Slow initial β-lactam infusion and oral paracetamol to treat childhood bacterial meningitis: a randomised, controlled trial

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Summary

Background **New antimicrobials or adjunctive treatments have not substantially reduced mortality from acute childhood bacterial meningitis. Paracetamol seems to have beneficial effects in bacteraemic adults and some experts recommend initial slow β-lactam infusion. We investigated whether these treatments had benefits in children with bacterial meningitis.**

Methods **We did a prospective, double-blind, single-centre study with a two-by-two factorial design in Luanda, Angola. 723 participants aged 2 months to 13 years were randomly assigned two 12 h intravenous infusions, without loading doses, of 125 mg/kg bodyweight cefotaxime (total dose 250 mg/kg) given over 24 h, or 250 mg/kg bodyweight cefotaxime given as four boluses, one every 6 h over 24 h. Patients also received oral paracetamol at an initial dose of 30 mg/kg then 20 mg/kg every 6 h for 48 h or placebo. Two primary endpoints, death or severe neurological sequelae and deafness, were analysed by intention to treat. The study was registered as ISRCTN62824827.**

Findings **183 patients were assigned cefotaxime infusion plus paracetamol and 180 patients to each of the other three treatment groups. Causative agents were identified in 63% of cases and were mostly *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, or *Neisseria meningitidis*. Death or severe neurological sequelae were seen in 340 (47%) of 723 children and deafness in 45 (12%) of 374 tested, both distributed similarly across treatment groups. In a predefined subgroup analysis of death or any sequelae, by causative agent, a benefit was seen in favour of infusion over bolus in children with pneumococcal meningitis (infusion plus placebo, odds ratio 0·18, 95% CI 0·03–0·90, p=0·04). A similar effect was seen for children receiving cefotaxime infusion plus paracetamol, but the difference was not significant (OR 0·22, 95% CI 0·04–1·09, p=0·06). A post-hoc analysis suggested that cefotaxime infusion plus paracetamol lowered mortality at least during the first 3 days, irrespective of cause.**

Interpretation **Although no tested regimen improved the final outcomes of these very ill children, studies of longer courses of β-lactam infusion plus paracetamol seem warranted.**

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Introduction

Acute childhood bacterial meningitis is a devastating disease in Africa[1–3] and elsewhere in low-income countries. The most common type of bacterial meningitis is pneumococcal meningitis. About 50% of children who develop pneumoccocal meningitis die and around 60% of survivors develop sequelae. New antimicrobials have not reduced mortality[4] and new adjuvant treatments are being sought. Dexamethasone lowers the host's inflammatory response,[5] but no paediatric study with sufficient statistical power has shown a major clinical benefit in the relief from or prevention of sequelae.[6–8] A large randomised, double-blind study in South America showed that oral glycerol was significantly associated with prevention of neurological sequelae,[9] but improved treatment of bacterial meningitis is still urgently needed.

The effectiveness of β-lactam antibiotics correlates with the duration that drug concentrations are higher than the minimum inhibitory concentrations in plasma. By convention these drugs are given as intermittent bolus every 4–6 h, but whether the effects are optimum with this regimen has been questioned.[10] Bolus administration triggers massive bacterial lysis and release of toxic cell-wall components into the bloodstream,[11–13] to which the host responds with an acute inflammatory reaction. An important feature of β lactams is that low doses effectively kill growing bacteria without major degradation,[14] and several small studies have shown that slow, continuous infusion is safe and at least as effective as intermittent administration.[10,15–20] However, sufficiently powered randomised studies are lacking.[15,18] Specifically, continuous infusion of β lactams in bacterial meningitis has not been investigated.

Outcomes with infused β lactams might be improved by concomitant administration of an anti-inflammatory agent. Retrospective analyses in Finland of 809 adult patients with bacteraemia showed that more patients treated with antibiotics who also received paracetamol survived than did those who received other non-steroidal anti-inflammatory agents.[21,22] The effect

was independently associated with a reduced risk of death (p=0·001).

We investigated whether the prognosis of childhood bacterial meningitis in the children in greatest need could be improved with a slow initial β-lactam infusion plus paracetamol.

Methods

Study design and patients

We did a prospective, randomised, double-blind, placebo-controlled, single-centre study with a two-by-two factorial design. The Luanda Children's Hospital's ethics committee approved the study on June 22, 2005, and an amendment with some substudies was added on Dec 21, 2007. Before the study, attending physicians were trained to do lumbar punctures and to check plasma haemoglobin and blood glucose concentrations, malaria thick film, and concentrations of C-reactive protein in serum.

All children aged 2 months to 13 years who attended the Luanda Children's Hospital, Luanda, Angola, between July 18, 2005, and June 26, 2008, with signs and symptoms of bacterial meningitis and a cerebrospinal fluid (CSF) sample that was cloudy, positive for Gram-staining, or contained more than 50×10⁶/L white blood cells (predominantly polymorphs) were screened for inclusion in the study. The exclusion criteria were trauma, intracranial shunt, previous neurological disorders, hearing impairment, and immunosuppression except for in patients with HIV infection. Parenteral antimicrobials are used indiscriminately in Angola and, therefore, one parenteral dose of one drug was allowed before treatment.

The diagnosis of bacterial meningitis was made by an attending physician. Bacterial meningitis was defined as positive CSF culture, positive PCR for CSF antigen, or positive blood culture in a child with compatible symptoms and signs, or at least two of the following: leucocyte concentrations in CSF exceeding 100×10⁶/L (predominantly polymorphs), CSF positive for Gram-staining, a positive latex agglutination test, or serum C-reactive protein concentration higher than 381 nmol/L (40 mg/L).[9] Basic bacteriology and sensitivity tests were done locally but some strains were transferred to the National Institute of Health, Lisbon, Portugal, for further investigation.

Before enrolment, trained attending physicians explained the study to the child's parent or guardian and obtained written informed consent, or a finger print on the form for those who were illiterate.

Randomisation and masking

A randomisation sequence for 1000 patients was generated by people independent of the study in Luanda. By means of a table of random numbers in blocks of 20, the patients were allocated equally (1:1:1:1) to four treatment groups: cefotaxime infusion plus paracetamol or placebo or bolus plus paracetamol or placebo. The treatment code was kept on site in a sealed envelope, and a copy was sent to an independent data safety monitoring board.

Treatment allocation was concealed with sealed, sequentially numbered envelopes, in a box on the meningitis ward. After a patient had been enrolled a specific ward nurse, who otherwise did not participate in the study, opened the next envelope and prepared medications for the first 48 h according to the treatment

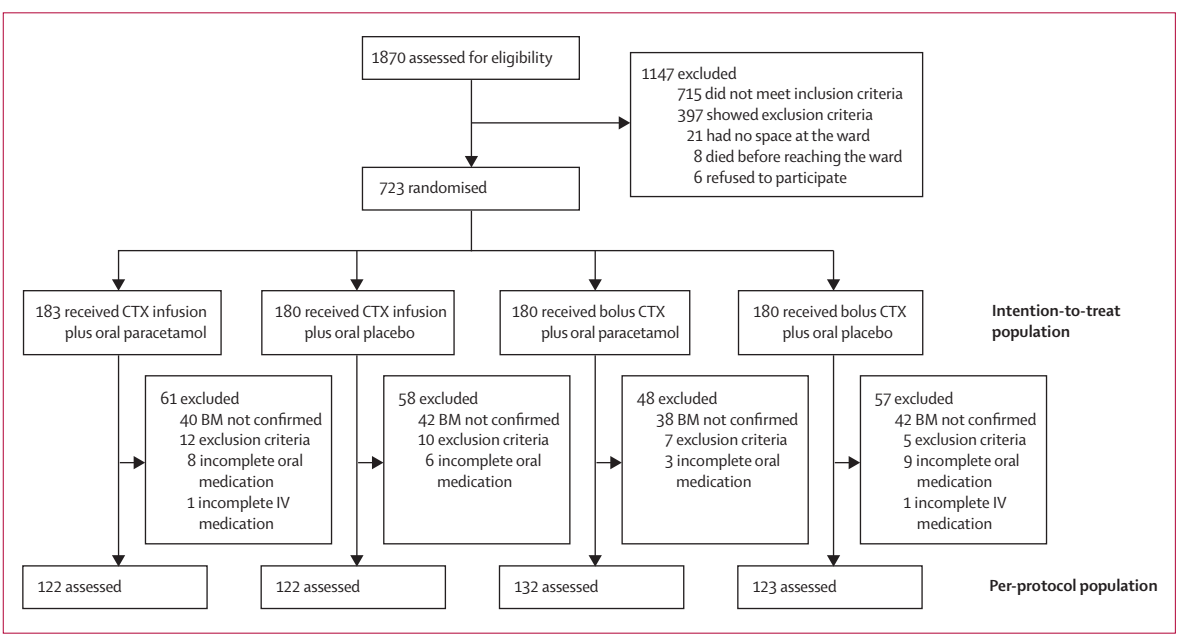

Figure 1: **Trial profile**
CTX=cefotaxime. BM=bacterial meningitis. IV=intravenous.

allocation. Yellow infusion lines, black 50 mL syringes (for infusions), and a foil covering on the three-way stopcocks short end leading to the skin-penetrating needle (for boluses) were used to prevent distinction of the slightly yellowish cefotaxime from the colourless saline placebo. Paracetamol was given as effervescent tablets because the solution had little taste and looked like the plain-water placebo once dissolved.

The data safety monitoring board had the treatment code opened and did planned interim analyses after each 100 new patients were enrolled. The study was to be interrupted if any significant differences were detected between groups.

Treatment

Children first received two 12 h infusions, without loading doses, of 125 mg/kg bodyweight cefotaxime (to prevent degradation) over 24 h or 250 mg/kg bodyweight cefotaxime given as four intravenous boluses, one every 6 h, over 24 h. Electric infusers were used to ensure steady dosing. After 24 h all patients received the 250 mg cefotaxime bolus regimen for 6 days, except those with salmonella meningitis, for whom the course lasted 14 days. Paracetamol was given at an initial dose of 30 mg/kg bodyweight and 20 mg/kg every 6 h for 48 h thereafter. Administration was via the oral route, or a nasogastric tube if necessary.

Concomitant treatments were kept to a minimum. Oral glycerol was started in all children at a minimum of 1·5 g or 1·5 mL/kg and up to 25 mL per dose, and given four times daily for 2 days. Ibuprofen was given for high fever and pain, intravenous diazepam, phenobarbitone, or both were used for seizures. Malaria was treated with quinine (unconscious children), sulfadoxine-pyrimethamine, artemisine derivatives, or chloroquine. Oxygen was given to severely ill patients, and those with dyspnoea.

Hypovolaemia was corrected with Ringer's fluid, and normovolaemia was maintained without reducing volumes. Blood was transfused if haemoglobin concentration decreased to 50 g/L. Hypoglycaemia was corrected by intravenous administration of 10% glucose solution.

Liaison staff checked the patients daily and ordered full blood counts, urine analysis, and HIV and tuberculin

	Cefotaxime infusion		Cefotaxime boluses	
	With oral paracetamol (n=183)	With oral placebo (n=180)	With oral paracetamol (n=180)	With oral placebo (n=180)
Median (range) age (months)	17 (1–157)	15 (2–154)	11 (1–146)	13 (2–146)
Male sex	107 (58%)	94 (52%)	90 (50%)	95 (53%)
Weight for age <–2 SD of the median	55 (30%)	55 (31%)	56 (31%)	64 (36%)
Duration of symptoms >3 days*	107/181 (59%)	129 (72%)	112 (62%)	108/179 (60%)
Previous antibiotics*†	73/171 (43%)	62/171 (36%)	64/171 (37%)	72/166 (43%)
Seizures before admission†	122 (67%)	132 (73%)	126 (70%)	126 (70%)
Glasgow coma score	11 (8–15)	12 (8–15)	12 (8–15)	10 (8–15)
Focal neurological signs	40 (22%)	43 (24%)	50 (28%)	41 (23%)
Another focus of infection	43 (23%)	46 (26%)	38 (21%)	55 (31%)
Dyspnoea	90 (49%)	78 (43%)	75 (42%)	90 (50%)
Dehydration	31 (17%)	34 (19%)	23 (13%)	28 (16%)
Blood				
Haemoglobin concentrations (g/L)	77 (66–85)	80 (65–90)	80 (67–90)	74 (60–85)
Glucose concentration (mmol/L)	4·6 (3·3–5·7)	4·7 (3·5–5·9)	4·6 (3·3–6·2)	4·6 (3·3–5·9)
Malaria parasites*	58/176 (33%)	51/168 (30%)	55/175 (31%)	58/175 (33%)
HIV positive*	11/143 (8%)	10/126 (8%)	11/137 (8%)	9/123 (7%)
Tuberculin test ≥10 mm*	17/113 (15%)	18/100 (18%)	12/95 (12%)	8/97 (8%)
Cerebrospinal fluid				
Leucocyte count (×10^6/L)	565 (160–1800)	873 (210–2897)	836 (230–2680)	980 (155–2945)
Glucose concentration (mmol/L)	0·8 (0·4–1·7)	0·8 (0·4–1·7)	0·7 (0·3–1·4)	0·9 (0·4–1·8)
Causative agent				
Haemophilus influenzae type b (n=188)	41 (22%)	46 (26%)	54 (30%)	47 (26%)
Streptococcus pneumoniae (n=184)	54 (30%)	38 (21%)	39 (22%)	53 (30%)
Neisseria meningitidis (n=49)	13 (7%)	16 (9%)	11 (6%)	9 (5%)
Other (n=32)	8 (4%)	10 (5%)	8 (4%)	6 (6%)
Unknown (n=270)	67 (37%)	70 (39%)	68 (38%)	65 (36%)

Data are number (%) or median (IQR), unless otherwise indicated. *Numbers of patients for whom data were available are shown. †During present illness.

Table 1: **Baseline characteristics of the patients in the intention-to-treat population**

	Cefotaxime infusion		Cefotaxime boluses	
	With oral paracetamol (n=183)	With placebo (n=180)	With oral paracetamol (n=180)	With placebo (n=180)
Duration of fever (days)	3·0 (2·0–5·0)	3·0 (1·0–5·0)	3·0 (1·0–5·0)	2·0 (1·0–5·0)
Secondary fever after 1 week*	53/126 (42%)	45/116 (39%)	41/115 (36%)	35/114 (31%)
Duration of Glasgow coma score <15 (days)	2·0 (1·0–5·0)	2·0 (1·0–5·0)	2·0 (1·0–5·0)	2·0 (1·0–5·0)
Seizures	107 (58%)	112 (62%)	115 (64%)	96 (53%)
Another focus of infection	99 (54%)	100 (56%)	106 (59%)	109 (61%)
Dehydration	74 (40%)	68 (38%)	61 (34%)	68 (38%)
Oedema	27 (15%)	32 (18%)	29 (16%)	22 (12%)
Non-study treatments				
Anticonvulsants	121 (66%)	107 (59%)	112 (62%)	107 (59%)
Supplementary oxygen	105 (57%)	111 (62%)	101 (56%)	106 (59%)
Malaria treatment	110 (63%)	92 (51%)	92 (51%)	99 (55%)
Blood transfusion	64 (35%)	60 (33%)	61 (34%)	62 (34%)
Ibuprofen during first 48 h	15 (8%)	21 (12%)	18 (10%)	23 (13%)
Second-line antimicrobials	46 (25%)	41 (23%)	41 (23%)	31 (17%)
Mortality	61 (33%)	73 (41%)	69 (38%)	69 (38%)
Haemophilus influenzae type b*	12/41 (29%)	18/46 (39%)	16/54 (30%)	16/47 (34%)
*Streptococcus pneumoniae**	21/54 (39%)	16/38 (42%)	19/39 (49%)	26/53 (49%)
*Neisseria meningitidis**	1/13 (8%)	1/16 (6%)	2/11 (18%)	3/9 (33%)
Other*	5/8 (63%)	5/10 (50%)	5/8 (63%)	4/6 (67%)
Unknown*	22/67 (32%)	33/70 (47%)	27/68 (40%)	20/65 (31%)
Severe neurological sequelae†	21/122 (17%)	13/107 (12%)	21/111 (19%)	13/111 (12%)
Haemophilus influenzae type b	5/29 (17%)	2/28 (7%)	7/38 (18%)	3/31 (10%)
Streptococcus pneumoniae	5/33 (15%)	5/22 (23%)	4/20 (20%)	5/27 (19%)
Neisseria meningitidis	0/12 (0%)	0/15 (0%)	1/9 (11%)	0/6 (0%)
Other	0/3 (0%)	2/5 (40%)	1/3 (33%)	0/2 (0%)
Unknown	11/45 (24%)	4/37 (11%)	8/41 (20%)	5/45 (11%)
Deafness‡	13/102 (13%)	11/94 (12%)	10/88 (11%)	11/90 (12%)
Haemophilus influenzae type b	2/23 (9%)	3/23 (13%)	4/30 (13%)	4/24 (17%)
Streptococcus pneumoniae	5/27 (19%)	4/20 (20%)	2/17 (12%)	3/22 (14%)
Neisseria meningitidis	1/11 (9%)	2/14 (14%)	0/7 (0%)	0/5 (0%)
Other	0/3 (0%)	0/5 (0%)	0/2 (0%)	1/2 (50%)
Unknown	5/36 (14%)	2/30 (7%)	4/32 (13%)	3/36 (8%)

Data are number (%) or median (IQR). *Numbers of patients for whom data were available are shown. †Blindness, quadriplegia or paresis, hydrocephalus requiring a shunt, or severe psychomotor retardation. Totals based on 451 surviving children. †Threshold >80 dB in better ear. Totals based on 374 survivors with hearing tested.

***Table 2*: Clinical course and outcome of disease in the intention-to-treat population**

test. Lumbar punctures were scheduled to be done by attending physicians on day 7. At discharge a thorough neurological examination was done by a liaison staff member. Brain stem auditory evoked potentials and transient evoked otoacoustic emissions were measured with MADSEN Octavus and MADSEN Accuscreen (Otometrics, Taastrup, Denmark), respectively, within 24 h of admission, on day 7, and at scheduled follow-up visits at 1, 3, 6, and 12 months after discharge. All adverse events potentially associated with the treatments were recorded on a special follow-up form.

The study had two primary endpoints: the first comprised death or severe neurological sequelae, defined as blindness, quadriplegia or paresis, hydrocephalus requiring a shunt, or severe psychomotor retardation, and the second was deafness (hearing threshold >80 dB in the better ear). The secondary endpoint comprised death or any audiological (>40 dB) or neurological sequelae (hemiparesis, monoparesis, psychomotor retardation of any degree, ataxia, or severe neurological sequelae). Times of deaths were recorded. All outcomes were checked at discharge from hospital and analysed by intention to treat.

Statistical analysis

We calculated that at least 176 patients with confirmed meningitis needed to be recruited to each infusion and each bolus group to detect a 15% decrease (from 45% to 30%) in either of the two primary endpoints in favour of cefotaxime infusion, when assessed by a two-tailed test

	Number of patients assessed	Cefotaxime infusion				Cefotaxime boluses with oral paracetamol (n=180)	
		With oral paracetamol (n=183)		With oral placebo (n=180)		Odds ratio (95% CI)	p
		Odds ratio (95% CI)	p	Odds ratio (95% CI)	p		
Death or severe neurological sequelae							
Intention-to-treat overall	723	0·97 (0·64–1·47)	0·89	1·09 (0·72–1·66)	0·67	1·20 (0·79–1·81)	0·40
Per-protocol overall	499	0·92 (0·55–1·54)	0·74	1·08 (0·66–1·80)	0·75	1·24 (0·76–2·04)	0·39
Intention-to-treat *S pneumoniae*	184	0·66 (0·31–1·42)	0·28	0·88 (0·38–2·03)	0·76	1·02 (0·44–2·36)	0·96
Per-protocol *S pneumoniae*	160	0·61 (0·26–1·41)	0·25	0·87 (0·36–2·11)	0·75	1·13 (0·47–2·71)	0·79
Deafness							
Intention-to-treat overall	374	1·05 (0·45–2·48)	0·91	0·95 (0·39–2·32)	0·91	0·92 (0·37–2·29)	0·86
Per-protocol overall	267	0·97 (0·35–2·68)	0·95	0·82 (0·28–2·40)	0·71	0·83 (0·28–2·44)	0·73
Intention-to-treat *S pneumoniae*	86	1·44 (0·30–6·83)	0·65	1·58 (0·31–8·15)	0·58	0·84 (0·13–5·72)	0·86
Per-protocol *S pneumoniae*	78	1·58 (0·33–7·59)	0·57	1·20 (0·21–6·84)	0·84	0·43 (0·04–4·58)	0·48
Death or any sequelae							
Intention-to-treat overall	676	1·06 (0·62–1·83)	0·83	0·81 (0·48–1·37)	0·43	0·98 (0·57–1·69)	0·95
Per-protocol overall	470	0·81 (0·41–1·58)	0·81	0·61 (0·32–1·16)	0·61	0·87 (0·45–1·70)	0·68
Intention-to-treat *S pneumoniae*	176	0·22 (0·04–1·09)	0·06	0·18 (0·03–0·90)	0·04	0·26 (0·05–1·43)	0·12
Per-protocol *S pneumoniae*	153	0·22 (0·04–1·13)	0·07	0·21 (0·04–1·11)	0·07	0·28 (0·05–1·54)	0·14

Table 3: **Endpoint outcomes in study treatment groups in the whole series and in children with pneumococcal meningitis**

with a power of 80%. To allow for a 5% error after adjustment for multiple testing (two endpoints and infusion *vs* bolus, and paracetamol *vs* placebo) we intended to enrol 750 patients.

Patients enrolled after initial screening and assigned to one of the four treatment groups before confirmation of bacterial meningitis formed the intention-to-treat cohort, and those in whom bacterial meningitis was confirmed formed the per-protocol group (figure 1). Interactions between infused cefotaxime and paracetamol were tested with two-way ANOVA. We used a χ^2 test to compare categorical primary and secondary outcomes for infusion with those for bolus and for paracetamol with those for placebo. Logistic regression was used to compare the primary and secondary outcomes in the treatment groups, with the cefotaxime bolus and oral placebo group as the reference group. Results are shown as odds ratios (OR) with 95% CI. The predefined subgroup analyses covered the causative agent and time of death within 6 h, within 12 h, or beyond 12 h. We used Kaplan-Meier analysis to assess mortality and Fisher's exact and sign tests for exploratory analysis of time of death beyond the predefined time-frames. The data were analysed with StatView (version 5.1). This trial is registered with the International Standard Randomized Controlled Trial Number Register, number ISRCTN62824827.

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1870 children with suspected meningitis were admitted to the hospital during the study period and were screened. 723 had suspected bacterial meningitis and were enrolled into the intention-to-treat dataset (figure 1). Of the 715 patients who were excluded at screening because they did not fulfil the inclusion criteria, the CSF findings suggested other diagnoses, such as cerebral malaria or convulsions due to other causes, in 458, the parents or guardians were unable to define previous treatments for 229, and no lumbar puncture was done in 28. Similar numbers of patients were assigned to all treatment groups (figure 1). The characteristics of patients in all groups were similar at presentation (table 1). Infective agents were identified in 453 (63%) patients, among whom *Haemophilus influenzae* type b was the most common, followed by *Streptococcus pneumoniae*, *Neisseria meningitidis*, and other bacteria, which were mostly *Proteus* spp or *Klebsiella* spp. 271 (40%) of 679 patients with data available had been treated with antimicrobials before enrolment. In the ward, ibuprofen was given to 77 (11%) of 723 children overall—33 (9%) of 363 in the paracetamol group, and 44 (12%) of 360 in the placebo group.

272 (38%) children died. Severe neurological sequelae were seen in 68 (15%) of the 451 surviving children (table 2). Any neurological sequelae were seen in 240 (53%) of the 451 survivors. Hearing was tested in 374 (83%) survivors, but only for 80 dB in 23 of these. 45 (12%) had deafness at a threshold higher than 80 dB

(table 2), and 96 (27%) of 351 had some degree of hearing loss (threshold in better ear >40 dB). 374 (56%) of 663 died or were discharged with severe neurological sequelae or deafness. Overall, 540 (80%) of 676 children died or returned home with some or severe neurological sequelae or with audiological impairment.

No significant differences were seen between groups for any of the primary or secondary endpoints. The outcomes for the intention-to-treat and per-protocol groups, overall and for children infected with *S pneumoniae*, are shown in table 3. In the children with pneumococcal meningitis, the risk of death or any sequelae was lower in the cefotaxime infusion plus placebo group than in the cefotaxime bolus plus placebo group (OR 0·18, 95% CI 0·03–0·90, p=0·04). A similar effect was seen for children receiving cefotaxime infusion and oral paracetamol, but the difference did not quite reach significance.

No differences were seen between groups for time of death, according to the predefined timepoints. Groups also did not differ overall in the Kaplan-Meier analysis (figure 2). However, mortality was significantly lower for 3 days among children receiving cefotaxime infusion and paracetamol than in the other groups, irrespective of the causative agent (figure 2).

In a post-hoc analysis, when compared with cefotaxime bolus plus placebo, mortality was clearly reduced at 48 h in the group that received cefotaxime infusion with paracetamol (OR 0·45, 95% CI 0·26–0·77, p=0·003), and at 72 h (0·52, 0·32–0·85, p=0·009; table 4). The differences between the cefotaxime infusion and

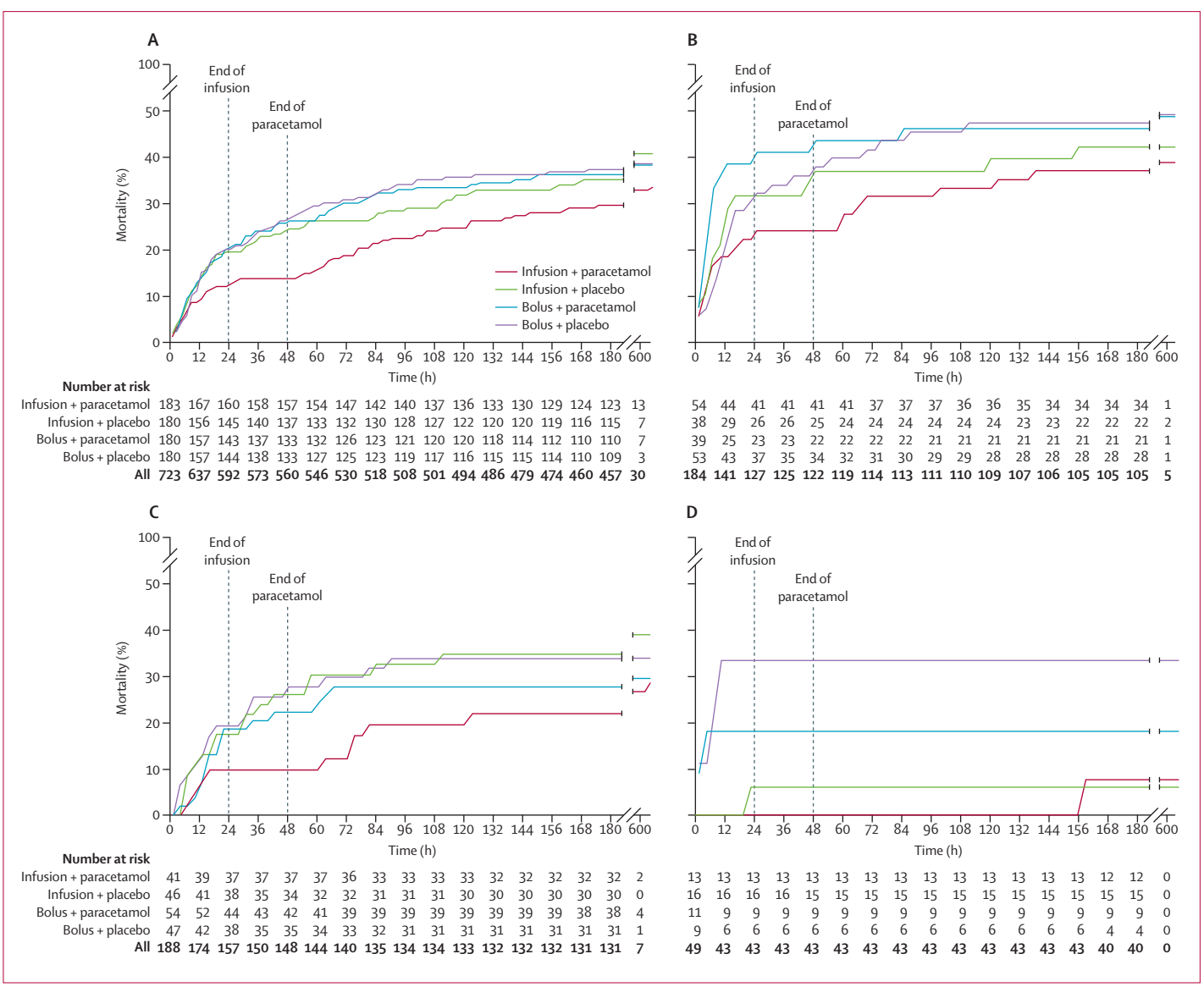

***Figure 2*: Mortality curves for per-protocol population**
(A) All children (n=723), (B) with pneumococcal (n=184), (C) with *Haemophilus influenzae* type b (n=188), and (D) with meningococcal meningitis (n=49).

	Number of patients assessed	Cefotaxime infusion				Cefotaxime boluses with oral paracetamol (n=180)	
		With oral paracetamol (n=183)		With oral placebo (n=180)		Odds ratio (95% CI)	p
		Odds ratio (95% CI)	p	Odds ratio (95% CI)	p		
Total mortality							
Intention-to-treat overall	723	0·80 (0·52–1·24)	0·32	1·10 (0·72–1·68)	0·67	1·00 (0·65–1·53)	>0·99
Per-protocol overall	499	0·84 (0·50–1·43)	0·53	1·13 (0·67–1·89)	0·66	1·06 (0·64–1·77)	0·82
Intention-to-treat *S pneumoniae*	184	0·66 (0·31–1·42)	0·29	0·76 (0·33–1·75)	0·51	0·99 (0·43–2·26)	0·97
Per-protocol *S pneumoniae*	160	0·64 (0·27–1·50)	0·30	0·83 (0·34–2·04)	0·69	1·26 (0·53–2·99)	0·61
48 h							
Intention-to-treat overall	723	0·45 (0·26–0·77)	0·003	0·89 (0·55–1·43)	0·63	1·00 (0·63–1·60)	>0·99
Per-protocol overall	499	0·48 (0·26–0·91)	0·02	1·01 (0·58–1·77)	0·97	1·06 (0·61–1·83)	0·84
Intention-to-treat *S pneumoniae*	184	0·57 (0·25–1·31)	0·19	0·93 (0·39–2·23)	0·87	1·38 (0·59–3·22)	0·45
Per-protocol *S pneumoniae*	160	0·57 (0·22–1·44)	0·23	0·90 (0·35–2·30)	0·82	1·59 (0·66–3·87)	0·30
72 h							
Intention-to-treat overall	723	0·52 (0·32–0·85)	0·009	0·80 (0·51–1·27)	0·35	0·97 (0·62–1·53)	0·91
Per-protocol overall	499	0·55 (0·30–0·99)	0·04	0·97 (0·57–1·68)	0·92	1·01 (0·59–1·71)	0·98
Intention-to-treat *S pneumoniae*	184	0·65 (0·29–1·43)	0·28	0·82 (0·35–1·94)	0·65	1·09 (0·47–2·51)	0·84
Per-protocol *S pneumoniae*	160	0·60 (0·25–1·47)	0·27	0·85 (0·34–2·13)	0·73	1·32 (0·55–3·18)	0·53

Table 4: **Mortality in hospital, overall and at 48 and 72 h, in the whole series and in children with pneumococcal meningitis for three study treatment groups**

paracetamol recipients and all other groups were greatest at 24 h (p=0·041), 48 h (p=0·0005), and 72 h (p=0·005).

Cefotaxime infusion, with or without paracetamol, was associated with lower mortality from 4 h to 48 h than was cefotaxime bolus, with or without paracetamol (54 [15%] of 363 *vs* 80 [22%] of 360, p=0·01). After 48 h, however, mortality reversed (66 [18%] of 363 *vs* 44 [12%] of 360, p=0·03). Paracetamol alone also showed a salutary effect since, for the first 6–60 h 53 (15%) of 363 paracetamol recipients died, compared with 81 (23%) of 360 placebo recipients (p=0·006).

No significant adverse events attributable to the study interventions were noted.

Discussion

We investigated the efficacy of β-lactam infusion to treat bacterial meningitis and whether concomitant high-dose oral paracetamol would add any benefits to this regimen. Overall, however, the risks of mortality, or neurological sequelae and deafness were not reduced.

The rationale behind expecting benefits from slow infusion of cefotaxime, a time-dependent antimicrobial, was that a massive inflammatory reaction might be lessened or avoided. A rabbit model of pneumococcal bacterial meningitis has demonstrated that killing bacteria without maximum cell degradation lowers the severity of inflammation and the number of neurons lost.[23]

The clinical evidence for beneficial effects with continuous β-lactam infusion is not overwhelming,[10,15,18,19] but results of several pharmacokinetic and pharmacodynamic studies favour this approach.[10,14,19,20] Clinical effectiveness is not reduced by use of infusion.[18] One therapeutic intervention occasionally produces a notable change in outcomes in critically ill patients. Thus, we kept all concomitant medications to a minimum to obtain clearcut results.

Continuous β-lactam infusion is safe, sustains necessary serum concentrations, achieves sufficient tissue levels,[20] enables a reduction in daily dose,[16,19,20] is cost effective,[24] is probably more efficacious against resistant organisms than bolus administration, and might slow the development of resistance.[25] Most patients are not sufficiently ill to benefit from infusion, but in life-threatening circumstances the situation might be profoundly different.

The non-steroidal anti-inflammatory drug ibuprofen inhibits cyclo-oxygenase (COX), an enzyme that mediates the production of prostaglandins, which are important facilitators of inflammation. However, in one randomised, placebo-controlled sepsis trial ibuprofen did not improve survival.[26] Instead, paracetamol, which is not deemed a classic non-steroidal anti-inflammatory drug, was associated with lowered mortality in adult patients with bacteraemia.[21,22] Paracetamol inhibits several COX enzymes, including COX-3,[27] which is exclusive to the CNS. The COX enzymes are highly active only when appropriately oxidised and, because paracetamol inhibits these activated forms, the concentrations of proinflammatory factors are also reduced.[28] These inhibitory properties might have played a part in the outcomes of our patients.

Paracetamol is generally very safe for children.[29] In the tropics, *Plasmodium falciparum* malaria is an important disease to be distinguished from meningitis. Paracetamol ostensibly prolongs the parasite's clearance time,[30] but

Panel: Research in context

Systematic review

References for this Article were identified by searches of Medline and PubMed for the terms "bacterial meningitis" or "bacteremia/sepsis" in conjunction with "therapy", "continuous infusion", "paracetamol", or "child". Relevant original or review references were selected on the basis of the aims of the Article. Continuous β-lactam infusion has proved at least as effective as traditional bolus administration in small series of critically ill patients or those with septicaemia. Paracetamol was associated with reduced mortality in adults with bacteraemia.

Interpretation

Our prospective, randomised, controlled trial was done to investigate the effects of initial β-lactam infusion over 24 h and high-dose paracetamol over 48 h in childhood bacterial meningitis. This combination treatment reduced mortality significantly in the first 72 h after its initiation. Whether an overall reduction in mortality can be achieved by longer treatment periods requires urgent further testing.

only because of delayed parasite development.[31] Prophylactic paracetamol can prevent fever in vaccinated children and thereby lower antibody response.[32] Our findings in bacterial meningitis might, therefore, reflect another example of paracetamol's ability to downregulate the host response.

Although no regimen tested in this study proved significantly beneficial in terms of the predefined endpoints, an exploratory, post-hoc analysis showed that a regimen of cefotaxime infusion for 24 h plus paracetamol for 48 h was associated with lowered mortality for at least 3 days, irrespective of the causative agent. This observation, combined with that of fewer deaths or any sequelae in patients with pneumococcal meningitis, calls for further studies with a longer administration of a β-lactam infusion plus oral paracetamol to confirm whether overall mortality is lowered (panel).

This study has several limitations, because anticipation of issues arising in clinical studies done in sub-Saharan Africa is frequently difficult. More than half the patients who were initially assessed did not fulfil the inclusion criteria, and many were excluded for features uncommon in developed countries. Nevertheless, selection bias was unlikely because in this population the patients fulfilling the selection criteria presented randomly. In many respects, our patients were dissimilar to those in earlier studies on bacterial meningitis. The children presented well after disease onset and, consequently, were very ill, with many being unconscious and having seizures. The risks of undernourishment, anaemia, and co-infection with malaria, HIV, or both, were high. Fever had frequently been treated previously with various agents. Nonetheless, our patients typically represented the populations for which the risk of bacterial meningitis is greatest.

The outcome in this series was gloomy: the 38% mortality was only slightly lower than values previously reported (46–50%).[2,33] However, only 15% of our patients developed severe neurological sequelae, which is notably less than the 24% we have seen in the same hospital.[34] We assume this outcome was due to the administration of glycerol, which reduces the risk of serious sequelae in children.[9] That said, 80% of the children in Luanda with bacterial meningitis still die or develop sequelae. Such a situation requires urgent intervention and development or identification of new treatments that are inexpensive and easy to administer. The enabling of earlier access to treatment is also of fundamental importance. Vaccination against *H influenzae* type b was included in the Angolan national programme in 2006, but we still await large-scale vaccinations against pneumococcal and meningococcal diseases.

We view our results as preliminary, but we believe they are positive enough to warrant further study of longer-term administration of β-lactam infusion and high-dose oral paracetamol.

Contributors

HP obtained funding for and TP, IR, and HP initiated the study. IR and HP conceived the study. TP and LC acquired the data and TP, IR, and MK did the statistical analysis. TP, IR, MK, and HP analysed and interpreted the data. TP and HP drafted the paper and all authors contributed to the critical revision and development of intellectual content. LC and AP provided administrative, technical, and material support. TP, IR, and HP were the study supervisors.

Conflicts of interest

HP is a clinical scientific consultant for the Serum Institute of India. The other authors declare that they have no conflicts of interest.

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