Hearing Impairment in Angolan Children with Acute Bacterial Meningitis With and Without Otitis Media and Otorrhea

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Research Article

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Abstract

Background: Bacterial meningitis (BM) is a common cause of hearing loss in childhood. Our aim was to investigate bacterial etiology, hearing impairment, and outcome in childhood BM with *vs.* without otitis media (OM) in the resource-poor settings of Angola.

Methods: Hearing was tested through brainstem-evoked response audiometry (ABR) in 391 (76%) of 512 children with confirmed BM. The bacteria identified from the ear discharge were compared to those from CSF and the relevance of findings was examined in terms of hearing among children with or without OM on day 1 and 7 of hospitalization, and at follow-ups of 1, 3 and 6 month(s).

Results: No correlation was found in bacteriology between the ear discharge and CSF, and the most common ear pathogens more likely reflected chronic than acute middle ear infections. On day 7 in hospital, hearing impairment (>40 dB) was common, regardless of whether concomitant OM or not (in 27% *vs.* 30%, respectively), whereas on day 7, profound hearing loss (>80 dB) was diagnosed slightly more in children without OM 16% *vs.* 10% accordingly. Any hearing deficit on day 7 was associated with a higher risk of complicated or fatal clinical course (OR 2.76, $CI_{95\%}$ 1.43-5.29, *P = .002*).

Conclusion: No significant difference prevailed in hearing thresholds between children with or without OM in hospital on day 7 or at later follow-ups. Any hearing impairment on day 7 associated with a higher risk for complicated clinical course or death.

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1. Introduction

Acute otitis media (AOM) is a common childhood infection, which usually runs a benign course of disease [1]. It may, however, lead to chronic suppurative otitis media (CSOM), especially in low-income countries.[2] Bacterial meningitis (BM) is the most common intracranial complication (ICC) of otitis media (OM) with incidence varying between 12% and 72% [3–5]. Up to 45% of childhood BM is otogenic [6]. Studies from low-income countries suggest that OM leads to BM in 0.4–2% of patients [3,7]. Central and western Sub-Saharan Africa countries continue to have a high burden of meningitis [8]. Surprisingly, the role of OM-associated BM in Sub-Saharan Africa and elsewhere has not been studied much.

According to a large meta-analysis (Edmond 2010), the main causative agents responsible for BM are *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* and *Neisseria meningitidis* [9]. BM is a common childhood cause for acquired sensorineural hearing loss, with an incidence of 10–34 % in BM survivors [9–11]. Edmond et al. found in their meta-analysis, that the risk for major sequelae such as bilateral hearing loss was twice as high in the African regions compared with European region [9]. In developed countries, approximately 10 to 14% of children surviving BM are left with permanent hearing loss [11,12]. Bilateral severe to profound hearing loss develops in approximately 5 % of BM patients [10,13]. The mechanisms behind hearing loss are thought to be the destruction of the inner ear's neural elements followed by labyrinthitis and ossification of the cochlear scalae [14,15]. In BM patients, *S. pneumoniae* is the most common agent causing hearing impairment in 21–50% of the cases [11–13, 16], in Hib and meningococccal meningitis, is seen in 2–26% and 3–17%, respectively [11,12,17,18].

Our aim was to investigate bacterial etiology, hearing impairment, and outcome in childhood BM with *vs.* without otitis media (OM) in the resource-poor settings of Angola.

2. Materials And Methods

This study is a part of a previously reported clinical trial (ISRCTN62824827) on 723 children with BM at the Children's Hospital of Luanda, Angola, 2005–2008 [19]. The Luanda Children's Hospital's Ethics Committee approved the study protocol, and a legal gardian's informed consent was obtained prior to each child's enrolment. The agreement was expressed with fingerprint, if the guardian was illiterate.

The set-up details of the study have published earlier [19]. A lumbar puncture was performed on all children attending with symptoms and signs suggestive of BM. Ear-discharge samples were obtained from the external auditory canal with a sterile cotton swab. The ear-discharge and CSF samples were gram-stained and cultured and analyzed in the hospital´s laboratory of microbiology according to the norms of the National Committee for Clinical Laboratory Standards. BM was considered confirmed in cases with a positive CSF culture or PCR, or if a child with symptoms and signs compatible with BM and positive blood culture had at least two of the following symptoms: positive CSF Gram-stain, positive CSF latex-agglutination test, CSF leukocyte count exceeding 100×10^6 /L (predominantly polymorphs), or serum C-reactive protein (CRP) concentration higher than 40 mg/L.

On hospital arrival, the study pediatrician (T.P.) examined the ears by pneumatic otoscopy. Diagnosis of OM was based on either purulent middle ear secretion combined with at least two of the following signs of the tympanic membrane: bulging position, decreased or absent mobility, abnormal color or opacity or suppurative middle ear secretion originating (otorrhea).

The clinical course of the disease was classified as complicated when the child also had a second infection focus (pneumonia, osteomyelitis), convulsions after the third day of treatment, focal convulsions anytime during the illness, or focal neurological symptoms.

We investigated hearing among children with or without OM and compared these hearing outcomes. The bacteriology of CSF and of possible ear discharge were also separately analyzed.

2.1. Hearing testing

Hearing was measured separately on each ear, using a brainstem-evoked response audiometry (ABR) [MADSEN Octavus Otometrics, Taastrup, Denmark)], with auditory click stimuli of 40 dB, 60 dB, and 80 dB. Specially trained research nurses performed ABR after pneumatic otoscopy. The tests were performed within 24 hours of admission, on day 7 (± 1) of the treatment, and at follow-up visits at 1, 3 and 6 month(s) post-hospitalization. The ABR results, sent by email, were analyzed by an independent expert at the Department of Audiology of the Helsinki University Hospital, Helsinki, Finland. The ears were tested and analyzed separately, and we report the hearing thresholds per each ear separately here, as well as according to the better ear's hearing level (BEHL).

Hearing was deemed normal if the hearing threshold was $\leq$ 40 dB, moderate if >40 dB, whereas the hearing deficit was considered severe if $\geq$ 60 dB, or profound with a threshold of >80 dB. Profound deafness was diagnosed with a bilateral threshold exceeding 80dB. If, during the follow-up visits, ABR was not available (due to technical problems), hearing was tested by asking questions. If the child answered the question correctly, the hearing threshold was evaluated to be 60 dB. Also at the one month follow-up, hearing was tested by otoacoustic emissions (OAEs) [Accuscreen; Danalink or GN ReSound Finland Oy/Absing], with an auditory click stimuli of 20 dB stimuli, when ABR was not available.

Data were analyzed using IBM SPSS 25.0 (IBM Corp. Armonk, NY, USA). Chi-square test were used to determine significant differences between categorical variables. Univariate logistic regression analysis was also used to predict a complicated or fatal clinical course on day 7. The results are expressed as odds ratios (OR) with a 95% confidence interval ($CI_{95\%}$). $P < .05$ was regarded to be statistically significant.

3. Results

Otoscopy was conducted, and the middle ear status recorded for 512 (out of 723) BM patients. Of these, 450 children (88%) did not have OM (non-OM) while 62 children had OM (39 with otorrhea). The middle ear status remained unexplored if thick wax prevented otoscopy - no suction device for its removal was available. One child diagnosed with dry tympanic membrane perforation was excluded because of no signs of acute infection.

Hearing was successfully tested for 391 of 512 children; this group met the inclusion criteria of this study. Of these children, 342 were non-OM while 49 children had OM. There were 225 boys (58%), the median age was 13 months (range 2 months to 13 years); 183 (47%) were infants (under 12 months).

If ABR was not available for the one month follow-up visit, hearing was tested either by asking questions on 13% (n = 21/168) patients or measured by OAEs on 11% (n = 19/168) patients.

3.1. Bacteriology

Bacterial culture results of the ear discharge are found in Table 1, whereas Table 2 projects the discharge cultures against the otorrhea patients' outcomes. The discharge samples were cultured in hospital for only 36% (n = 14 of 39) children who had otorrhea and were positive in 93% of these cases (n = 13 of 14); the one patient with no growth had received prior antibiotics. The most common pathogens were *Proteus vulgaris* (n = 6, 33%), followed by *Pseudomonas aeruginosa* (n = 3, 17%), unidentified Gram-negative bacilli (n = 3, 17%) and *Klebsiella* (n = 2, 11%). *Enterobacter, Proteus mirabilis* and *Citrobacter freundii* were found in one patient (6%) each. Detection of a single organism was more common 64% (n = 9 of 14) than finding of a mixed/multiple etiology (Table 2). Single cultures were found for *Proteus vulgaris* (n = 4), *Pseudomonas aeruginosa, Proteus mirabilis, Citrobacter freundii* and gram-negative bacilli. Of all pathogens cultured from the ear discharge, 50 % (n = 9/18) were resistant to the antibiotic used for the particular patient.

Table 1
The bacteriological culture results of the ear discharge of the otorrhea patients*

Pathogen	N (%)
Proteus vulgaris	6 (33%)
Pseudomonas aeruginosa	3 (17%)
Gram-negative bacilli	3 (17%)
Klebsiella	2 (11%)
Enterobacter	1 (6%)
Proteus mirabilis	1 (6%)
Citrobacter freundii	1 (6%)
No growth	1 (6%)
Total	18
*(n = 14/39)	

Of the 13 otorrhea patients with positive ear discharge culture, seven (54%) also showed positive CSF culture. These included *S. pneumoniae* (n = 5, 38%), *H. influenzae* (n = 1, 8%), and *Proteus* (n = 1, 8%), this agent being the only one identified in both CSF and ear discharge. Focal neurological signs were diagnosed in 10 (77%) of the 13 children with otorrhea, mainly being the cranial nerves affected with subsequent strabismus, ptosis and facial paresis. One child aged 8 year 7mth was diagnosed with osteomyelitis and mastoiditis.

3.2. Hearing results

Table 3 presents the results of all the ears´ hearing threshold levels (80 dB, 60 dB and 40 dB) in patients with or without OM, at hospital or at the follow-up visits (1, 3 and 6 months). On day 1, deafness (> 80dB) was diagnosed less often in patients with OM (15%, n = 15/98) than among those with non-OM (25%, n = 170/683) (*P* = *.04*). However, on day 7, no difference was found anymore in one-ear deafness (> 80 dB) between patients with OM vs. non-OM (16% [13/81] *vs.* 21% [113/534], respectively, ns.).

Table 2. The positive ear discharge culture vs. outcome of the otorrhea patients having BM in Luanda, Angola (n=13/39).

Patient	Age	Bacterial culture from the ear discharge	Susceptibility to antibiotics (S= sensitive, R=resistant)*	Middle ear finding day 1 (right/left)	CSF culture	Day 1 ABR (right/left)	Day 7 ABR (right/left)	Focal neurological symptom† during hospital stay	Outcome a discharge (neurologic sequelae†; hearing impairmen
1	9m	Gram-negative bacilli Enterobacter	S-cipro, ampi, amox, linco R-ceftatzidim	Otorrhea/Normal	*S. pneumoniae*	40dB/40dB	40dB/80dB	Monoparesis	Blindness, Monopares Moderate psychomo retardation
2	9m	*Pseudomonas aeruginosa*	-	Otorrhea/Otorrhea	*H. influenzae*	ABR not done	80dB/60dB	Strabismus	Severe hearing impairmen
3	1y9 m	*Proteus vulgaris*	S-cipro, genta R-cotrimox, chl, amox	Normal/Otorrhea	Negative	-	40dB/80dB	Strabismus	Ataxia, Blindness, Psychomo retardation
4	2y 2m	*Proteus vulgaris*	S-ciprofl R-genta, amp, cotrimox	Unknown/Otorrhea	*S. pneumoniae*	40dB/40dB	40dB/40dB	Ptosis	Ataxia, Moderate psychomo retardation
5	3y 3m	*Proteus vulgaris* *Klebsiella* spp.	-	Otorrhea/Otorrhea	*S. pneumoniae*	40dB/60dB	80dB/Deaf	No focal neurological sequelae	Ataxia Severe hearing impairmen
6	4y 5m	*Citrobacter freundii*	S-ceftriaxone, amox+clav R-cotrimox, penicillin	Otorrhea/Unknown	Negative	40dB/40dB	40dB/40dB	Facialis paresis	Ataxia
7	6y	*Pseudomonas aeruginosa*	S-ciprofloxacin R-canam, carbenic, ampic, sulphamid	Otitis Media/ Otorrhea	Negative	ABR not done	ABR not done	No focal neurological sequelae	Death
8	6y 2m	Gram-negative bacilli *Klebsiella* spp.	S-doxicyclin R-cefotaxime, gentamycin, chloramphenicol, lincomycin	Normal/Otorrhea	Negative	Deaf/Deaf	80dB/80dB	No focal neurological sequelae	Severe hearing impairmen
9	6y 10m	*Proteus vulgaris*	S-ceftazidime, eryth, dox R-chl, genta, oxa, amox	Unknown/Otorrhea	Negative	deaf/deaf	Deaf/Deaf	Hemiparesis	Blindness, Hemipares (moderate) Deaf
10	7y 9m	Gram-negative bacilli	-	Otorrhea/Normal	*S. pneumoniae*	40dB/40dB	60dB/Unknown	Strabismus	Death Severe hearing impairmen
11	8y 3m	*Proteus mirabilis*	S-amp, chl, genta R-amox	Perforation TM/ Perforation TM	*S. pneumoniae*	60dB/Deaf	ABR not done	Strabismus	Death
12	8y 7m	*Proteus vulgaris*	S-neomycin, ciprofl, gentam R-lincomycin, erythromycin	Otorrhea/Otorrhea	Negative	40dB/40dB	40dB/40dB	Strabismus	Death
13	10y 3m	*Proteus vulgaris* (day23), *Pseudomonas aeruginosa* (day29)	-	Normal/Unknown	*Proteus*	ABR not done	40dB/40dB	Monoparesis	Ataxia, Monopares (moderate)

=resistant)

amox = amoxicillin	cefo = cefotaxime	genta =gentamycin
amox + clav = amoxicillin clavulanic acid	cipro = ciprofloxacin	linco = lincomycin
amp = ampicillin	chlora = chloramphenicol	oxa =oxacillin
carpe = carbenic	cotri = cotrimox	neo =neomycin
cefta = ceftatzidim	ery =eruthromycin	sulpha = sulphamid

† Defined as monoparesis, strabismus, ptosis, facialis paresis, hemiparesis

†‡ Defined as monoparesis, strabismus, ptosis, facialis paresis, hemiparesis, blindness, quadriplegia, hydrocephalus, severe psychomotor retardation or any psychomotor retardation.

Table 3
The hearing thresholds levels of 40 dB, 60 dB, 80 dB and deaf (> 80 dB) tested by ABR in all ears of the children diagnosed with bacterial meningitis with normal middle ear (Non-OM) versus those with concomitant otitis media (OM)* or otorrhea

	All Ears		
Hearing Threshold Level	**Non-OM n = 900**	**OM n = 124**	**Otorrhea n = 78**
Day 1			
Deaf	170/683 (25%)	**15/98 (15%)** .04	10/58 (17%)
80 dB	48/683 (7%)	8/98 (8%)	7/58 (12%)
60 dB	86/683 (13%)	14/98 (14%)	8/58 (14%)
40 dB	379/683 (55%)	61/98 (62%)	33/58 (57%)
Day 7			
Deaf	113/534 (21%)	13/81 (16%)	8/53 (15%)
80 dB	38/534 (7%)	10/81 (12%)	**10/53 (19%)** .003
60 dB	51/534 (10%)	11/81 (14%)	8/53 (15%)
40 dB	332/534 (62%)	47/81 (58%)	27/53 (51%)
At 1 month†			
Deaf	27/247 (11%)	3/38 (8%)	2/17 (12%)
80 dB	9/247 (4%)	2/38 (5%)	2/17 (12%)
60 dB	22/247 (9%)	4/38 (11%)	3/17 (18%)
40 dB	189/247 (77%)	29/38 (76%)	10/17 (59%)
At 3 months			
Deaf	8/140 (6%)	0/16 (0%)	0/6 (0%)
80 dB	3/140 (2%)	0/16 (0%)	0/6 (0%)
60 dB	14/140 (10%)	1/16 (6%)	0/6 (0%)
40 dB	115/140 (82%)	15/16 (94%)	6/6 (100%)
At 6 months			
Deaf	14/75 (19%)	0/12 (0%)	0/6 (0%)
80 dB	2/75 (3%)	0/12 (0%)	0/6 (0%)
60 dB	3/75 (4%)	1/12 (8%)	0/6 (0%)
40 dB	56/75 (75%)	11/12 (92%)	6/6 (100%)
*OM group includes otorrhea.			
† If ABR was not available, hearing was tested by asking questions on 13% (n = 21/168) and by otoacoustic emissions on 11% (19/168)			
Data are n (%) unless otherwise stated. Statistical significance when $P < .05$.			

Table 4. Hearing findings of children diagnosed with bacterial meningitis with normal middle ear (non-OM) versus those with concomitant otitis media (OM)* or otorrhea. The hearing was tested by brainstem-evoked response audiometry (ABR).

	All patients			≤12 months old			>12months old		
	Non-OM (n = 450)	OM (n = 62)	Otorrhea (n = 39)	Non-OM (n = 229)	OM (n = 20)	Otorrhea (n = 8)	Non-OM (n = 221)	OM (n = 42)	Otorrhea (n = 31)
BEHL Day 1									
Deaf	57/342 (17%)	3/49 (6%) *0.06*	2/29 (7%)	29/167 (17%)	0/16 (0%) *.07*	0/6 (0 %)	28/175 (16%)	3/33 (9%)	2/23 (9%)
80 dB	23/342 (7%)	3/49 (6%)	3/29 (10%)	13/167 (8%)	2/16 (13%)	**2/6 (33%)** *.029*	10/175 (6%)	1/33 (3%)	1/23 (4%)
60 dB	42/342 (12%)	8/49 (16%)	4/29 (14%)	25/167 (15)	2/16 (13%)	0/6 (0%)	17/175 (10%)	6/33 (18%)	4/23 (17%)
40 dB	220/342 (64%)	35/49 (71%)	20/29 (69%)	100/167 (60%)	12/16 (75%)	4/6 (67%)	120/175 (69%)	23/33 (70%)	16/23 (70%)
BEHL Day 7									
Deaf	42/269 (16%)	4/41 (10%)	3/27 (11%)	28/136 (21%)	0/14 (0%) *.06*	0/7 (0%)	14/133 (11%)	4/27 (15%)	3/20 (15%)
80 dB	14/269 (5%)	2/41 (5%)	2/27 (7%)	10/136 (7%)	0/14 (0%)	0/7 (0%)	4/133 (3%)	2/27 (7%)	2/20 (10%)
60 dB	25/269 (9%)	5/41 (12%)	4/27 (15%)	13/136 (10%)	3/14 (21%)	2/7 (29%)	12/133 (9%)	2/27 (7%)	2/20 (10%)
40 dB	188/269 (70%)	30/41 (73%)	18/27 (67%)	85/136 (63%)	11/14 (79%)	5/7 (71%)	103/133 (77%)	19/27 (70%)	13/20 (65%)
BEHL at 1 month *†*									
Deaf	8/147 (5%)	0/21 (0%)	0/10 (0 %)	8/70 (11%)	0/9 (0%)	0/4 (0 %)	0/77 (0 %)	0/12 (0%)	0/6 (0%)
80 dB	3/147 (2%)	1/21 (5%)	1/10 (10%)	3/70 (4%)	1/9 (11%)	1/4 (25%)	0/77 (0%)	0/12 (0%)	0/6 (0%)
60 dB	29/147 (20%)	2/21(10%)	2/10 (20%)	9/70 (13%)	0/9 (0%)	0/4 (0 %)	20/77 (26%)	2/12 (17%)	2/6 (33%)
40 dB	107/147 (73%)	18/21 (86%)	7/10 (70%)	50/70 (71%)	8/9 (89%)	3/4 (75%)	57/77 (74%)	10/12 (83%)	4/6 (67%)
BEHL at 3 month									
Deaf	2/70 (3%)	0/8 (0%)	0/3 (0%)	1/36 (3%)	0/4 (0%)	0/1 (0%)	1/34 (3%)	0/4 (0%)	0/2 (0%)
80 dB	0/70 (0%)	0/8 (0%)	0/3 (0%)	0/36 (0 %)	0/4 (0%)	0/1 (0%)	0/34 (0%)	0/4 (0%)	0/2 (0%)
60 dB	4/70 (6%)	0/8 (0%)	0/3 (0%)	0/36 (0 %)	0/4 (0%)	0/1 (0%)	4/34 (12%)	0/4 (0%)	0/2 (0%)
40 dB	64/70 (91%)	8/8 (100%)	3/3 (100%)	35/36 (97%)	4/4 (100%)	1/1 (100%)	29/34 (85%)	4/4 (100%)	2/2 (100%)
BEHL at 6 month									
Deaf	5/40 (13%)	0/7 (0%)	0/3 (0%)	4/25 (16%)	0/1 (0%)	0/1 (0%)	1/15 (7%)	0/4 (0%)	0/2 (0%)
80 dB	0/40 (0%)	0/7 (0%)	0/3 (0%)	0/25 (0%)	0/1 (0%)	0/1 (0%)	0/15 (0%)	0/4 (0%)	0/2 (0%)
60 dB	3/40 (8%)	0/7 (0%)	0/3 (0%)	1/25 (4%)	0/1 (0%)	0/1 (0%)	2/15 (13%)	0/4 (0%)	0/2 (0%)
40 dB	32/40 (80%)	7/7 (100%)	3/3 (100%)	20/25 (80%)	1/1 (100%)	1/1 (100%)	12/15 (80%)	4/4 (100%)	2/2 (100%)

*OM group includes otorrhea.

† If ABR was not available, hearing was tested by asking questions on 13% (n = 21/168) and by otoacoustic emissions on 11% (19/168)

Data are n (%) unless otherwise stated. Statistical significance when $P < .05$.

On day 7, one-ear hearing loss 80 dB was diagnosed more often in patients with otorrhea 19% (n = 10/53) *vs.* in 7% (n = 38/534) among those with non-OM ($P = .003$). At one month control, no difference was found in one-ear hearing loss 80 dB between patients with otorrhea vs. without OM (12% [2/17] *vs.* 4% [9/247], respectively, ns.).

As seen in Table 4, no significant differences in BEHLs was observed among patients with or without OM at the threshold levels of 80 dB, 60 dB and 40 dB in hospital or at the control visits of 1, 3 and 6 months. On day 1, deafness was diagnosed in patients with OM in 6% (n = 3/49) *vs.* in 17% (n = 57/342) among those with non-OM. None of the 16 infants with OM was deaf, while 17% (29) of the 167 infants without OM were, ns. More infants with otorrhea had a hearing threshold of 80 dB on day 1 than had those without ear discharge (33% [2/6] *vs.* 13% [13/167]; $P = .029$).

3.2. Clinical outcome of the patients

Table 5 summarizes the risk factors for complicated or fatal clinical course. In univariate analysis, a patient diagnosed with a threshold at 40 dB on day 7 showed lower odds for a complicated or fatal clinical course (OR .36, [0.19–0.70], *P = .002*). However, on day 7, the odds for a complicated or fatal clinical course were higher, if the patient was diagnosed deaf on day 7 (OR 2.65, [1.08–6.50], *P = .034*), had a hearing threshold of ≥ 80dB on day 7 (OR 3.34, [1.45–7.68], *P = .004*) or a hearing deficiency (BEHL >40dB) on day 7 (OR 2.76, [1.43–5.29], *P = .002*).

Table 5
The risk factors for complicated clinical course* or death in patients with bacterial meningitis

Variable	**Complicated Clinical Course or Death**	
	Univariate analysis	
	OR (95% CI)	***P***
Day 1	N = 391	
Deaf (> 80 dB)	1.30 (0.65–2.64)	*.46*
BEHL 80 dB	3.59 (0.83–15.49)	*.09*
BEHL 60 dB	1.56 (0.70–3.46)	*.28*
BEHL 40dB	.53 (0.31–0.92)	*.024*
BEHL ≥ 80 dB	1.77 (0.93–3.37)	*.084*
Hearing loss (BEHL > 40dB)	1.55 (0.96–2.51)	*.075*
Day 7	N = 310	
Deaf (> 80 dB)	2.65 (1.08–6.50)	*.034*
BEHL 80 dB	5.61 (0.73–43.15)	*.10*
BEHL 60 dB	1.46 (0.58–3.72)	*.42*
BEHL 40dB	0.36 (0.19–0.70)	*.002*
BEHL ≥ 80 dB	3.34 (1.45–7.68)	*.004*
Hearing loss (BEHL > 40dB)	2.76 (1.43–5.29)	*.002*
* The clinical course of disease was classified as complicated if the child had a second infection focus (pneumonia, osteomyelitis), convulsions after the third day of treatment, focal convulsions anytime during the illness, or focal neurological symptoms.		
Statistical significance when *P* < .05.		

4. Discussion

In this study, our aim was to investigate bacterial etiology, hearing impairment, and outcome in childhood BM with *vs.* without otitis media (OM) in the resource-poor settings of Angola. In our results, hearing deficiency was common, being diagnosed in a third of the children a after a week BM diagnosis. In previous results from this clinical trial data [19], Roine et al. found that 3 months after BM, of all 124 children (in 244 ears), 74% recovered without hearing impairment, 5% had unilateral and 11% bilateral hearing impairment [20]. In other study Roine et al. found that almost half of all ears (n = 235) showed thresholds changes after admission during recovery [21]. In both study a part of the patient was excluded from the study because of the middle ear disease. Karppinen et al. results showed that *S. pneumoniae* was the most common cause of impaired hearing at > 60dB threshold among infants and it caused deafness more often than Hib and *N. meningitidis* [16]. In our study, there was no difference in hearing between children with or without OM on day 7, or later at the follow-ups of 1, 3 and 6 months. However, any hearing impairment or full deafness a week after the BM diagnosis showed a higher risk for complicated or fatal clinical course.

According to the literature review from Africa, the most common micro-organisms in children causing CSOM are *Proteus* sp (22–43%), *Staphylococcus* spp. (37%), *Pseudomonas* spp. (13–15%) and *S. aureus* (5–14%) [22]. We found that the most common pathogen causing otorrhea was Proteus, which is in correspondence with the literature review from Africa [22]. In studies from Kenya for instance, Proteus is frequently detected as the most common agent causing otorrhea among children and young adults [23,24]. In our study, the most common pathogens found in the ear discharge of the children with BM were likely to be related more to chronic than acute middle ear infections.

Barry et al. who found in their study on otogenic intracranial complications that the ear and the CSF specimens only grew the same pathogen in 17% [25]. In line with those findings, we also found no correlation between the bacteriology of the ear discharge *vs.* that of CSF. Thus, bacterial OM may occurs coincidentally with BM [25].

Antibiotics, conjugate vaccines for the three major causes of bacterial meningitis in children aged less than 5 years (HIB, *Streptococcus pneumoniae* and *Neisseria meningitidis*), early innovative surgical techniques to treat the complications of OM, an increase in social welfare, and the development of health care systems have resulted in a dramatical reduction of ICC rates in industrialized countries. However, the diagnostics and management of OM still cause major challenges in developing countries, and the growing bacterial resistance to antibiotics is also cause for concern. The prevention of OM, and its

ay to reduce significant morbidity and mortality caused by OM-associated BM in developing countries.

Even if BM is the most common (12–72%) intracranial complication of OM [3–5], its pathophysiological mechanisms remain poorly understood. Evidently, otogenic meningitis may develop via direct extension through preformed pathways, the mastoid bone, membranous labyrinth, by hematogenous spread [26] or possibly, by passage through the cochlear aqueduct and the internal auditory canal [27]. Interestingly, when in an animal study *S. pneumoniae* were injected into the middle ear, bacteria were able to spread to the brain tissue without invading the bloodstream [28]. Eavey et al. studied temporal bones of children who had died from meningitis, and concomitant otitis media showed no evidence of a direct expansion or vascular spread [29]. Mastoiditis is a known complication of OM [30,31], but it is likely to often remain undiagnosed in resource-poor settings, as are also other severe complications such as brain abscess and otitic hydrocephalus, due to unavailability of diagnostic methods such as computed tomography (CT).

Inflammatory responses of the inner ear in BM develop due to the spread of infection via the internal auditory canal and/or via cochlear aqueduct. Damage is caused to the intracochlear structures, most importantly the organ of Corti and neural elements - and then hearing is impaired. Suppurative labyrinthitis may result from meningogenic, tympanogenic or hematogenic processes, an example being *S. pneumoniae* meningitis which rather frequently causes sensorineural hearing loss [11–13].

Hearing impairment (> 40dB) on day 7 was diagnosed in patients with or without OM in 27% and 30%, respectively, which coincides with previous studies [9]. Deafness (> 80 dB) on day 7 was found here in 16% and 10%, respectively, and this finding exceeds the previously reported 2 to 5% frequency of profound hearing loss from developed countries [11,32]. This observation reflects the severity of childhood BM in low-income countries. Any hearing impairment on day 7 associated with a higher risk for complicated or fatal clinical course. And *vice versa*: if a child had normal hearing ($\leq$ 40 dB) on day 7, they had lower odds for complications.

On day 1, by analyzing one-ear hearing thresholds separately, profound hearing loss (> 80dB) was diagnosed less often in 15% patients with OM *vs*. 25% in patients without OM. Also of interest, none of the infants with OM was deaf ($\geq$ 80dB) on day 7, while 21% of those without OM were. This might suggest that OM, in itself, does not impair hearing in BM; instead, the BM-related inflammatory process in the inner ear may account for the disorder and bacterial OM likely occurs coincidentally with BM [25]. The transient hearing deficiency seen in our study during the early days of BM is partly due to middle ear effusion. In one prospective BM study, hearing loss was transient in 16% of children [18].

Labyrinthitis ossification (LO) commonly associates with BM [33]. In LO, inflammation of the membranous labyrinth proceeds to fibrosis and/or rapid neo-osteogenesis, which may lead to a partial or total obliteration of the labyrinth´s lumen [34,35]. Since profound hearing loss due to LO can occur within two weeks from the onset of BM, it is imperative that BM patients undergo timely monitoring of their hearing and that imaging is planned if cochlear implantation seems necessary [36,37].

The use of data from our previous large treatment study [19] is a limitation of this study. However, all data were collected prospectively with specifically designed forms. This approach ensured the best feasible data collection method in a developing world setting, where there were no suction devices for ear cleaning and no possibility for an ear-, nose- and throat specialist consultation. All maneuvers were performed by skilled pediatricians. Some intracranial complications might have remained undetected because of a lack of diagnostic imaging, and not every child could be tested with ABR. In that situation, hearing was tested by otoacoustic emissions, or by asking questions, which, of course, gave less precise information. Finally, some patients were lost from follow-up due to long distances, poverty, and the isolated location. Despite all these shortcomings, we believe that our findings are reliable enough to document the frequency of BM-related hearing impairment in Angola.

6. Conclusion

In this study evaluating hearing impairment in childhood BM in Angola, no significant difference in hearing was found in children with or without OM on day 7 or at later follow-ups. Overall, variable hearing loss was detected in a third of patients one week from the BM diagnosis. Any degree of hearing deficit was associated with a higher risk for a complicated clinical course of disease or death. The most common pathogens found in the ear discharge were likely to be related more to chronic than acute middle ear infections. No correlation was observed between the bacteria identified from the ear discharge or CSF.

Adequate treatment and timely evaluation of hearing are needed to treat these infections. However, in order to reduce significant BM morbidity and mortality in developing countries, vaccinations are of paramount importance. Although unfortunately still at reach of very few children in developing countries, a hearing aid, or cochlear implantation, would mitigate severe or profound hearing loss.

Abbreviations

Acute otitis media (AOM), chronic suppurative otitis media (CSOM), otitis media (OM), bacterial meningitis (BM), cerebrospinal fluid (CSF), *Haemophilus influenzae* type b (Hib), intracranial complications (ICC), brainstem-evoked response audiometry (ABR), the better ear's hearing level (BEHL), computed tomography (CT).

Declarations

Ethics approval and consent to participate

This study is a part of a previously reported clinical trial (ISRCTN62824827). The Luanda Children's Hospital's Ethics Committee approved the study protocol on June 22, 2005, and an amendment with some substudies on Dec 21, 2007. A legal guardian's informed consent was obtained prior to each child's enrolment.

Consent for publication

Not applicable.

Availability of data and materials

Authors confirm that all relevant data are included in the article. The datasets generated and analysed during the current study are not publicly available due to them containing information that could compromise research participants. Data are however available from the author (TP) upon reasonable request.

Competing interests

The authors have no competing interests to declare.

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Authors' contributions':

LL analyzed and interpreted the study data and wrote the manuscript. ALH, AAA and JJ were major contributors in interpreting the study data and in writing the manuscript. JJ also had a big role in the design of this particular study, and in analyzing the results. HP, TP, and LB had a major role in setting up the original prospective meningitis study conducted in Angola. HP took part in writing the manuscript. AP was a major contributor setting up hearing testing in Angola and took part in writing the manuscript. TP was a major contributor collecting the data in Angola, she examined the study patients´ ears and was a major contributor in writing the manuscript.

All authors have approved the final manuscript and have agreed to be accountable for their contributions and to have ensured that questions related to the accuracy and integrity of the work have been appropriately investigated, resolved and documented.

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