01540838)

INTRODUCTION

Bacterial meningitis (BM) remains a serious threat to global child health, being the 10th most common cause of death in children under 5 years old [1]. The disease burden falls in particular on children in resource-poor settings, where the mortality rates may still rise up to 50%, survivors being often left with disabling neurological or audiological sequelae. Although vaccination against *Haemophilus influenzae* type b (Hib), several types of *Streptococcus pneumoniae,* and the essential serogroups of *Neisseria meningitidis* have reduced the burden [2-4], the poor disease outcomes urgently call for more effective treatment modalities.

Dexamethasone, and to a lesser extent, glycerol have been evaluated as adjunctive treatments for childhood BM. The results have been controversial [5-8], as their effects likely relate to the study environment, causative bacteria, patient age, and likely most importantly, to the clinical condition on admission [9]. Neither treatment has, however, significantly reduced the high mortality rate of this potentially devastating disease. This said, oral glycerol prevented severe neurological sequelae in a large (N= 654) randomized placebo-controlled study in Latin America, the odds ratio (OR) for glycerol being 0.31 (95% confidence interval [CI] 0.13–0.76) compared to the placebo recipients [7]. Although a similar effect was not obtained later in a smaller study in Malawi [8], the clear results from Latin America prevented us, for ethical grounds, from withdrawal of the utilization of glycerol in our further BM studies in Africa.

As β-lactam antibiotics exert time-dependent killing of bacteria, prolonged or continuous infusions may optimize the pharmacodynamic performance of these compounds [10]. A continuous infusion may also produce other benefits, such as a better controlled inflammatory response due to less fluctuating target antibiotic concentrations. We therefore performed a randomized, double-blind, and placebo-controlled study at the Hospital Pediátrico David Bernardino in Luanda, Angola in 2005–2008, in which the effects of initial continuous infusion of cefotaxime were examined [11]. In addition, large-dose oral acetaminophen (paracetamol) was administered, the basis for this

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intervention deriving from a large retrospective analysis of bacteremic adult patients in Finland [12]. Our main finding from this series of 723 BM patients was that the children receiving cefotaxime infusion for 24 hours and oral acetaminophen for 48 hours showed significantly lower mortality, this effect starting within the first 24 hours from treatment initiation and lasting for several days [11]. Although there was insufficient evidence of a difference at discharge from hospital, this encouraging result prompted us to examine our finding further in another study.

With this background a new trial was carried out at the same institution in Angola, now with a prolongation of our modified treatment. We here report the results of this particular investigation.

METHODS

Study Design and Participants

This was a single-center, randomized, double-blind, placebo-controlled parallel-group study conducted at the Hospital Pediátrico David Bernardino in Luanda, Angola. With its 300 beds and 250 daily attendees of whom 70 are hospitalised, the institute is the largest pediatric referral center and teaching hospital in Angola. The ethics committee of the hospital approved the study protocol on 19.1.2012.

The study entry was assessed for all children aged 2 months to 15 years presenting with the symptoms and signs suggestive of BM to whom lumbar puncture was performed. The child was enrolled, if the cerebrospinal fluid (CSF) appeared cloudy, was positive by Gram staining or showed at least 50 leukocytes per mm^3. Exclusion criteria included previous known neurological abnormalities or hearing impairment, immunosuppression except for HIV infection, active tuberculosis, known hepatic disease, or pre-treatment with more than one dose of parenteral antibiotic. Before enrolment, the attending physician explained the study to the child's legal

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guardian, whose consent was expressed by a signature or, in case of illiteracy, a finger print. If participation was refused, the child was treated as routinely in the hospital.

The intention-to-treat population comprised all enrolled children, excluding the patients who succumbed before the initiation of treatment. The per-protocol analysis included the patients who received the allocated treatment and had confirmed BM, defined as a positive CSF culture or PCR; those with compatible symptoms and signs of BM and a positive blood culture; or the children with compatible symptoms and at least two of the following criteria: CSF pleocytosis ≥ 100 cells/mm3 (predominantly polymorphs), a positive CSF Gram stain result, a positive CSF latex agglutination test, or serum C-reactive protein (CRP) level ≥ 40 mg/L.

Basic laboratory analyses, bacterial cultures and sensitivity tests were performed at the hospital's laboratory with standard techniques. As of October 2016, CSF samples were also sent to the National Institute for Communicable Diseases in Johannesburg, South Africa, for identification of *N. meningitidis*, *S. pneumoniae* and *H.influenzae* by PCR [13].

Randomization and Masking

Randomization was done using a computer generated list in fixed blocks of 20 which allocated the participants in a 1:1 ratio. The code was kept in a sealed envelope in the office of the head of the hospital, and a copy was sent to the external Data Safety Monitoring Board for the interim analyses. For emergency purposes, the opening key was kept sealed also in Helsinki.

The cards disclosing the specific treatment were kept in sealed envelopes in a box at the hospital ward. Once the attending physician had included a patient in the study, an otherwise non-participating study nurse opened the next envelope, prepared the medications and placebos as advised, and gave the preparations for 96 hours (4 days). Thus, the patients, guardians, attending physicians and the investigators were kept blinded to the intervention.

For further masking, all children received both infusions and boluses intravenously for the entire 4-day course. Since the ready-to-use cefotaxime is slightly yellowish liquid, yellow i.v. lines (Becton-Dickinson GmbH, Art.No. 300326) and black 50 ml syringes (B Braun, Ref No 8728828F) were 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. This setup allowed the same one line for the antimicrobial and placebo administrations, each always given as infusion or boluses.

As black syringes and yellow i.v. lines were used, saline could be used as a placebo preparation for cefotaxime, no matter how administered. The oral acetaminophen solution from effervescent tablets looked like plain water once the bubbles had disappeared. Being practically tasteless, regular drinking water served as its placebo.

Procedures

All children were treated with cefotaxime in a dose of 250 mg/kg/24 hours for seven days. For the first four days, the children were randomized to receive the agent as a continuous intravenous infusion with high-dose acetaminophen orally (first dose 30 mg/kg, then 20 mg/kg every 6 hours for 4 full days), or as conventional intravenous boluses (62.5 mg/kg every 6 hours) with placebo orally. To prevent degradation of the antibiotic, the daily dose of cefotaxime was administered as two 12-hour infusions (125mg/kg each). The dissolved acetaminophen (Panadol®) tablets formed a solution with 10 mg/ml of acetaminophen.

Based on our previous studies [7, 11], all children were given oral glycerol (6.0g/kg per day divided into 4 equal doses, maximum dose of 25g) for 2 days. Antipyretics (besides scheduled acetaminophen as part of the intervention) were avoided. If hyperpyrexia or pain required medication, ibuprofen was given at a dose of 15mg/kg twice daily. Seizures were treated as was the routine in the hospital, most commonly with diazepam, while for malaria, quinine and artemisine

derivatives were used. A blood transfusion (10ml/kg) was administered to children with a haemoglobin level < 50 g/L, and sometimes also if considered clinically relevant. Fluid therapy aimed at normovolemia. Blood glucose was monitored four times daily, and hypoglycaemia was corrected with intravenous 10% glucose solution. All treatments were recorded in the specifically designed follow-up sheets.

Outcomes

The primary outcome measure was mortality by day seven in hospital. The secondary outcome measures included later in-hospital mortality, the composite outcomes of death or severe neurological sequelae (hydrocephalus, severe psychomotor retardation, quadriparesis, or blindness), and death or any neurological sequelae (hemi- or monoparesis, ataxia, or psychomotor retardation of any degree, besides the above-mentioned sequelae). The secondary neurological outcomes were recorded on day seven and at discharge from hospital.

We also aimed at measuring the hearing impairment quantitatively, but due to economical and practical constraints, precise audiological measurements were eventually performed only in a handful of survivors. Adverse events and the safety of our treatment were assessed as part of the detailed follow-up of all participants.

Statistical Analysis

Based on our previous study in Angola [11], we assumed to attain a 13% decrease in mortality with our intervention in patients with confirmed BM. Accepting a 5% error after adjustment for multiple testing in one-tailed test with a power of 80%, at least 165 patients were required in each treatment group. Because of several confounding factors, such as dissimilar age, severity on admission,

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malnutrition and malaria, we intended to enrol 400 patients. An external Data Safety Monitoring

Board obtained the 7-day results after each 100 patients had been evaluated. Had an indisputable

significance between the treatment modalities been found, the board would have interrupted

enrolment for ethical reasons.

Differences between the study groups regarding the in-hospital clinical course were assessed using

chi-square test or Mann-Whitney U test, as appropriate. Potential differences between the study

groups in terms of the primary and secondary outcomes were analysed by chi-square test, or in the

case of low expected cell values in the 2x2 table, Fisher's exact test. The treatment effects on the

primary and secondary outcomes were presented as risk ratios with 95% confidence intervals (CI);

the absolute risk difference and its confidence intervals were obtained using a 2-sample z-test.

Kaplan-Meier analysis and the log-rank test were used when comparing the time of death and

potential differences in survival, while treatment interactions between subgroups were examined

with logistic regression analysis. All subgroup analyses were predefined in the study protocol. P-

values < 0.05 were considered statistically significant, and to detect potential adverse effects of the

treatments, all analyses were conducted using a two-sided hypothesis. Furthermore, differences

between the participants of the current study and our previous trial in Luanda were assessed using

chi-square test or Mann-Whitney U test.

RESULTS

Recently commenced Hib and pneumococcal vaccinations in Angola had reduced the incidence of

BM to the extent that patient enrolment was extended to the predefined maximum of five years

(from January 22, 2012 to January 21, 2017). In all, 1128 children were assessed for eligibility, 753

were excluded, and 375 children were randomized into the treatment groups. Since two patients

succumbed before treatment initiation, 373 children comprised the intention-to-treat population (Figure 1).

Of those, 43 were protocol violators: in 16 cases paralytic ileus prevented oral administration, while the remaining 27 treatment failures were due to insurmountable practical difficulties such as dysfunctional intravenous lines. The number of treatment failures was similar in both treatment arms (Figure 1). Finally, our strict criteria for confirmed BM excluded additional 126 participants from the per-protocol population which ultimately comprised 204 children (Figure 1).

As summarized in Table 1, the patient characteristics and laboratory results proved similar in both groups. Since the median prehospital duration of illness was five days, the child was usually severely ill: 67% had suffered from seizures and some 1/3 showed focal neurological signs on admission. Malnutrition was common, and according to the WHO reference [14], 26% of the children presented with a weight-for-age Z-score under -2 SD. The causative agent was identified in 152/373 (41%) of cases, *S. pneumoniae* being the most common bacterium (Table 1). Interestingly, other not-so-common agents such as *Klebsiella spp.* (n = 6) and *Proteus spp.* (n = 6) were also detected.

After 7 days of treatment, 125 (34%) of the 373 patients had died. The composite outcomes of death or severe neurological sequelae (SeNeSe), and of death or any neurological sequelae (AnNeSe) were observed in 45% (155/345) and 54% (182/334) of the series, respectively (Table 2). As 21 patients succumbed after the first week, the final fatality rate increased to 39%. At discharge, 47% (175/369) of patients had either died or survived with severe neurological sequelae. Adding any neurological sequelae to the calculation, the proportion rose to 54% (193/360) (Table 2).

The day-7 mortality and the death rate at discharge were similar in the treatment groups (Table 2). Nor did their composite outcomes differ, albeit the effect of the interventional treatment seemed somewhat more consistent (all risk ratios staying below one) in the per-protocol population (Table

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2). Overall, our prolonged modified treatment did not show significant benefits, as depicted in Figure 2.

Since the prognosis of BM differs substantially in different populations, we also analysed certain predefined subgroups (Table 3). While the overall mortality varied largely, the given treatment did not relate to improved survival in any subgroup. Regarding the course of illness on the ward, ibuprofen was given more often in the control group, likely due to the higher need of antipyresis among these children (Table 4).

Potential adverse events of the treatments were registered as part of the normal follow-up. Furthermore, any abnormal signs of illness, not compatible with the diagnosis of meningitis, were registered in the follow-up sheet. In this regard, the groups did not differ.

DISCUSSION

No benefit from using prolonged four-day infusion of cefotaxime combined with oral acetaminophen was found in this trial on childhood BM in Luanda, Angola. Mortality and neurological sequelae remained the same regardless of whether cefotaxime with or without oral acetaminophen was administered conventionally in boluses every 6 hours, or as continuous infusion for four days.

Our rationale for using continuous infusion of antibiotic in BM relies, in addition to the pharmacodynamic advantages, also on relieving the initial inflammatory burst triggered by the strongly bacteriolytic β-lactam in the central nervous system. The basis for using oral acetaminophen at the same time laid, on the other hand, in the large retrospective study in which it significantly associated with decreased mortality in adult bacteraemia [12]. In our previous trial in Angola [11], an initial 24-hour cefotaxime infusion with the simultaneous 48-hour oral acetaminophen reduced BM mortality in children for several days – this effect being finally lost at discharge from hospital. It was

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thus logic to assume that prolonging our modified treatment would lead to permanent mortality decrease. As disappointing as it was, this was not the case here: no benefit was achieved with such a treatment prolongation.

To find explanations for this discrepancy, we searched for differences between these two patient populations (Supplementary Table 1 in Supplementary Material). Shortly, participants in this study arrived to hospital more severely ill, were more frequently malnourished and dehydrated, and clearly differed in etiology. The role of Hib meningitis was dramatically reduced while the proportion of less common meningitis agents increased, and more participants were left with an unknown bacterial etiology. The participants of this study were also older and had received pre-admission antibiotics more often, while compared to the participants of our previous trial.

Our interpretation is that many children here had already passed the moment when the new treatment would have had a potential to help the patient [15]. Of special note is our earlier finding that in childhood BM, the presenting condition surpasses all other cofactors predicting death, being as a single covariant even more important than the causative agent as such [9]. The major changes in bacterial etiology might also contribute to the discrepancy between our two trials.

Some correlation to the adult studies, in which continuous or prolonged antibiotic infusions have also led to non-consistent results, might here be justifiably drawn [16]. Slow, continuous infusion probably performs best in some patient subpopulations whose identification poses a challenge to future trials.

Successful Hib and pneumococcal vaccinations in Angola hindered our collection of the targeted minimum of 165 confirmed BM cases in both study groups. The large heterogeneous group, which was excluded from the per-protocol analysis, comprised children with diseases such as tuberculous meningitis, cerebral malaria and rabies – and among them there probably were some cases of partially treated BM as well. A major limitation was also the lack of adequate audiological

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measurements in survivors, which prevented us from evaluating the treatment's possible effect on hearing impairment.

All these shortcomings no doubt lessened the value of our observations. This said, however, our experience is a truthful description of the circumstances prevailing today in many sites of sub-Saharan Africa. Acknowledging the frequent lack of diagnostic tools and the challenging differential diagnostics, our intention-to-treat population probably well represents children who are treated for BM in these settings. Therefore, in spite of the large drop-out rate, we believe our main result remains valid and applicable for this kind of patient populations.

Our study underlines the gloomy prognosis of childhood BM in Angola. A continuous antibiotic infusion and oral acetaminophen did not improve the outcome of these severely ill children, who often came late for treatment. Since the prehospital delay is unbearably long, more efforts should be put into the parents' knowledge of the symptoms and signs of BM. Also better availability of healthcare would hasten the adequate treatment. Large-scale vaccinations against the relevant agents are good servants when combating this devastating disease.

NOTES

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TABLES

Table 1. Baseline patient characteristics of the intention-to-treat population

Characteristic	Bolus + placebo (N = 186)	Infusion + acetaminophen (N = 187)
Age in months (range)	31 (1-161)	28 (2-177)
Male sex	115 (62%)	101 (54%)
Weight-for-age under -2SD[a]	48 / 185 (26%)	48 / 186 (26%)
Duration of symptoms > 3 days[a]	116 / 181 (64%)	136 / 184 (74%)
Previous antibiotics[a]	73 / 165 (44%)	95 / 170 (56%)
Seizures before admission[a]	122 / 175 (70%)	116 / 178 (65%)
Glasgow Coma Scale score	11 (8-15)	12 (9-15)
Focal neurological signs[a]	53 / 181 (29%)	60 / 176 (34%)
Another focus of infection[a]	46 / 169 (27%)	62 / 178 (35%)
Dyspnoea[a]	111 / 177 (63%)	100 / 181 (55%)
Dehydration[a]	43 / 183 (23%)	46 / 182 (25%)
Blood test results:		
Hb (g/L)[b]	73 (60-92)	74 (62-89)
Leukocyte count (x 10^9/L)[b]	15.1 (9.0-21.0)	13.7 (8.8-19.7)
CRP (mg/L)[b]	160 (96 - >160)	160 (91 - >160)
Malaria test positive[c]	51 / 186 (27%)	40 / 187 (21%)
HIV test positive	4 / 98 (4%)	11 / 93 (12%)

CSF test results:

Leukocyte count (x 10^6/L)	495 (130-2770)	800 (140-2289)
Protein level (mg/dL)	197 (123-265)	187 (110-250)
Glucose level (mmol/L)	0.9 (0.5-2.7)	1.1 (0.5-2.4)
Causative agent		
Streptococcus pneumoniae (n=73)	38 (20%)	35 (19%)
Neisseria meningitidis (n=37)	21 (11%)	16 (9%)
Haemophilus influenzae (n=7)	4 (2%)	3 (2%)
Other bacteria (n=39)	16 (9%)	23 (12%)
Unknown (n=217)	107 (58%)	110 (59%)

Data are presented as number of patients (%) or median value (IQR), unless otherwise indicated.

[a]Denominator indicates the number of patients of whom the information was available

[b]Highest (CRP, leukocyte count) and lowest (Hb) value of days 1-2

[c]Positive malaria thick smear within first week in hospital

Table 2. The two treatment modalities *versus* the risk of adverse outcomes in the intention-to-treat and per-protocol populations

Outcome	Infusion + acetaminophen, % (n)	Bolus + placebo, % (n)	Risk Ratio (95% CI)	Absolute risk difference, % (95% CI)[a]
Intention-to-treat				
Day 7 death	32.6% (61/187)	34.4% (64/186)	0.95 (0.71 – 1.26)	1.8 (-7.8 – 11.4)
Death at discharge	38.0% (71/187)	40.3% (75/186)	0.94 (0.73 – 1.21)	2.3 (-7.6 – 12.2)
SeNeSe or death, day 7	46.5% (80/172)	43.4% (75/173)	1.07 (0.85 – 1.36)	3.1 (-7.4 – 13.6)
SeNeSe or death, at discharge	48.4% (90/186)	46.4% (85/183)	1.04 (0.84 – 1.29)	2.0 (-8.2 – 12.2)
AnNeSe or death, day 7	57.8% (96/166)	51.2% (86/168)	1.13 (0.93 – 1.38)	6.6 (-4.1 – 17.3)
AnNeSe or death, at discharge	57.5% (104/181)	49.7% (89/179)	1.16 (0.95 – 1.40)	7.8 (-2.5 – 18.1)
Per-protocol				
Day 7 death	30.6% (33/108)	34.4% (33/96)	0.89 (0.60 – 1.32)	3.8 (-9.1 – 16.7)
Death at discharge	33.3% (36/108)	37.5% (36/96)	0.89 (0.61 – 1.29)	4.2 (-8.9 – 17.3)
SeNeSe or death, day 7	40.6% (41/101)	44.8% (39/87)	0.91 (0.65 – 1.26)	4.2 (-10.0 – 18.4)

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SeNeSe or death, at discharge	42.6% (46/108)	45.2% (42/93)	0.94 (0.69 – 1.29)	2.6 (-11.2 – 16.4)
AnNeSe or death, day 7	53.1% (51/96)	54.8% (46/84)	0.97 (0.74 – 1.27)	1.7 (-12.9 – 16.3)
AnNeSe or death, at discharge	50.0% (52/104)	50.6% (45/89)	0.99 (0.75 – 1.31)	0.6 (-13.6 – 14.8)

[a]The absolute risk difference and its confidence intervals were obtained using a 2-sample z-test.

Abbreviations: SeNeSe, severe neurological sequelae; AnNeSe, any neurological sequelae

Table 3. Day 7 mortality in different patient subgroups

Variable	Bolus + placebo, % (n)	Infusion + acetaminophen, % (n)	Subgroup-specific	Test for interaction
Age			P[a]	P[b]
Age < 12 months (n = 107)	33% (18/54)	34% (18/53)	0.95	
Age ≥ 12 months (n = 265)	35% (46/132)	32% (42/133)	0.57	0.72
Presenting condition[c]				
GCS < 12 (n = 178)	49% (46/94)	49% (41/84)	0.99	
GCS ≥ 12 (n = 181)	20% (17/87)	17% (16/94)	0.66	0.74
Duration of illness before hospital admission[d]				
Ill ≤ 3 days (n = 113)	22% (14/65)	19% (9/48)	0.72	
Ill > 3 days (n = 252)	41% (47/116)	38% (51/136)	0.62	0.93
Weight-for-age Z-score[e]				
Slightly malnourished or normal (≥ -2 SD) (n = 275)	31% (43/137)	29% (40/138)	0.66	
Severely malnourished (< -2 SD) (n = 96)	42% (20/48)	42% (20/48)	1.00	0.82
Bacterial etiology				
Streptococcus pneumoniae (n = 73)	45% (17/38)	34% (12/35)	0.36	
Non-pneumococcal or unknown (n	32% (47/148)	32% (49/152)	0.93	0.40

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= 300)

These subgroup analyses were predefined, and conducted within the intention-to-treat population.

[a]Obtained using a chi-squared test within the subgroup

[b]Calculated, using logistic regression analysis, for interaction between each variable and the

treatment

[c]Data on the GCS score was missing from 14 participants

[d]Duration of illness unknown in 8 participants

[e]Information missing from 2 participants

Abbreviations: GCS, Glasgow Coma Scale score

Table 4. Course of illness in hospital

Variable	Bolus + placebo	Infusion + acetaminophen	P[a]
Duration of fever (days)	2 (1-3)	2 (1-3)	1.00
Duration of GCS < 15 (days)	3 (1-5)	2 (1-5)	0.45
Seizures	130 / 185 (70%)	123 / 185 (67%)	0.43
Focal neurological signs	76 / 181 (42%)	79 / 175 (45%)	0.55
Duration of survivors' hospital stay (days)	12 (10-17)	14 (10-20)	0.14
Non-study treatments given			
Supplementary oxygen	76 / 186 (41%)	76 / 186 (41%)	1.00
Blood transfusion	44 / 186 (24%)	47 / 187 (25%)	0.74
Anticonvulsive medication	89 / 185 (48%)	87 / 186 (47%)	0.80
Malaria treatment	92 / 186 (50%)	90 / 187 (48%)	0.80
Ibuprofen, during first four days	71 / 185 (38%)	49 / 187 (26%)	0.01
Additional antibiotic treatment (after first seven days)	70 / 184 (38%)	79 / 186 (43%)	0.39
Tuberculosis treatment	11 / 185 (6%)	15 / 187 (8%)	0.43

Data are displayed as number of patients (%) or median value (IQR).

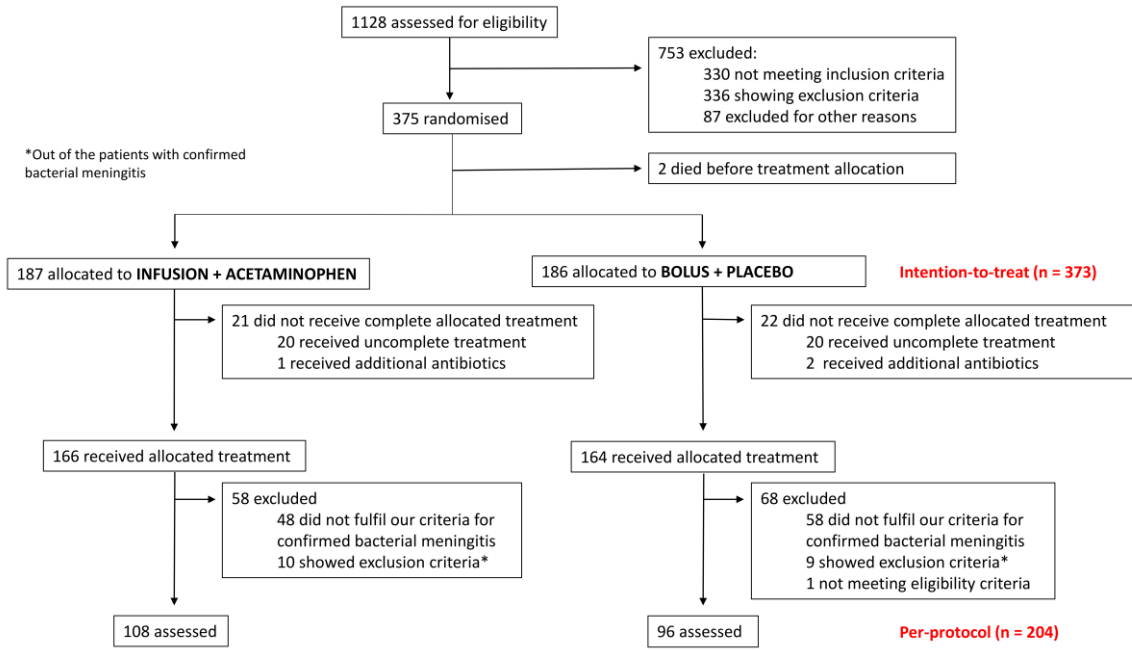[a]Obtained using chi-square test or Mann-Whitney U test, as appropriate

Abbreviations: GCS, Glasgow Coma Scale score

FIGURE LEGENDS

Figure 1. Flowchart of patient inclusion

Figure 2. Mortality curves for intention-to-treat (A) and per-protocol (B) populations,

shown for the first 7 days. Ticks indicate censored participants.

Figure_1

1128 assessed for eligibility

753 excluded:
330 not meeting inclusion criteria
336 showing exclusion criteria
87 excluded for other reasons

375 randomised

2 died before treatment allocation

*Out of the patients with confirmed bacterial meningitis

187 allocated to **INFUSION + ACETAMINOPHEN**

186 allocated to **BOLUS + PLACEBO**

Intention-to-treat (n = 373)

21 did not receive complete allocated treatment
20 received uncomplete treatment
1 received additional antibiotics

22 did not receive complete allocated treatment
20 received uncomplete treatment
2 received additional antibiotics

166 received allocated treatment

164 received allocated treatment

58 excluded
48 did not fulfil our criteria for confirmed bacterial meningitis
10 showed exclusion criteria*

68 excluded
58 did not fulfil our criteria for confirmed bacterial meningitis
9 showed exclusion criteria*
1 not meeting eligibility criteria

108 assessed

96 assessed

Per-protocol (n = 204)

27

Figure_2