# Prognostic Value and Changes of Auditory Brain Stem Response in Children With Bacterial Meningitis in Luanda, Angola

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**ABSTRACT**

**OBJECTIVE:** To assess the role of single and repeated auditory brain stem response (ABR) in predicting mortality and severe neurological injury among children having bacterial meningitis (BM) in Luanda, Angola.

**METHODS:** The morphology of ABR traces of 221 children (aged 2 months to 12 years) from admission day was analyzed and compared with age-matched normative data. Absence and delay of traces were compared with mortality and mortality or severe neurological injury in subgroup analyses. Outcome was also evaluated with repeated ABR of 166 children based on presence or absence of responses at 80 dB nHL (normal hearing level) stimulation level.

**RESULTS:** Individually, the absence of typical ABR waveform did not signify poor outcome. At the group level, latencies and interpeak latencies (IPLs) were significantly prolonged among patients with BM in comparison with controls, and the prolongation correlated with higher mortality or severe neurological sequelae.

**CONCLUSIONS:** We confirmed the effect of BM on neural conduction time in auditory pathway. However, ABR in similar settings seems not useful for individual prognostication, although at the group level, delayed latencies, IPLs, or both associated with poorer outcome.

**KEYWORDS:** Auditory brain stem response, childhood bacterial meningitis, prognosis, developing country

## Introduction

Childhood bacterial meningitis (BM) is a devastating disease that affects children worldwide. The incidence, death rate, and complications are, however, higher in developing countries. Many aspects of the disease, such as outcome prediction, still remain unclear. Any means to predict the outcome would be helpful for clinicians, particularly in resource-poor settings.

Auditory brain stem responses (ABRs) reflect the neural activity along the auditory pathway in the brain stem. Auditory brain stem responses can be used to (1) indirectly evaluate hearing (especially in small children) and (2) evaluate the intactness of the brain stem in patients with, eg, tumors, trauma, or infections involving the brain stem.

Auditory brain stem response recordings often show alterations in conditions that affect brain stem structures, such as acoustic neuroma or other tumors, central pontine myelinolysis, and multiple sclerosis. However, neuroradiological imaging has widely replaced ABRs in otoneurological diagnostics.

Auditory brain stem response monitoring is, nonetheless, still useful in posterior fossa surgery and can help distinguish drug-induced coma from true central nervous system (CNS) damage.[1] In comatose patients, ABRs can serve to assess the prognosis,[2] although the cause of coma affects the prognostic value of ABR.[1] In adults, the prognostic value is more notable in head trauma than in brain anoxia. In head trauma, normal ABRs have positive predictive values of 90% for awakening and 75% to 80% for good outcome, whereas major alterations (distortion or disappearance of peaks II-V) are associated with death or vegetative state.[3] In anoxic coma, normal ABRs have no prognostic value, whereas abnormal ABRs (loss of brain stem components III-V), although rarely seen, are associated with ominous prognosis.[3]

In hypoxic-ischemic encephalopathy, severely abnormal ABRs (distorted or abolished) in newborns older than 35 weeks' gestational age predict ominous outcome[2–4] and in older
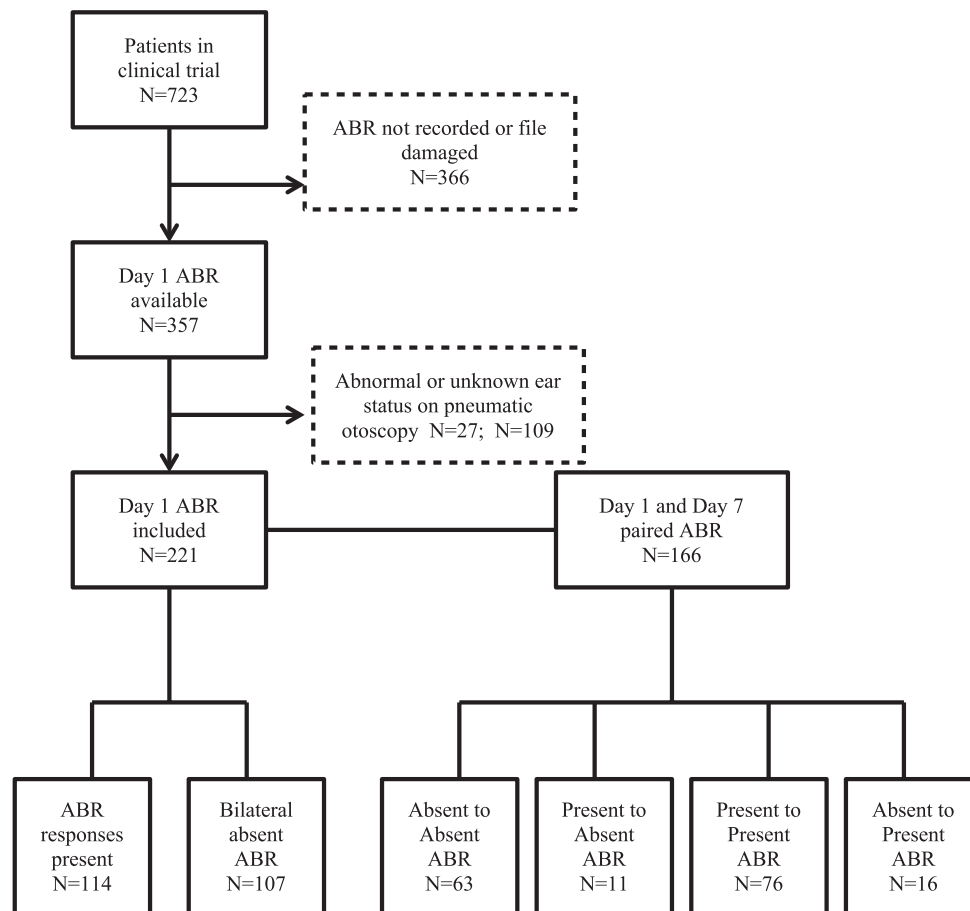
**Figure 1.** Flow of patients diagnosed with bacterial meningitis included in the study.

children can provide predictive value of survival versus death.[5] In posttraumatic coma, ABRs together with somatosensory evoked potentials can also indicate prognostic value, with absent evoked potentials predicting death.[6] Studies of children with coma due to different causes found that patients with ABR abnormalities had a greater probability of dying than patients with a normal ABR.[7,8]

Alterations in ABR patterns have also been described in CNS infections.[9–12] In a study of 50 children diagnosed with BM, overall abnormalities were detected in 64% of patients, including prolonged peak latencies and interpeak latencies (IPLs), unilateral, and bilateral absent responses.[9] Studies including 24 to 50 children with tuberculous meningitis also reported lengthening of latencies and IPLs, absence of waves, and reduction in I/V ratio.[13–15]

As the mortality and neurological injuries remain high for BM, and the disease might affect the brain stem structures via several mechanisms, we aimed to evaluate the role of ABRs in predicting the outcome after BM in a post hoc analysis of a large prospective pediatric cohort in Luanda, Angola. More specifically, we hypothesized that (1) missing or delayed ABRs would signify unfavorable outcome and that (2) BM affects the conduction properties of the brain stem structures.

## Methods

Our study forms a part of a large ($N = 723$) randomized treatment trial on childhood BM (ISRCTN62824827) aiming to improve treatment outcome with a slow initial β-lactam infusion and paracetamol in children 2 months to 13 years in the Hospital Pediátrico David Bernardino, Luanda, Angola, between 2005 and 2008 (described in detail in the original publication).[16] The ethics committee of the local hospital approved the study including the ABR protocol. Trained physicians explained the study to the child's parent or guardian, who provided written consent prior to enrollment. In case of illiteracy, the consent was signed with a fingerprint.

Bacterial meningitis was diagnosed with a positive culture or polymerase chain reaction from cerebrospinal fluid (CSF) or with BM-compatible symptoms and signs and either a positive blood culture or at least 2 of the following: high CSF leukocyte concentration ($>100 \times 10^6$/L, predominantly polymorphs), positive for Gram staining, positive for latex agglutination test, or serum C-reactive protein concentration higher than 381 nmol/L (40 mg/L). All patients received cefotaxime treatment, an antimicrobial not classified as ototoxic.

A total of 357 ABR traces recorded on admission day (within 24 hours) were available. After excluding patients with abnormal or unknown ear status on pneumatic otoscopy (T.P.), we included
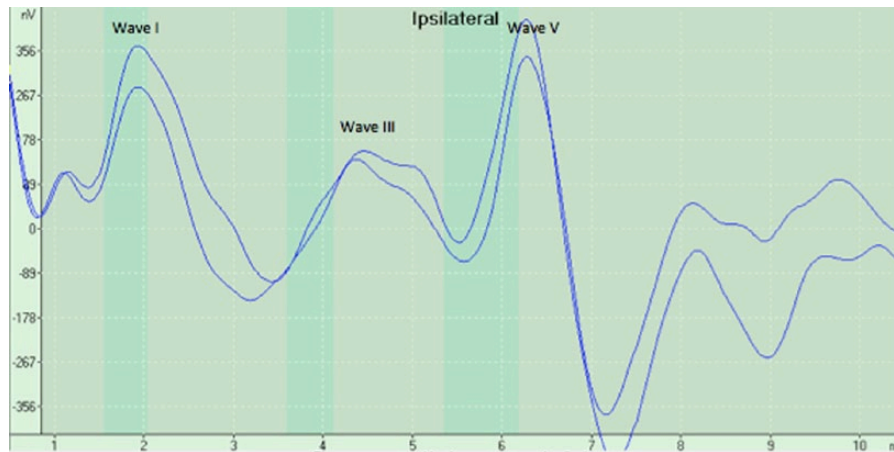
**Figure 2.** Auditory brain stem response recorded from a child having bacterial meningitis on admission day to hospital. The trace is recorded from left side with 80-dB nHL stimulation level.

ABR traces from 221 children (age range: 2 months to 12 years) and 166 corresponding follow-up traces after 7 days (±1 day). Figure 1 presents the flow of patients included in the study.

### ABR protocol and characterization

Before initiating the trial, study nurses received detailed training to perform 1-channel ABR recording. An ENT specialist (A.P.) programmed the appliance settings and protocol for the ABR procedure. Study doctor (T.P.) performed pneumatic otoscopy and the study nurses recorded the ABR responses with MADSEN Octavus BERA (Otometrics, Taastrup, Denmark) at predetermined time points.

The recording was performed bedside in natural sleep or in a comfortable position, with child usually held on his or her parent's lap. The electrodes were positioned on the mastoids and the high forehead for 1-channel ABR recording. The auditory stimuli (a broadband click) with rarefaction polarity were delivered using headphones to both ears separately with intensities of 80, 60, and 40 dB nHL (normal hearing level) at a rate of 20 Hz, whereas the contralateral side received masking with 20-dB lower stimuli. In total, 2000 sweeps were averaged. The potential differences between the ipsilateral mastoid and the vertex electrode ($Cz$) were recorded, whereas the mastoid electrode at the nonstimulated ear served as a neutral electrode. Analysis window was of 10.5 ms. A band-pass filter of 300 to 1000 Hz was used for analysis. The project manager (T.P.) monitored the measuring procedures throughout the study.

The authors of the study (A.S. and M.K.), both trained for ABR evaluation, evaluated the responses by visual analysis. The study authors were blinded to the outcome of each patient. An expert audiologist (A.A.A.) was consulted if necessary. In Figure 2, one normal ABR trace is shown as an example.

We measured the peak latencies of waves I, III, and V when they were identifiable from the traces to 80-dB nHL clicks and calculated the IPLs I to III, III to V, and I to V in those 114 subjects in whom all the 3 responses were identifiable. The better ear was chosen for analysis with asymmetrical cases. If no V wave was noted from either side, the recording was considered bilaterally absent.

The ABR latency and IPL parameters were compared with age-matched control values obtained from 101 children (63 men and 38 women; age range from 1 month to 13 years), outpatients, or their siblings of the same hospital. The upper limit of normal was defined as mean +2 SD of control. Table 1 presents the characteristics of the control population. Table 2 shows the normative values for age groups derived from control children.

We compared the characterized ABR type (bilateral absent or delay of latency parameters) with (1) fatal outcome alone and (2) death combined with severe neurological sequelae in all patients and separately in those with altered level of consciousness (Glasgow Coma Scale [GCS] < 15) and coma (GCS < 7) and also for infants (<1 year) and children ≥1 year of age.

Auditory brain stem responses were dichotomized as follows. If ABRs were bilaterally or unilaterally present, they were considered as present. If the responses were absent from both sides, the ABRs were considered as absent. Paired traces were available from 166 children. These children were divided into 4 groups based on the repeated ABR recordings. In group 1, the responses were absent in both recordings, and in group 2, they shifted from present to absent. In group 3, the responses were present in both recordings, and in group 4, the initially absent traces turned present in the control recording.

For group comparisons of latencies and IPLs between patients and controls, the subjects were divided into 2 age groups, less than and more than 24 months, as after 24 months the latencies do not shorten markedly.[17]

### Statistical analyses

Dichotomous categorical variables were compared using $\chi^2$ test and continuous variables using nonparametric Mann-Whitney $U$ test, as the data did not follow normal distribution. $P < .05$

**Table 1.** Characteristics of control population from Luanda.

| | MEDIAN, N | IQR, % | | |
|---|---|---|---|---|
| Control patients, all | 101 | 100 | | |
| Age, mo | 47 | 62 | | |
| Male sex | 63 | 62 | | |
| | **ABR RESPONSE** | | **NO ABR RESPONSE** | |
| | MEDIAN, N | IQR, % | MEDIAN, N | IQR, % |
| All | 65 | 64 | 36 | 36 |
| Age, mo | 47 | 62.5 | 40.5 | 63.5 |
| Male sex | 39 | 60 | 24 | 67 |
| Reason for visiting hospital | | | | |
| General pediatrics, control/consultation | 19 | 30 | 11 | 31 |
| Surgical, control/consultation | 40 | 63 | 24 | 67 |
| Accompanying family member | 4 | 6 | 1 | 3 |
| Diagnosed with acute infection | 28 | 44 | 9 | 25 |
| Respiratory infection | 25 | 40 | 8 | 22 |
| Gastroenteritis | 2 | 3 | 0 | 0 |
| Other | 1 | 2 | 1 | 3 |
| Excluded, otorrhea | 1 | 2 | 0 | 0 |

Abbreviations: ABR, auditory brain stem response; IQR, interquartile range.

was considered statistically significant. A logistic regression model was used to examine the predictive value of repeated ABR.

## Results

The children were overall very ill and often came to hospital after several days of illness with altered level of consciousness. Of the 221 patients (age range: 2 months to 12 years) included in the study, 22 were diagnosed with severe neurological sequelae determined as blindness, quadriplegia, severe psychomotor retardation, or hydrocephalus at discharge. Of patients, 42 died before and 13 patients after the follow-up recording on the seventh day of hospitalization. Mortality rate was lower in infants (<1 year of age, 19%) than in older children (≥1 year of age, 28%). Figure 3 presents different types of ABR traces from the study.

In the successfully recorded 221 patients, the absence (N = 107, 48%) of typical ABR waveform (ie, absent ABR, Figure 3C) on the admission day did not signify fatal outcome (80% survived the follow-up period) or poor outcome combining death and severe neurological sequelae. In the subgroup analyses including only children with altered consciousness or coma, there was a correlation neither between absent ABR and death nor between absent ABR and death or severe neurological sequelae. In the age-specific analyses, performed separately for age groups <1 year and ≥1 year of age, absent ABR did not indicate a statistical relationship with mortality or mortality combined with severe neurological injury at hospital (Table 3).

We further examined a possible association between abnormal ABR latency parameters and poor outcome in those children with ABRs present. Delayed latencies of waves III or V or IPLs correlated with a higher rate of mortality or severe neurological sequelae (P = .024). The same was true in the subgroup analysis, which included only patients with altered level of consciousness (P = .043). However, in the age group analyses, the correlation was significant only in children ≥1 year of age (P = .008). Table 4 presents the characteristics and outcome of patients with abnormal latency and IPL parameters.

We then evaluated the value of repeating the ABR assessment for outcome prediction. Table 5 presents the results of the paired ABR recordings in the 4 groups. Initially absent ABR remained absent in 63 children and appeared present in 16 children. Of these children, 5 (8%) and 0 (0%) died, respectively. Of the initially present ABRs, 11 shifted to absent in the control measurement; 3 (27%) of these patients died. Of the 76 patients whose responses remained present, only 5 (7%) died. In logistic regression analyses, belonging to a certain group did not associate with death or severe neurological sequelae significantly.

We also performed group-level comparisons of the latency parameters between the patients with BM and the controls as

**Table 2.** Age-related ABR latency and IPL values calculated from 64 control children.

| AGE GROUP | LATENCY/IPL | MEAN | SD | +2 SD UPPER LIMIT |
|---|---|---|---|---|
| ≤6 mo | | | | |
| N = 7 | I | 1.66 | 0.30 | 2.25 |
| | III | 4.26 | 0.35 | 4.96 |
| | V | 6.13 | 0.56 | 7.25 |
| | I-III | 2.61 | 0.29 | 3.19 |
| | III-V | 1.86 | 0.34 | 2.54 |
| | I-V | 4.47 | 0.57 | 5.61 |
| 7–12 mo | | | | |
| N = 8 | I | 2.01 | 0.26 | 2.52 |
| | III | 4.28 | 0.32 | 4.93 |
| | V | 6.05 | 0.32 | 6.69 |
| | I–III | 2.27 | 0.22 | 2.72 |
| | III–V | 1.78 | 0.07 | 1.91 |
| | I–V | 4.05 | 0.21 | 4.46 |
| 13–24 mo | | | | |
| N = 13 | I | 1.71 | 0.20 | 2.12 |
| | III | 4.10 | 0.37 | 4.85 |
| | V | 5.73 | 0.36 | 6.46 |
| | I–III | 2.39 | 0.34 | 3.08 |
| | III–V | 1.63 | 0.33 | 2.28 |
| | I–V | 4.02 | 0.33 | 4.68 |
| >24 mo | | | | |
| N = 39 | I | 1.68 | 0.33 | 2.34 |
| | III | 3.81 | 0.32 | 4.44 |
| | V | 5.55 | 0.44 | 6.43 |
| | I–III | 2.13 | 0.38 | 2.88 |
| | III–V | 1.74 | 0.24 | 2.23 |
| | I–V | 3.87 | 0.41 | 4.69 |

Abbreviations: ABR, auditory brain stem response; IPL, interpeak latency.

well as between survived and deceased patients with BM. Table 6 shows the age group–specific ABR characteristics in the 114 patients with BM (with all responses present) compared with the control population (n = 64). There was a significant difference between the BM children and the control population in the latency of wave V ($P = .001$) and IPLs of III to V ($P = .005$) and I to V ($P = .003$) in infants and small children <24 months and in children older than 24 months in waves I ($P = .041$), III ($P = .003$), and V ($P = .001$) and IPLs of I to III ($P = .04$) and I to V ($P = .019$). In patients, these latencies were delayed. No

significant difference was detected between survived and deceased patients.

## Discussion

We studied the prognostic value of ABRs in childhood BM in a developing country setting. Despite the relatively large sample size, our findings contradict our first hypothesis that absent ABRs at hospitalization would show prognostic value in these very ill children under these circumstances. However, in the patients in whom the responses were successfully recorded, the
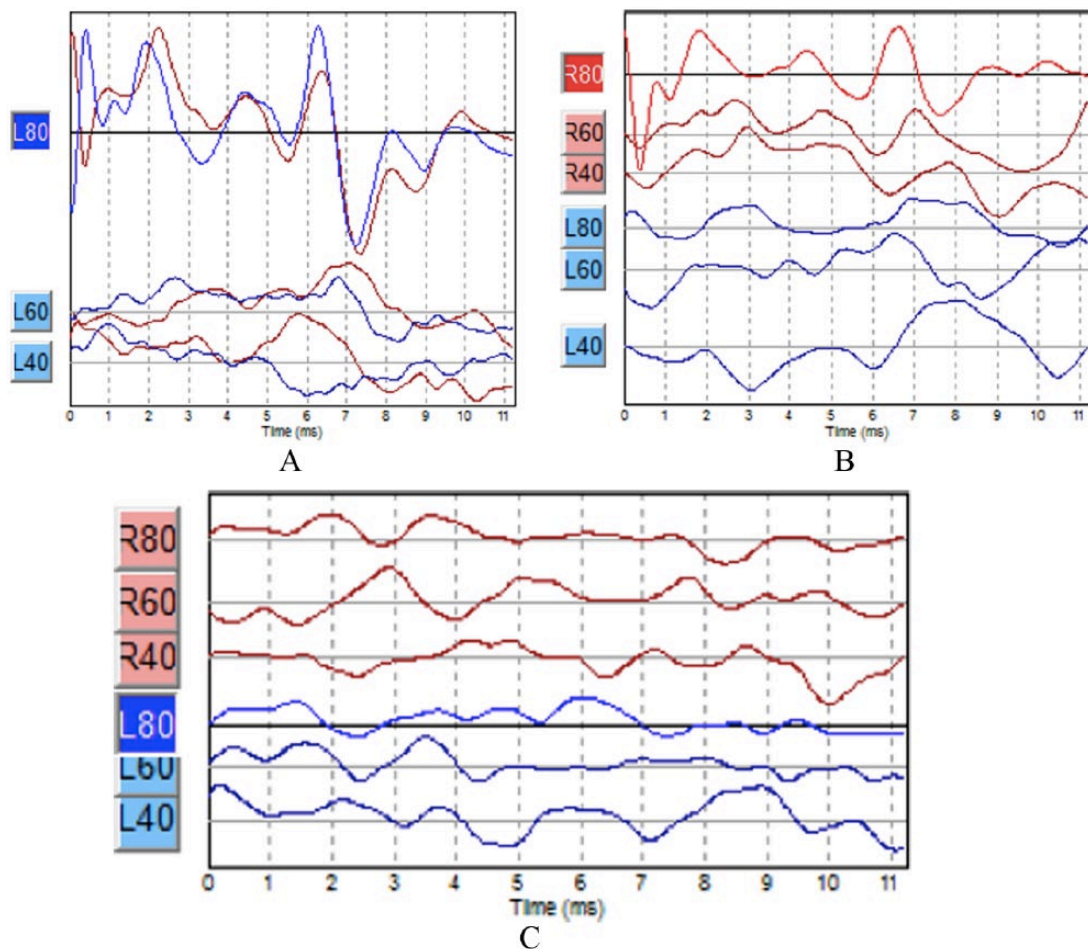
**Figure 3.** Auditory brain stem responses (ABRs) recorded from 3 children having bacterial meningitis with normal pneumatic otoscopy on admission day to hospital. (A) ABR with normal latencies and interpeak latencies (IPLs), elevated hearing threshold. (B) Delayed latency of wave V and IPLs of I to V and III to V, right ear, obtained from a 48-month-old child who died. (C) Bilateral absent response.

**Table 3.** Fatal outcome in crosstabulatios in day 1 ABR traces of children having bacterial meningitis.

| | N | FATAL OUTCOME | SURVIVED | P VALUE | DEATH OR SEVERE NEUROLOGICAL SEQUELAE | SURVIVED WITHOUT SEVERE NEUROLOGICAL SEQUELAE | P VALUE |
|---|---|---|---|---|---|---|---|
| | | NO. (%) | | | NO. (%) | | |
| Bilateral absent response | | | | | | | |
| All | 107 | 23 (43) | 84 (50) | NS | 35 (46) | 72 (50) | NS |
| <GCS | 68 | 22 (46) | 46 (50) | NS | 33 (49) | 35 (49) | NS |
| Delayed latency of waves III, V, or IPL | | | | | | | |
| All | 33 | 12 (40) | 21 (26) | NS | 17 (43) | 16 (22) | .024 |
| <GCS | 23 | 10 (40) | 13 (28) | NS | 15 (44) | 8 (22) | .043 |
| <1 y | 17 | 3 (60) | 14 (38) | NS | 6 (50) | 11 (37) | NS |
| ≥1 y | 16 | 9 (36) | 7 (16) | NS (.051) | 11 (39) | 5 (12) | .008 |

Abbreviations: ABR, auditory brain stem response; GCS, Glasgow Coma Scale; IPL, interpeak latency; NS, nonsignificant.

**Table 4.** Characteristics of children having bacterial meningitis with abnormal ABR latency of waves III or V, or IPL.

| ABNORMAL ABR PARAMETER(S) | AGE, MO | GCS ON ADMISSION | GENERAL CONDITION | NEUROLOGICAL FOCAL SIGNS | OUTCOME AT DISCHARGE | HEARING LOSS AT CONTROL(S) | NEUROLOGICAL SEQUELAE AT CONTROL |
|---|---|---|---|---|---|---|---|
| ≥2.0 SD | | | | | | | |
| III | 34 | 10 | Poor | Strabismus, abducens paresis | Severe neurological sequelae | Yes, hears 60 dB | Quadriplegic, blind, ataxic |
| III | 27 | 11 | Poor | No | Died | | |
| III | 5 | 11 | Poor | Monoparesis | Severe neurological sequelae | No | Monoparesis, blind, ataxic |
| III | 31 | 13 | Not poor | No | Died | | |
| III | 35 | 15 | Not poor | Strabismus, abducens paresis | Died | | |
| III | 45 | 9 | Poor | Strabismus, abducens paresis | Died | | |
| V | 16 | 5 | Poor | No | Survived | No | |
| I, V | 44 | 15 | Not poor | No | Survived | No | |
| I, III | 5 | 10 | Poor | Strabismus, abducens paresis | Died | | |
| I–III | 4 | 15 | Not poor | No | No | No | |
| III–V | 7 | 10 | Not poor | Strabismus, abducens paresis | Severe neurological sequelae | Yes, hears 80 dB | Blind, ataxic |
| III–V | 8 | 15 | Not poor | No | Survived | No | |
| III–V | 13 | 15 | Not poor | No | Survived | No | |
| III–V | 9 | 12 | Poor | Fixed gaze | Moderate neurological sequelae | Deaf at 6 mo | Monoparesis, ataxic |
| III–V | 54 | 3 | Poor | No | Died | | |
| III–V | 5 | 8 | Poor | No | Mild neurological sequelae | No | Ataxic |
| III–V | 7 | 15 | Not poor | No | Survived (died later) | No | |
| III–V | 8 | 11 | Poor | No | Died | | |
| I–V | 16 | 13 | Not poor | No | Died | No | |

*(Continued)*

**Table 4.** (Continued)

| ABNORMAL ABR PARAMETER(S) | AGE, MO | GCS ON ADMISSION | GENERAL CONDITION | NEUROLOGICAL FOCAL SIGNS | OUTCOME AT DISCHARGE | HEARING LOSS AT CONTROL(S) | NEUROLOGICAL SEQUELAE AT CONTROL |
|---|---|---|---|---|---|---|---|
| V, I–V | 12 | 11 | Poor | No | Mild neurological sequelae | No | Ataxic |
| I–III, I–V | 7 | 14 | Poor | No | Died | | |
| I–III, I–V | 35 | 12 | Poor | Strabismus, abducens paresis | Severe neurological sequelae | No | Quadriplegic, blind, ataxic |
| I–III, I–V | 12 | 11 | Not poor | No | Died | | |
| III–V, I–V | 43 | 10 | Poor | No | Died | | |
| III–V, I–V | 9 | 11 | Poor | Strabismus, abducens paresis | Survived | Deaf at discharge | |
| III–V, I–V | 8 | 15 | Not poor | No | Survived | No | |
| III, I–III, I–V | 9 | 5 | Poor | Strabismus, abducens paresis | Moderate neurological sequelae | Yes, hears 80 dB | Monoparesis, ataxic |
| V, I–III, I–V | 11 | 12 | Not poor | Fixed gaze | Severe neurological sequelae | No | Quadriplegic, ataxic |
| V, III–V, I–V | 48 | 15 | Not poor | No | Died | | |
| V, III–V, I–V | 7 | 10 | Not poor | No | Survived | No | |
| I–III, III–V, I–V | 7 | 15 | Not poor | Strabismus, abducens paresis | Survived | No | |
| I–III, III–V, I–V | 10 | 15 | Not poor | No | Survived | No | |
| III, V, I-III, III–V, I–V | 136 | 14 | Not poor | No | Survived | No | |

Abbreviations: ABR, auditory brain stem response; GCS, Glasgow Coma Scale; IPL, interpeak latency.

**Table 5.** Repeated auditory brain stem response traces recorded on days 0 and 7, divided into 4 groups.

| GROUP<br>GROUP DEFINITION[a] | 1<br>ABSENT;<br>ABSENT<br>NO. (%) | 2<br>PRESENT;<br>ABSENT | 3<br>PRESENT;<br>PRESENT | 4<br>ABSENT;<br>PRESENT | ALL |
|---|---|---|---|---|---|
| | N = 63 (38) | N = 11 (7) | N = 76 (46) | N = 16 (10) | N = 166 (100) |
| Death at discharge | 5 (8) | 3 (27)[b] | 5 (7) | 0 (0) | 13 (8) |
| Severe neurological sequelae at discharge | 8 (13) | 1 (9) | 9 (12) | 2 (13) | 20 (12) |
| Any neurological sequelae at discharge | 35 (56) | 7(64) | 31 (41) | 11 (69) | 84 (51) |
| Profound hearing loss at control (0-3 mo) | 0 (0) | 1 (9) | 3 (4) | 1 (6) | 5 (3) |

[a]Obtainable (present) recording from at least one side or unobtainable (absent) bilateral recording at 80 dB nHL stimuli.
[b]In addition, 3 deaths after discharge.

**Table 6.** ABR latencies and IPLs from patients and controls with normal ear status on pneumatic otoscopy.

| | PATIENTS | CONTROLS | *P* VALUE |
|---|---|---|---|
| All | N = 114 | N = 64 | |
| Age <24 mo | N = 61 | N = 25 | |
| | Mean/median (SD/IQR) | | |
| Median age | 7 (8) | 11(11.5) | NS |
| I latency | 1.85 (0.26) | 1.78 (0.29) | NS |
| III latency | 4.34 (0.45) | 4.20 (0.36) | NS |
| V latency | 6.30 (0.44) | 5.93 (0.46) | .001 |
| IPL I–III | 2.48 (0.37) | 2.43 (0.33) | NS |
| IPL III–V | 1.93 (0.30) | 1.80 (0.20) | .005 |
| IPL I–V | 4.45 (0.40) | 4.15 (0.43) | .003 |
| Age ≥24 mo | N = 53 | N = 39 | |
| | Mean/median (SD/IQR) | | |
| Median age | 54 (43.5) | 71 (49) | NS |
| I latency | 1.80 (0.29) | 1.66 (0.22) | .041 |
| III latency | 4.05 (0.40) | 3.80 (0.32) | .003 |
| V latency | 5.83 (0.51) | 5.55 (0.44) | .001 |
| IPL I–III | 2.30 (0.34) | 2.12 (0.38) | .04 |
| IPL III–V | 1.78 (0.27) | 1.75 (0.24) | NS |
| IPL I–V | 3.97 (0.44) | 3.81 (0.42) | .019 |

Abbreviations: ABR, auditory brain stem response; IPL, interpeak latency; IQR, interquartile range; NS, nonsignificant.

mortality rate combined with severe neurological sequelae was significantly higher with delayed response in all patients and in children ≥1 year of age, and the mortality rate alone was higher in children ≥1 year of age.

With repeated ABR measurements, the percentage of fatal outcome for those whose ABR remained or turned absent (11%, N = 8/74) was higher than for those whose ABR persisted or turned present (5%, N = 5/92). However, this was not

statistically significant. Furthermore, our findings suggest that meningitis affects the conduction time of neural impulses in the auditory pathway in the brain stem, prolonging the ABR latencies.

Although studies of coma with traumatic origin and stroke showed prognostic value of progressive ABR degradation in adults in bedside recordings,[18] we failed to find similar results in our patients with childhood BM in a developing country setting. The few studies of meningitis, but of different causes, have ended up with the same result. In Japanese encephalitis, ABR abnormalities correlated with brain stem lesions on computed tomographic and magnetic resonance imaging scans, but not with severity of coma or outcome.[12] As in cortical evoked responses from primary somatosensory and auditory cortex in comatose patients,[19] the cause of altered level of consciousness seems to play a major role when the prognostic value of ABR is studied.

As in this study of BM, more subtle ABR pattern changes at the group level, especially the lengthening of absolute and IPLs, have been previously reported in meningitis of varying causes, such as tuberculous[13,14] and mixed cause.[13,14]

Our study has some limitations. First of all, hearing loss is a well-known sequelae of childhood BM, which causes elevation in the ABR thresholds or deafness unilaterally or bilaterally. Hearing loss fluctuation is known to occur in the course of the disease[20,21] and was also observed in the original cohort.[22] This might explain some of the variance and lability in our ABR results. Processes causing conductive hearing loss may also prolong the absolute ABR latencies. The IPLs, however, are not markedly affected by the conductive or sensorineural dysfunctions in the outer or inner ear level. In addition, in our study design, the repeated measurement was set for quite late, whereas the occurrence of death usually happened early after the hospitalization. Accordingly, in our setting, we could only measure the late in-hospital mortality of the disease.

Medication may also affect the ABR tracings. Even though the ABR is thought to be affected minimally by sedatives or anesthetics, other medications may have an effect on the inner ear. In our study, we did not use ototoxic antibiotics. However, some of the patients did use antibiotics prior to hospitalization that we were not able to control. Finally, 31% of our patients had positive malaria smear and most of them were given quinine. Although quinine is thought to raise the hearing threshold only to a lesser degree and after the loading dose, its role particularly in the first ABR testing remains unclear.

Finally, the ABR was not performed in quiet laboratory settings, nor could we control the examination room temperature, availability of electricity, or interference in the hospital, which sometimes complicated performing the ABR testing. Thus, ABR was not tested with all children initially or at the preset control time.

The missing brain stem–evoked responses (waves III and V) could be validated if the wave I was present in ABR, thus confirming the activation of the auditory system. However, the signal-to-noise ratio of the recordings did not permit this analysis, meaning that the absent ABRs may possibly be a result of inadequate stimulation or recording. This may explain the lack of prognostic value of the missing ABR at hospitalization. However, to partly overcome this obstacle in a developing country setting, we analyzed the follow-up recordings to obtain validation from repeated recording. We are aware that our results do not apply to ABR recordings performed in a neurophysiology laboratory. However, because our aim was to test the prognostic value of ABRs particularly in a developing country setting, we believe our data demonstrate that in such settings absent ABRs at hospitalization are unable to provide prognostic information in patients with BM.

## Conclusions

To the best of our knowledge, this is the largest study assessing the role of ABR in prognosis of childhood BM in a developing country setting. At the group level, we observed that childhood BM affects the neural conduction time in the auditory neural pathway in brain stem. However, at the individual level, we found no clear benefit from a single ABR recording in predicting the outcome. In other words, even absent ABRs in similar settings cannot be taken as an indication for poor outcome. However, delayed latencies of waves III or V or IPLs correlated with a higher rate of mortality or severe neurological sequelae. The role of delayed latency and IPL parameters in individual prognostication deserves further confirmation.

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## Author Contributions

TP, LB, AP, and AAA conceived and designed the experiments. MK, AS, TP, IR, and AAA analyzed the data. MK and AS wrote the first draft of the manuscript. TP, IR, PN, and LL contributed to the writing of the manuscript. MK, AS, TP, LB, IR, AP, AAA, PN, and LL agree with manuscript results and conclusions. MK, TP, IR, AP, PN, and LL jointly developed the structure and arguments for the paper. TP, LB, IR, AP, AAA, PN, and LL made critical revisions and approved final version. All authors reviewed and approved the final manuscript.

## Disclosures and Ethics

As a requirement of publication, authors have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published

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