BRIEF REPORT

Risk Factors for Death and Severe Neurological Sequelae in Childhood Bacterial Meningitis in Sub-Saharan Africa

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We report a morality rate of 33% among 403 children with bacterial meningitis in Angola. A fatal outcome was associated with impaired consciousness, severe dyspnea, and seizures, and severe neurological sequelae (found in 25% of our patients) was associated with delayed presentation to the hospital, impaired consciousness, and seizures. Being underweight was of secondary importance. Treatment with ceftriaxone, rather than with penicillin plus chloramphenicol, did not improve outcome.

Despite the virtual elimination of *Haemophilus influenzae* type b (Hib) meningitis from the developed world by means of vaccination, childhood bacterial meningitis remains a major problem globally. In industrialized countries, only ~5% of patients with childhood bacterial meningitis die, and 15%–20% develop sequelae; in nonindustrialized countries, however, 12%–50% of patients die, and 25%–50% of patients experience sequelae [1–3].

Because many clinical and laboratory features are associated with the outcome of bacterial meningitis [4–7], various scoring systems have been developed to assess the severity of the disease [8, 9]. Identification of the risk factors for poor outcome at hospital admission and characterization of those risk factors that develop during the course of illness would give valuable information for clinicians attempting to find a balance between the patient's needs and existing resources. In this study, we applied multivariate analysis to identify the most important independent predictors of poor outcomes in a large series of patients with childhood bacterial meningitis in Angola.

Patients and methods. The Pediatric Hospital of Luanda is a teaching hospital in the capital (population, ~5 million) of Angola. In 2004, it was the only hospital in the country with resources for routine microbiological analysis of CSF. It was also a bacterial meningitis referral hospital for other hospitals in Luanda. Bacteriological analysis was performed if CSF samples were visibly cloudy or if the patient had a leukocyte count >10 cells/μL or had a glucose level <25 mg/mL [10].

We reviewed the charts of 555 patients aged 2 months through 12 years who were treated for bacterial meningitis at the infectious diseases ward during 2004. In 2004, 123 of 717 children who were admitted to the Pediatric Hospital with suspected bacterial meningitis died in the emergency department, 136 infants (age, <2 months) were admitted to the neonatal ward, and 458 children were admitted to the infectious disease ward, which also admitted 97 patients with bacterial meningitis from other wards. Bacterial meningitis was considered to have been diagnosed if a pathogen was detected on culture, by latex agglutination testing, or by PCR of a CSF sample or if the CSF leukocyte count was >50 cells/μL (predominantly polymorphs) and had positive Gram stain results [10].

Various clinical and laboratory parameters, which are listed in table 1, were recorded. The data were computerized and analyzed with StatView software, version 5.1 (SAS Institute). Fisher's exact test was used for nominal variables, and the unpaired Student's *t* test was used for continuous variables. Continuous variables without normal distribution were log transformed before analysis. Variables with a P value <.1 in univariate analysis were submitted to a logistic regression model as independent variables, using each outcome, one by one, as a dependent variable. If the level of $P < .05$ was reached, the covariate was deemed to be an independent predictor of the dependent variable. The results are expressed as ORs with 95% CIs.

The main outcome measures were death in the ward or severe neurological sequelae at hospital discharge (very few patients attended follow-up appointments). In 2004, hearing tests were not yet routinely performed at our institution for evaluation of patients with bacterial meningitis. Severe neurological sequelae were defined as blindness, quadriplegia and/or paresis, hydrocephalus requiring a shunt, or severe psychomotor retardation.

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Table 1. Univariate analysis of risk factors at hospital admission for death or severe neurological sequelae due to bacterial meningitis.

	Death (n = 403)			Severe neurological sequelae (n = 249)		
Variable	Yes	No	*P*	Yes	No	*P*
No. (%) of patients	133 (33)	270 (67)		62 (25)	187 (75)	
Age, median months (IQR)	9 (19)	9 (19)	.84	7 (13)	10 (21)	.05
Duration of illness, median days (IQR)	6.5 (10.0)	6.0 (6.0)	.63	7.0 (9.0)	6.0 (6.0)	.04
Seizures prior to hospital admission	83/111 (75)	144/235 (61)	.01	42/56 (75)	101/178 (57)	.01
Weight for age under −2 SDs of the median	43/114 (38)	65/243 (27)	.04	23/60 (38)	41/181 (23)	.02
Poor general condition[a]	46/87 (53)	45/207 (22)	<.001	14/43 (33)	30/163 (18)	.04
Impaired consciousness	87/110 (79)	130/238 (55)	<.001	43/58 (74)	86/179 (48)	<.001
Glasgow coma score,[b] mean value ± SD	12.6 ± 3.9	14.2 ± 2.4	.005	12.6 ± 3.9	14.5 ± 1.9	.002
Blantyre coma score,[c] mean value ± SD	3.5 ± 1.5	4.4 ± 1.4	<.001	3.7 ± 1.4	4.6 ± 1.0	<.001
Seizures at hospital admission	47/101 (47)	66/220 (30)	.004	26/52 (50)	40/167 (24)	<.001
Focal neurological signs	27/99 (27)	48/223 (22)	.26	14/51 (27)	33/171 (19)	.21
Additional focus of infection present						
Any	47/101 (47)	75/228 (33)	.02	19/53 (36)	55/174 (32)	.56
Pneumonia	42/101 (42)	69/228 (30)	.05	19/53 (36)	49/174 (28)	.28
Severe dyspnea	23/98 (23)	25/220 (11)	.005	9/50 (18)	16/169 (9)	.10
CSF leukocyte count,[d] median cells/mm^3 (IQR)	505 (1893)	809 (2145)	.09	720 (1842)	810 (2190)	.70
CSF glucose level[e], median mg/dL (IQR), median	18 (16)	20 (24)	.57	15 (17)	20 (22)	.005
Hemoglobin level,[f] median g/dL (IQR)	6.6 (3.7)	6.6 (3.3)	.69	6.6 (3.3)	6.7 (3.4)	.64
Positive malaria test result	31/102 (30)	77/232 (33)	.61	19/55 (35)	58/176 (33)	.83
Positive HIV test result	6/30 (20)	12/142 (8)	.06	2/30 (7)	10/111 (9)	.68
Causative agent						
Haemophilus influenzae	76/127 (60)	156/257 (61)	.87	38/56 (68)	106/180 (59)	.23
Streptococcus pneumoniae	35/122 (29)	58/254 (23)	.22	14/56 (25)	38/178 (21)	.57
Neisseria meningitidis	5/127 (4)	35/257 (14)	.004	3/56 (5)	30/180 (17)	.03
Other bacteria	11/127 (9)	8/257 (3)	.02	1/56 (2)	6/180 (3)	.55

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range.

[a] Defined as weight for age less than −2 SDs and/or severe dyspnea.
[b] Calculated on the basis of data for 139 patients.
[c] Calculated on the basis of data for 175 patients.
[d] Calculated on the basis of data for 401 patients.
[e] Calculated on the basis of data for 399 patients.
[f] Calculated on the basis of data for 259 patients.

Results. Of the 555 children, 422 fulfilled our criteria for bacterial meningitis [10], but outcome was not recorded for 19 patients. Data for the remaining 403 children were analyzed. The median patient age was 9.0 months. The causative agents were as follows: Hib, 232 cases; *Streptococcus pneumoniae,* 93 cases; *Neisseria meningitidis,* 40 cases; unspecified streptococcus, 8 cases; *Streptococcus agalactiae,* 7 cases; *Streptococcus pyogenes,* 2 cases; and *Klebsiella pneumoniae,* 2 cases. In 19 cases, bacteriological identification of the pathogen was not made [10].

The main clinical characteristics of the patients have been described elsewhere [10]. Most patients presented to the hospital late in the course of the illness; the median duration of illness before hospital admission was 6 days. Consciousness was impaired in 193 (55%) of 348 patients, and deep coma was present in 24 (7%) of 348 patients, and 131 (38%) of 348 were fully conscious. Severe dyspnea was found in 148 (5%) of 318 patients. Seizures before, at, or after hospital admission were recorded in 227 (66%) of 346 patients, 113 (35%) of 321 patients, and 188 (59%) of 318 patients, respectively.

The in-ward fatality rate was 33% (133 of 403 patients died). Among the survivors, severe neurological sequelae developed in 25% (62 of 249 patients). Overall, 195 (51%) of 382 children either died or experienced severe neurological sequelae. The mortality rates associated with Hib meningitis, pneumococcal meningitis, and meningococcal meningitis were 33%, 38%, and 13%, respectively; the mortality rate associated with "other" types of meningitis was 58%. Mortality was especially high among infants with meningitis caused by *S. agalactiae* (5 [71%] of 7 patients died) or caused by unidentified streptococcus (5 [63%] of 8 patients died). Severe neurological sequelae developed in 26% (38 of 144) of the patients with Hib meningitis, 27% (14 of 52) of those with pneumococcal meningitis, 9% (3 of 33) of those with meningococcal meningitis, and 14% (1 of 7) of those with "other" bacterial meningitis.

In univariate analysis (table 1), the risk factors for death were

seizures (at any time), weight for age less than −2 SDs, poor general condition, altered level of consciousness, low Glasgow or Blantyre coma score, other focus of infection, and severe dyspnea. Mortality was lowest among patients with meningococcal meningitis and was highest among patients with "other" types of bacterial meningitis. A history of malaria or receipt of antimicrobial medication before hospital admission did not change the risk, nor did having a positive malaria test result. The mortality rate was 33% among HIV-positive patients (6 of 18 patients died) and was 16% among HIV negative patients (24 of 154 patients died; $P = .06$). Multivariate analysis of the data indicated that the independent predictors of death were impaired consciousness, severe dyspnea, and seizures (table 2).

In univariate analysis, the following 9 findings at hospital admission were found to be risk factors associated with severe neurological sequelae (table 1): delayed presentation, seizures, weight for age less than −2 SDs, poor general condition, impaired consciousness, low Glasgow or Blantyre coma score, severe dyspnea, and low CSF glucose level. Meningococcal meningitis was associated with a lower risk, compared with other forms of meningitis. Multivariate analysis indicated that delayed presentation, impaired consciousness, and seizures were independent predictors of severe neurological sequelae (table 2). During hospitalization, severe neurological sequelae were associated with prolonged fever ($P < .001$), secondary fever ($P < .001$), prolonged altered consciousness ($P < .001$), seizures ($P < .001$), focal neurological signs ($P = .008$), an extrameningeal focus of infection ($P = .02$), and dehydration ($P < .001$).

Treatment with ceftriaxone, instead of with the primary regimen of penicillin plus chloramphenicol, did not improve the prognosis. The mortality rate among patients who received ceftriaxone was 29% (17 of 59 patients died), compared with 29% among those who received penicillin plus chloramphenicol (77 of 268 patients died; $P > .99$). Severe neurological sequelae developed in 10 (24%) of 41 patients who received ceftriaxone and 48 (25%) of 190 patients who recceived penicillin plus chloramphenicol ($P > .99$).

Conclusions. The gloomy prognosis associated with bacterial meningitis in sub-Saharan Africa [1, 3, 9] was clearly documented in this study. Many children died even before being admitted to a hospital ward, 133 (33%) of 403 patients died while hospitalized, and 62 (25%) of 249 survivors experienced severe neurological sequelae.

An association between short duration of illness and poor outcome has been found in industrialized countries, whereas in nonindustrialized countries, poor prognosis is often associated with delayed presentation [7–9]. This agrees with our findings. As in other studies [5–9], impaired consciousness and lowered Glasgow or Blantyre coma scores strongly predicted both death and severe neurological sequelae. The longer the duration that the child was unconscious, the greater was the risk for severe neurological sequelae. In addition, seizures [4–9] and focal neurological symptoms [6] were warning signs of poor outcome.

In line with previous experience of pneumococcal and Hib meningitis, a concomitant focus of infection (in most cases, pneumonia) was associated with poor prognosis in univariate analysis. However, this association was not statistically significant in multivariate analysis. A similar association occurred with malnutrition; weight for age less than −2 SDs initially seemed to be an important prognostic factor but was not statistically significant in multivariate analysis. Nevertheless, 7 of 10 children with severe malnutrition died.

Because it was retrospective in nature, our study has certain limitations. Complete data were not obtained for all patients, especially in those cases in which the patient died soon after presentation. However, by performing a multivariate analysis,

Table 2. Binomial logistic regression analysis of independent risk factors for death or severe neurological sequelae in patients with bacterial meningitis.

	Death ($n = 290$)		Severe neurological sequelae ($n = 200$)	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Age <12 months	…	…	0.91 (0.39–2.14)	.83
History of symptoms >3 days	…	…	3.73 (1.24–11.26)	**.02**
Weight for age less than −2 SDs	1.21 (0.67–2.19)	.53	1.81 (0.79–4.18)	.16
Impaired consciousness	2.61 (1.44–4.72)	**.002**	2.96 (1.32–6.63)	**.009**
Severe dyspnea	2.42 (1.17–5.03)	**.02**	1.44 (0.50–4.13)	.50
Additional focus of infection present	1.03 (0.57–1.87)	.93	…	…
Convulsions during hospitalization	2.49 (1.36–4.58)	**.003**	9.34 (3.49–25.00)	**<.001**
CSF leukocyte count <100 cells/mm^3	1.63 (0.83–3.20)	.15	…	…
CSF glucose level <20 mg/dL	…	…	1.73 (0.79–3.79)	.17
Meningitis due to *Neisseria meningitidis*	0.33 (0.09–1.19)	.09	0.86 (0.19–3.91)	.85

NOTE. *P* values indicating independent risk factors for death or severe neurological sequelae are given in boldface type.

we increased the probability of detecting the essential predictors of death and severe neurological sequelae. Few earlier studies on childhood bacterial meningitis in developing countries [4–7] have analyzed data to this depth. Because no audiological testing was being performed in 2004, we have no data on hearing impairment. If this information had been available, the outcomes for these children would almost certainly have been found to be even poorer than our study indicates. A prospective study that we are conducting in the same hospital [11] will cast light on this important issue.

Encouraging parents to seek medical care for their children sooner, asking the primary health care posts to transfer patients without delay, and keeping the indications for lumbar puncture flexible to distinguish bacterial meningitis from malaria are some of the tools at hand today to improve the prognosis of childhood bacterial meningitis in sub-Saharan Africa. However, we believe that, in the long run, only large-scale vaccination will bring major improvement.

Scoring systems that require laboratory indices are of little use where resources are limited. Therefore, our findings regarding some easily measurable clinical variables may be of value in resource-limited countries. Because intensive care facilities are virtually nonexistent, the clinicians alarmed by these signals may have a slightly better chance to offer the best available treatment to the child who is in danger. Importantly, not all new tools to improve the prognosis of bacterial meningitis are expensive; our group found oral glycerol to be greatly beneficial in the prevention of severe neurological sequelae [12]. New paths to other inexpensive treatment alternatives should also be actively explored.

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