Hearing Impairment in Childhood Bacterial Meningitis Is Little Relieved by Dexamethasone or Glycerol

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KEY WORDS

dexamethasone, glycerol, meningitis, hearing impairment, deafness

ABBREVIATIONS

Hib—*Haemophilus influenzae* type b
CSF—cerebrospinal fluid
BERA—brainstem evoked response audiometry
OR—odds ratio
CI—confidence interval

This trial has been registered at www.clinicaltrials.gov (identifier ISRCTN35932399).

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WHAT'S KNOWN ON THIS SUBJECT: Adjuvant dexamethsasone is believed to prevent or relieve hearing impairment, especially in Hib meningitis if instituted before antimicrobial treatment, but no single study has documented this effect. All information derives from meta-analyses in which profoundly different populations have been combined.

WHAT THIS STUDY ADDS: This randomized, double-blind clinical trial, the largest in pediatrics, revealed no significant relief in hearing impairment by adjuvant intravenous dexamethsone, oral glycerol, or their combination. Instead, the child's presenting status and age were the most important predictors of hearing loss.

abstract

FREE

OBJECTIVE. Several studies have evaluated dexamethasone for prevention of hearing loss in childhood bacterial meningitis, but results have varied. We compared dexamethasone and/or glycerol recipients with placebo recipients, and measured hearing at 3 threshold levels.

METHODS. Children aged 2 months to 16 years with meningitis were treated with ceftriaxone but were double-blindly randomly assigned to receive adjuvant dexamethasone intravenously, glycerol orally, both agents, or neither agent. We used the Glasgow coma scale to grade the presenting status. The end points were the better ear's ability to detect sounds of >40 dB, ≥60 dB, and ≥80 dB, with these thresholds indicating any, moderate-to-severe, or severe impairment, respectively. All tests were interpreted by an external audiologist. Influence of covariates in the treatment groups was examined by binary logistic regression.

RESULTS: Of the 383 children, mostly with meningitis caused by *Haemophilus influenzae* type b or *Streptococcus pneumoniae*, 101 received dexamethasone, 95 received dexamethasone and glycerol, 92 received glycerol, and 95 received placebo. Only the presenting condition and young age predicted impairment independently through all threshold levels. Each lowering point in the Glasgow scale increased the risk by 15% to 21% (odds ratio: 1.20, 1.21, and 1.15 [95% confidence interval: 1.06–1.35, 1.07–1.37, and 1.01–1.31]; $P = .005$, .003, and .039) for any, moderate-to-severe, or severe impairment, respectively. Each increasing month of age decreased the risk by 2% to 6% ($P = .0001$, .0007, and .041, respectively). Neither dexamethasone nor glycerol prevented hearing loss at these levels regardless of the causative agent or timing of antimicrobial agent.

CONCLUSIONS: With bacterial meningitis, the child's presenting status and young age are the most important predictors of hearing impairment. Little relief is obtained from current adjuvant medications. *Pediatrics* 2010;125:e1–e8

A child who survives bacterial meningitis but is left with a serious hearing impairment is always a tragedy, but especially so if chances for rehabilitation and having a hearing device do not exist. This is the reality for most of the world's children. In a resource-poor setting, a deaf child, unable yet to speak, remains socially isolated, and the long-term survival is unlikely.[1,2] The best solution would be to implement large-scale *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* vaccinations, [3,4] but globally, few children are privileged to those.

Hearing impairment occurs early in meningitis,[5,6] and once developed, alleviates little in time, if at all.[6–8] Overall, impairment is reported in 30% to 50% in pneumococcal, in 10% to 30% in Hib, and in 5% to 25% in meningococcal meningitis.[9–13] Almost certainly these estimates are too low,[13–17] because most data arrive from the best centers. Worldwide, most survivors are discharged without reliable information on hearing. Furthermore, "hearing impairment" has been defined dissimilarly in different studies. Childhood hearing impairment is no doubt an understated and a growing problem, especially in developing countries.[18]

Because modern antimicrobial agents such as third-generation cephalosporins have not improved the situation,[19] patients have sought relief from adjuvant medications. Dexamethasone has well documented favorable biochemical effects in Hib meningitis,[20–24] but no single pediatric study which has used an optimal antimicrobial agent has reached significance, when hearing impairment has been examined as an outcome of its own. Distinguishing different outcomes is, however, important, because hearing is likely impaired by other mechanisms than those leading to neurologic sequelae or death.[25,26]

Animal studies[21] suggest that the timing of dexamethasone versus the institution of antimicrobial agents is crucial (dexamethasone should be given first or, at the latest, with antimicrobial agents). However, even taking this requirement into account, the first sufficiently powered ($N = 598$) human study from Malawi did not find dexamethasone beneficial.[27] Unfortunately, economic constraints hindered routine use of third-generation cephalosporins in that pivotal trial. A Cochrane analysis[28] concluded that "data support the use of adjunctive corticosteroids in children in high-income countries," but the populations included were profoundly dissimilar, different thresholds for hearing were used, and the child's presenting condition was totally neglected—despite the presenting status is the single most important predictor of death and/or severe neurologic sequelae,[29] and likely, of hearing impairment. Obviously, the final status of adjuvant dexamethasone in childhood meningitis remains still unsettled.

In *Pediatrics* more than 30 years ago, Herson and Todd[30] reported that glycerol (1-propanetriol, 2-propanetriol, and 3-propanetriol), an essential compound of human metabolism, a hyperosmolar agent, and an osmotic diuretic[31–35] might be of some benefit in the prevention of sequelae in Hib meningitis. The results of our pilot study in Finland[36] agreed with this view, because they hinted that glycerol may equal intravenous dexamethasone in the prevention of hearing loss. However, the size of that study was too small to allow conclusions. Therefore, we launched a much larger trial in Latin America. One of the main lessons from that major undertaking[25] was that neither dexamethasone nor glycerol prevented deafness, this being defined as the better ear's hearing threshold level at ≥80 dB.

Although that message was clear, 2 questions remained unanswered: first, would dexamethasone, glycerol, or their combination relieve milder impairment (moderate or more severe impairment has been examined in most previous trials)? Second, could the earlier studies favoring dexamethasone in Hib meningitis[20–23] be explained by their too small sample size, and/or by confounding covariates (patient characteristics)?

METHODS

Setting and Patients

The study setup has been described earlier.[25] In short, the trial was prospective, randomized, and double-blind, comprising children aged 2 months to 16 years with bacterial meningitis from 10 institutions (listed in the author affiliations) of Argentina, Brazil, Dominican Republic, Ecuador, Paraguay, and Venezuela in 1996–2003. The study was approved by the ethical committees of the institutions, and legal guardians' consent was required. The trial was designed, conducted, and analyzed independently of any pharmaceutical companies.

The main aim was to examine whether the dismal outcomes of bacterial meningitis—death, severe neurologic sequelae, and/or hearing impairment—could be prevented with adjuvant dexamethasone, oral glycerol, or their combination. A child at an appropriate age was included in the study if the results of the cerebrospinal fluid (CSF) culture proved positive, or, if the results of the blood culture were positive, he or she had compatible symptoms and signs of meningitis. If the results of both cultures proved negative, a child with clinical meningitis was still included if at least 3 of the following 4 criteria were fulfilled: CSF showed pleocytosis (≥1000 leukocytes per μL); decreased CSF glucose level (<40 mg/dL); increased CSF protein concentration

(>40 mg/dL); or serum C-reactive protein level was increased (>40 mg/L).

The exclusion criteria were a history of recent head injury, previous neurosurgical procedure (eg, intracranial shunt placement), previous neurologic disease (eg, cerebral palsy and Down syndrome), immunosuppression, and known hearing impairment. Preadmission antimicrobial therapy was registered in detail but did not prevent study enrollment.

Ceftriaxone, with a dose of 80 to 100 mg/kg once daily for 7 to 10 days intravenously was given to all children who were randomly assigned to receive also adjuvant dexamethasone intravenously (0.15 mg/kg administered every 6 hours for 48 hours,[38] first dose 15 minutes before ceftriaxone, whenever possible) and placebo orally; 85% of patients received glycerol orally (1.5 g [1.5 mL] per kg every 6 hours for 48 hours, the maximum per dose being 25 mL for 48 hours) and placebo intravenously; both agents; or neither agent. Dexamethasone, glycerol, and their placebo preparation (saline and carboxymethylcellulose, respectively) were delivered in identical ampoules or bottles, and were labeled with a study code. No person treating the child or being otherwise involved in the study was aware of a child's specific treatment until the code was broken. Because all children received a drug or placebo orally and via intravenous line and the preparations looked similar, the approach was entirely double-blind.

The Glasgow coma scale, adjusted for age, was used to grade the presenting status.[37] Among other registered covariates were the potential use of pretreatment antimicrobial agents, signs of increased intracranial pressure, convulsions, and several blood and CSF indices.

Audiology

The data on profound deafness, better ear's ability to detect sounds of ≥80 dB, have been published earlier.[25] Here we give more detailed information because, resources permitting, 3 different thresholds of hearing were used, >40 dB, ≥60 dB, and ≥80 dB, with these end points indicating any moderate-to-severe, or severe impairment, respectively. Brainstem evoked response audiometry (BERA) (auditory brainstem response) was applied, unless the child was old enough for traditional pure tone audiometry. Before testing, otitis media or other benign reasons for reduced hearing were excluded with otoscopy or tympanometry. The test personnel were kept unaware of all treatment details.

A copy of the test curves was sent to an external audiologist (Dr Jauhiainen, former head of Department). Kept blinded of all other details, he gave a written interpretation for each child. In pure tone threshold audiometry, the mean threshold value (0.5, 1.0, and 2.0 kHz) was used. A test result of BERA was interpreted only if the threshold level showed an indisputably detectable wave V response at the minimum level of acoustic stimulation. Recordings of only the supra-threshold stimulation led to the exclusion of the child because of unreliable extrapolating of such result into sensorineural hearing impairment.

Because a hearing defect begins to trouble the child at >40 dB, all findings up to this level were deemed normal. The impairment was considered mild at thresholds 41 to 59 dB, moderate at 60 to 79 dB, and severe at 80 dB. In addition, we checked how many children failed to respond to tones of 100 dB (total deafness, would need cochlear implant).

Sample Size and Statistical Analysis

The sample size for the whole study[25] was based on the assumption that a given adjuvant therapy versus placebo would decrease the sequela rate from 20% to 5%. Accepting an α error of 5% in a 2-tailed test, and a power of 80%, at least 88 patients in each arm were required.

For comparing means, Student's t test was used, χ^2 being adopted for proportions. To identify factors potentially associating with the audiological outcomes, all covariates registered on admission were examined 1 by 1 in univariate binary logistic analysis. The 3 dependent variables were as follows: (1) any degree (better ear's threshold >40 dB) of hearing impairment; (2) at least moderate hearing loss (≥60 dB); and (3) severe impairment (≥80 dB). All variables with a P value of <.1 were included together as independent variables in a multivariate logistic models, by using the same dependent variables as before. When examining the 3 different treatment groups, the placebo recipients served as the reference group. Thus, each treatment's effects on hearing could be individualized, and the variables predicting hearing loss could be independently identified.

Because the strongest evidence for dexamethasone in pediatric meningitis stems from Hib meningitis without pretreatment antimicrobial agents and with dexamethasone instituted before or simultaneously with the first dose of an antimicrobial agent,[20–24] a preplanned subgroup analysis was performed for patients with these characteristics. The results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) and P values, of which those <.05 were considered significant.

RESULTS

Patient Characteristics

Figure 1 shows the trial profile. Of the 654 children entering the study, 87 (13%) died, but of them, hearing was tested in 4 cases. Testing was not done or was defectively performed in 33

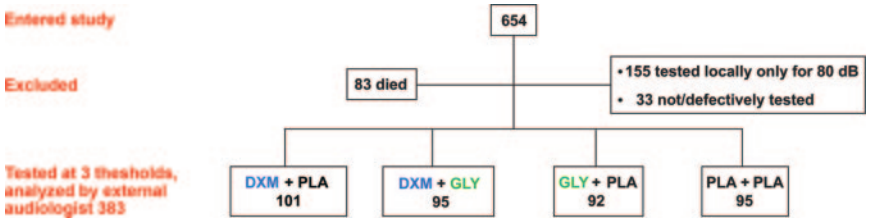

FIGURE 1

Study profile. In all, 87 patients (13%) died in the study, but hearing could be tested in 4 of these children. DXM indicates dexamethasone; PLA, placebo; GLY, glycerol.

cases, and of 155 children, only the locally measured 80 dB test result was available. Thus, 383 children remained for our detailed analysis.

The 188 excluded patients did not differ from the 383 included patients in age (37 ± 43 vs 31 ± 41 months; $P = .13$), the Glasgow coma score (12.9 ± 2.2 vs 12.7 ± 2.5; $P = .23$), adjuvant treatment (Fig 1; $P = .35$), or the frequency of the 80 dB hearing defect measured locally (10 of 155 vs 33 of 383; $P = .40$). They did differ in country of origin (84 of 155, vs 81 of 383 [$P = .0001$] were from Argentina, where only the 80 dB threshold was frequently used), in etiology (more meningococcus [55 of 188 vs 54 of 383; $P < .0001$] and less cases caused by "other" agents [5 of 188 vs 7 of 383; $P < .0001$]), use of preadmission antimicrobial agents (41 of 156 vs 145 of 360; $P = .002$), and the time of the Glasgow score to return to 15 (2.5 vs 3.5 days; $P = .002$). Two children had only 1 ear tested (normal); they were included in analysis.

Of the 383 children, 91 were from Venezuela, 87 from Dominican Republic, 81 from Argentina, 74 from Ecuador, 40 from Paraguay, and 10 from Brazil. The series comprised 146 cases of Hib, 70 of pneumococcal, 54 of meningococcal, and 7 of other type of meningitis; 106 cases remained bacteriologically unidentified. The 4 treatment groups distributed evenly (Fig 1): 101 children had received dexamethasone only; 95 children received the dexamethasone-glycerol combination; 92 children received glycerol only; and 95 children received placebo only.

Audiology

Two of 3 children ($n = 248$ [66%]) recovered without meaningful hearing loss. Mild impairment was detected in 44 children (11% of all 383 children, 33% of 132 impaired children), moderate-to-severe impairment was detected in 46 children (12%, 35%), and severe impairment was detected in 27 children (7%, 20%); 15 children (4%, 11%) became totally deaf. The results for all meningitides, and for Hib, pneumococcal, and non-Hib nonpneumococcal meningitis are presented in Table 1. Regardless of the threshold level, no treatment differed from each other or placebo. Deletoriousness of Hib and non-Hib nonpneumococcal meningitides was striking, being close to that of pneumococcal meningitis. Ineffectiveness of all adjuvant medications

TABLE 1 Hearing Status After Any Type of Meningitis and Specifically After Hib, *S pneumoniae*, or Non-Hib, Non–*S pneumoniae* Meningitis (Better Ear Recording)

Threshold dB	Dexamethasone		Dexamethasone + Glycerol		Glycerol		Placebo	
	n	%	*n*	%	*n*	%	*n*	%
All meningitides ($N = 383$)								
n	101		95		92		95	
≤40	72	71	59	62	59	64	61	64
41–59	10	10	13	14	10	11	11	12
60–79	13	13	13	14	10	11	10	11
80–99	3	3	6	6	10	11	8	8
≥100	3	3	4	4	3	3	5	5
Hib meningitis ($N = 146$)								
n	38		34		32		42	
≤40	27	71	18	53	17	53	25	59
41–59	3	8	7	20	2	6	5	12
60–79	5	13	6	18	4	13	4	10
80–99	2	5	1	3	7	22	5	12
≥100	1	3	2	6	2	6	3	7
S pneumoniae meningitis ($N = 70$)								
n	18		17		18		17	
≤40	10	56	8	47	9	50	11	64
41–59	2	11	1	5	3	17	1	6
60–79	5	28	4	24	3	17	3	18
80–99	0	0	4	24	3	17	1	6
≥100	1	5	0	0	0	0	1	6
Non-Hib, non–*S pneumoniae* meningitis ($N = 167$)[a]								
n	45		44		42		36	
≤40	35	78	33	75	33	79	25	69
41–59	5	11	5	11	5	12	5	14
60–79	3	7	3	7	3	7	3	8
80–99	1	2	1	2	0	0	2	6
≥100	1	2	2	5	1	2	1	3

[a] The series comprises cases caused by *N meningitidis* ($n = 54$) and by other bacteria ($n = 7$); 106 cases remained without etiology disclosed.

TABLE 2 Influence of Patient Characteristics (Covariates) on Hearing at Various Threshold Levels (Univariate Binary Logistic Model)

Variable	*n*	>40 dB			≥60 dB			≥80 dB		
		OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age	379	0.97	0.96–0.99	<.0001	0.96	0.95–0.98	<.0001	0.96	0.94–0.99	.005
Male patients	383	1.22	0.79–1.87	.364	1.16	0.72–1.89	.547	1.10	0.57–2.11	.772
Increased intracranial pressure for ≥24 h[a]	339	1.01	0.48–2.11	.976	1.01	0.44–2.32	.982	1.04	0.35–3.12	.943
No convulsions	356	0.43	0.27–0.68	.0003	0.37	0.22–0.62	.0001	0.81	0.41–1.59	.534
Previous antimicrobial agents[b]	360	1.28	0.82–1.98	.276	1.59	0.97–2.58	.065	2.31	1.19–4.48	.013
Each point <15[c] in Glasgow coma scale	366	1.20	1.10–1.31	<.0001	1.18	1.08–1.30	.0004	1.15	1.02–1.29	.019
Systolic blood pressure, mm Hg	287	0.99	0.98–1.01	.355	0.99	0.97–1.003	.107	0.99	0.98–1.02	.810
Pulse, frequency per min	347	1.01	1.001–1.02	.028	1.01	0.99–1.02	.263	1.01	0.99–1.02	.130
Capillary filling time, s	323	1.53	1.17–2.02	.002	1.24	0.92–1.65	.156	1.19	0.82–1.73	.369
CSF										
Leukocytes per μL	321	1.00	1.00–1.00	.489	1.00	1.00–1.00	.903	1.00	1.00–1.00	.736
Glucose, mg/dL	349	0.99	0.98–0.99	.008	0.98	0.97–0.99	.003	0.99	0.97–1.001	.072
Protein, g/dL	333	0.99	0.99–1.001	.318	0.99	0.99–1.001	.415	0.99	0.99–1.002	.681
Blood										
Leukocytes per μL	357	0.98	0.95–1.00	.052	0.94	0.91–0.97	.0006	0.95	0.91–0.99	.026
Hemoglobin, g/dL	363	0.70	0.61–0.80	<.0001	0.68	0.58–0.79	<.0001	0.68	0.55–0.83	.0003
Sodium, mmol/L	287	0.99	0.95–1.04	.686	1.05	0.99–1.10	.083	1.04	0.97–1.11	.307
Glucose, g/dL	326	1.00	0.99–1.01	.958	1.00	0.99–1.01	.795	1.00	0.99–1.01	.615
Etiology										
Hib	383	1.72	1.01–2.91	.044	2.00	1.09–3.68	.026	2.345	1.05–5.72	.037
S pneumoniae	383	2.13	1.14–3.98	.017	2.75	1.37–5.50	.004	2.19	0.82–5.84	.118
N meningitidis	383	0.51	0.22–1.16	.106	0.19	0.04–0.585	.030	0.25	0.03–2.03	.194

[a] Irritability, vomiting, absent look, neck rigidity, or convulsions observed by mother.
[b] During 72 hours before the diagnosis of bacterial meningitis.
[c] Maximum score is 15.

remained essentially the same when cases with and without a proven etiology were examined.

Six covariates were associated with poorer hearing through all threshold levels: low age; low Glasgow coma score; low CSF glucose concentration; low blood leukocyte count; low hemoglobin level; and the Hib etiology (Table 2). To a lesser extent, impairment was associated with convulsions, pretreatment antimicrobial agents, low CSF glucose concentration, blood leukocyte count, and the pneumococcal etiology. Meningococcal meningitis left often hearing undamaged.

Effects of the 3 adjuvant medications versus placebo are presented in Table 3. Dexamethasone showed some tendency toward protection against hearing loss, but significance was not reached at any particular level. Nor was a difference found in the 130 cases of nonpretreated Hib meningitis in which ceftriaxone was instituted only after dexamethasone (Table 4). The most favorable result for dexamethasone was at the level of 80 dB, all meningitides combined (OR: 0.40 [95% CI: 0.15–1.10]; $P = .075$).

Once the significant covariates were submitted to multivariate logistic model, the picture became even clearer (Table 5): the child's presenting condition and age were the only factors that independently predicted hearing impairment through all threshold levels. Notably, each lowering point in the Glasgow scale, starting from the maximum score of 15, increased the risk significantly; OR varied from 1.20 for any impairment (95% CI: 1.06–1.35; $P = .005$) to 1.15 for deafness (95% CI: 1.01–1.31; $P = .039$).

Inversely, each increasing month of age decreased the risk of hearing impairment by 2% to 6% for any, moderate-to-severe, and severe im-

TABLE 3 Bilateral Hearing Impairment in the 3 Adjuvant Medication Groups Versus Placebo Recipients at Various Threshold Levels (All Meningitides Combined, Univariate Logistic Model)

Threshold, dB	Dexamethasone ($N = 101$)				Dexamethasone + Glycerol ($N = 95$)				Glycerol ($N = 92$)			
	n[a]	OR	95% CI	*P*	*n*[a]	OR	95% CI	*P*	*n*[a]	OR	95% CI	*P*
>40	29	0.72	0.40–1.32	.290	36	1.10	0.61–1.97	.764	33	1.00	0.55–1.83	.991
≥60	19	0.73	0.37–1.44	.358	23	1.00	0.52–1.94	.999	23	1.04	0.54–2.03	.900
≥80	6	0.40	0.15–1.10	.075	10	0.74	0.31–1.79	.506	13	1.04	0.45–2.38	.930

[a] Number of children.

TABLE 4 Bilateral Hearing Impairment in Hib Meningitis in the 3 Adjuvant Medication Groups Versus 38 Placebo Recipients at Various Threshold Levels

Threshold, dB	Dexamethasone ($N = 33$)				Dexamethasone + Glycerol ($N = 28$)				Glycerol ($N = 31$)			
	n^a	OR	95% CI	P	n^a	OR	95% CI	P	n^a	OR	95% CI	P
>40	11	0.77	0.29–2.03	.593	14	1.53	0.57–4.11	.395	14	1.26	0.48–3.30	.634
≥60	8	0.90	0.31–2.63	.841	8	1.12	0.38–3.34	.839	12	1.77	0.64–4.91	.274
≥80	3	0.44	0.11–1.87	.269	3	0.53	0.12–2.27	.393	8	1.54	0.49–4.86	.461

No previous antimicrobial agent was given, and dexamethasone was instituted before or, at the latest, with the first dose of ceftriaxone. Univariate logistic model was used.
[a] Number of children.

pairment (OR: 0.97, 0.96, and 0.98 [95% CI: 0.96–0.98, 0.94–0.98, and 0.95–0.99]; $P < .0001$, .0007, and .041, respectively).

Pretreatment antimicrobial agents increased the risk of severe hearing impairment, OR: 2.25 (95% CI: 1.04–4.83; $P = .039$). Also a blood leukocyte count below 15 000/μL increased the risk of severe impairment (OR: 2.32 [95% CI: 1.03–5.26]; $P = .043$), but overall, the effects of these 2 cofactors were much smaller than those of the presenting status and low age (Table 5). Surprisingly, etiology per se played a less prominent role.

Our expert of audiology agreed very well with the local interpretations, because his diagnosis of deafness was the same in 97% of patients (373 of 383). In 2.5% of patients (11 of 383), the external audiologist detected deafness which was not found locally. Examined vice versa, our expert disagreed on the local interpretation of deafness in only 0.5% of patients (2 of 383).

DISCUSSION

The comprehensiveness of our series, being manifold to all previous childhood meningitis trials except that from Malawi,[27] allowed us to relate hearing impairment to a number of covariates, not only to the causative agent or timing of antimicrobial agents. As 3 threshold levels were used, we believe that it is difficult to reach better accuracy from children who were mostly infants or at toddler age. The randomized, double-blind design, and the test results interpreted by an independent expert with decades-long experience in pediatric audiology add to the reliability of data. The on-admission characteristics of patients[25,29] were comparable to those in a privileged country, and previous information from the same institutions[13,17,39] shows that the outcomes in these centers compete well to those in the industrialized world.

Insufficient funding in this study, which sought for simple and inexpensive treatment modalities, was a major obstacle. Therefore, economic constraints hindered full audiological testing in all cases. The possibility that this shortcoming biased the results cannot be excluded, but we deem it very unlikely because all nontesting occurred at random.

The main lesson learned was that, instead of the causative agent or timing of antimicrobial agents,[20–24] it were fundamentally the child's presenting status and young age that affected the

TABLE 5 Risk of Bilateral Hearing Impairment at Various Threshold Levels in the 3 Adjuvant Medication Versus Placebo Groups

	>40 dB ($N = 281$)[a]			≥60 dB ($N = 307$)			≥80 dB ($N = 319$)		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age, each increasing mo	0.97	0.96–0.98	<.0001	0.96	0.94–0.98	.0007	0.98	0.95–0.99	.041
Etiology									
Hib	1.09	0.53–2.23	.822	1.24	0.57–2.70	.587	1.74	0.65–4.65	.267
S pneumoniae	1.84	0.79–4.33	.159	1.73	0.76–4.29	.236	1.65	0.52–5.28	.396
N meningitidis	0.26	0.05–1.26	.093	—	—	—	—	—	—
Previous antimicrobial agents	—	—	—	1.80	0.96–3.36	.066	2.25	1.04–4.83	.039
No previous convulsions	0.99	0.53–1.85	.973	1.02	0.53–1.97	.953	—	—	—
Blood leukocytes <15 000/μL	1.06	0.60–1.88	.841	1.55	0.82–2.92	.178	2.32	1.03–5.26	.043
Blood hemoglobin <7 g/dL	0.52	0.18–1.55	.243	0.56	0.17–1.75	.322	0.18	0.02–1.51	.115
CSF glucose ≤20 mg/dL	1.36	0.75–2.46	.312	1.57	0.82–2.98	.171	1.12	0.50–2.52	.789
Each point <15 in Glasgow coma scale	1.20	1.06–1.35	.005	1.21	1.07–1.37	.003	1.15	1.01–1.31	.039
Pulse frequency >120/min	0.70	0.38–1.29	.252	—	—	—	—	—	—
Capillary filling time >3 s	3.31	1.04–10.61	.044	—	—	—	—	—	—
Adjuvant medication									
Dexamethasone	0.79	0.36–1.73	.552	0.63	0.27–1.50	.298	0.49	0.15–1.58	.232
Dexamethasone + glycerol	1.26	0.60–2.95	.478	1.64	0.70–3.82	.252	1.19	0.43–3.27	.737
Glycerol	1.27	0.57–2.81	.572	0.89	0.38–2.10	.788	1.39	0.52–3.69	.510

Multivariate logistic model was used, including covariates reaching $P < .1$ in univariate analysis.
[a] Number of children with all data for multivariate analysis.

audiological outcome. The effect of the clinical condition was so dramatic that each lowering point in the Glasgow coma scale increased the risk of hearing impairment by 15% to 20% (Table 5). No adjuvant medication abated this effect, not even if the data were sorted agentwise or according to the timing of antimicrobial therapy. Thus, the experience[8–10] (albeit not demonstrated by this study) that pneumococcal meningitis in survivors is more deletorious to the hearing organ than other meningitides, seems to be more associated with the patient's frequently poor clinical condition in this type of meningitis[29] than with the agent per se—as such an interesting finding.

Neither adjuvant prevented hearing impairment, but because dexamethasone showed a tendency toward protection when all meningitides were combined, there seems to be a subset of patients which sometimes benefits from dexamethasone. They are, however, not straightforwardly those with Hib meningitis who have not received pretreatment antimicrobial agents. For the time being, we simply are unable to identify these few patients.

Studies and meta-analyses in which statistical significance for an adjuvant medication has been reached by combining different outcomes should not be taken as a proof of that treatment's benefit regarding hearing. Also, neglecting a key issue, the presenting condition,[29] in such a variable disease as bacterial meningitis is a shortcoming which blurs a well-balanced interpretation of the results from dissimilar studies. A direct comparison is founded only if the disease severity is scored with the same criteria, and all the major covariates affecting the outcomes are taken into account. We foresee that the future meta-analyses will look different from those which are currently cited.

Although the results of this study were rather negative, it is of special note that our audiologist agreed very well with the local interpretations. An overall 97% accordance was reached, although our expert confined himself in indisputable observations, used stringent criteria, and accepted only the responses one recognized beyond doubt. Possibly our results were so negative because, for the first time, hearing impairment was quantitatively related to a series of covariates some of which affected the hearing more than one previously has realized.

We underline the need of an external expert to interpret all test results with the same criteria. In Malawi, an expert visited the site from the United Kingdom,[27] but we cannot easily compare the results, because in Malawi also behavioral distraction test was used. Here we arrive at another problem in meningitis studies: audiology is measured with dissimilar methods, and where the methods are the same (preferably BERA), different thresholds are used. We should soon start using methodology that allows direct comparisons between studies. And in those studies, the presenting status and the age should be taken into account.

CONCLUSIONS

Neither intravenous dexamethasone nor oral glycerol (or their combination) prevented hearing impairment in bacterial meningitis of childhood, when the effects were studied at the threshold levels of 40, 60, and 80 dB. Meningitis being caused by Hib, nonreceipt or pretreatment antimicrobial agents, and the adjuvant started before antimicrobial therapy did not change the results. To save a child from hearing loss in meningitis, better agents than dexamethasone or glycerol should be sought.

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