Culture- and antigen-negative meningitis in Guatemalan children

Erica L. Dueger,[1,2] *Edwin J. Asturias,*[2] *Neal A. Halsey,*[2]
and Guatemala Pediatric Bacterial Surveillance Working Group[3]

Suggested citation Dueger EL, Asturias EJ, Halsey NA, Guatemala Pediatric Bacterial Surveillance Working Group. Culture- and antigen-negative meningitis in Guatemalan children. Rev Panam Salud Publica. 2008;24(4): 248–55.

ABSTRACT

Objective. *To compare children with confirmed bacterial meningitis (CBM) and those with culture- and latex-negative meningitis (CLN).*

Methods. *Children 1 to 59 months of age admitted to three major referral hospitals in Guatemala City with clinical signs compatible with bacterial infections were evaluated prospectively between 1 October 1996 and 31 December 2005. Bacterial cultures and latex agglutination antigen testing were performed on samples of cerebrospinal fluid (CSF).*

Results. *The case-fatality rate was significantly higher in the 493 children with CBM than in the 528 children with CLN (27.6% and 14.9%, respectively; P < 0.001). Children with CBM were less likely to have received antibiotics and more likely to have seizures, shock, or coma on admission than children with CLN. Among the 182 CBM survivors and 205 CLN survivors studied between October 2000 and December 2005, clinically observed sequelae were present at discharge in a higher percentage of the CBM than of the CLN group (78.6% and 46.8%, respectively; P < 0.0001). CSF glucose < 10 mg/dL, peripheral neutrophils < 2 000 cells/mm^3, coma or shock at admission, and concurrent sepsis or pneumonia were risk factors for mortality in children with CBM; only coma or shock at admission predicted mortality in children with CLN.*

Conclusions. *The high case-fatality and sequelae rates suggest that many children with CLN may have had bacterial meningitis. Estimates based on confirmed meningitis alone underestimate the true vaccine-preventable disease burden. Additional studies to determine etiologies of CLN in this population are indicated.*

Key words Viral meningitis, bacterial meningitis, aseptic meningitis, Guatemala.

Meningitis is an important cause of pediatric morbidity and mortality worldwide. Sequelae may include hearing loss, mental retardation, seizures, behavioral changes, spastic cerebral palsy, and hydrocephalus (1–4). In Guatemala, the incidence of meningitis has been estimated at 85.4 per 100 000 children/year among children under 5 years of age in Guatemala City, with a case-fatality rate of 23% (5).

Most reports on the clinical characteristics and outcomes of meningitis

[1] Centers for Disease Control and Prevention, International Emerging Infections Program, PSC 452 Box 115; FPO, AE 09835. Send correspondence and reprint requests to: Erica L. Dueger, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Room w5041, Baltimore, Maryland 21205, USA; e-mail: edueger@jhsph.edu.

[2] Johns Hopkins Bloomberg School of Public Health, International Health, Baltimore, Maryland 21205, United States.

[3] Members of the Guatemala Pediatric Bacterial Surveillance Working Group, Guatemala City, Guatemala, include: Monica Soto, Ricardo A. Menendez, Fabio A. Recinos, Patricia Ramirez, Tamara Velasquez, Jorge R. Matheu, M. Remei Gordillo, and Mirsa Ariano.

focus on bacterial meningitis confirmed by culture or antigen testing of cerebrospinal fluid (CSF) or description of meningitis caused by specific organisms. Most reports of culture-negative or latex agglutination-negative meningitis (CLN) have focused on developing methods to aid in early differentiation of bacterial versus nonbacterial meningitis (6–10). CLN generally has a more benign course with less mortality and morbidity than confirmed bacterial meningitis (CBM) (1–5, 11–22). We noted a higher than expected mortality in children with CLN. To gain an increased understanding of this illness, we compared the characteristics, outcomes, and risk factors for mortality in Guatemalan children with CLN to those for children with CBM.

MATERIALS AND METHODS

Study population

Children 1 to 59 months of age admitted to the three major referral hospitals (Roosevelt Hospital, San Juan Dios Hospital, and General Hospital of the Instituto Guatemalteco de Seguridad Social) in Guatemala City with clinical signs compatible with bacterial infections were evaluated prospectively between 1 October 1996 and 31 December 2005. Study physicians reviewed admission and laboratory logbooks daily to identify children with possible invasive bacterial disease. Demographic data, clinical and laboratory data including blood and CSF culture results, and latex agglutination results were collected from medical charts by the study physicians. Serious sequelae (convulsions, cerebral vascular accidents, cranial nerve paralysis, and hydrocephalus) present at discharge were collected by reviewing discharge notes beginning in October 2000. Cerebral vascular accidents included cases of infarct or thrombosis, and hydrocephalus was diagnosed by computed tomography. Additional diagnostic testing such as audiologic and neurologic testing are not performed as part of standard hospital practice in Guatemala unless signs of impairment are present; therefore, because of the inconsistent availability of data on deafness, blindness, quadriparesis, quadriplegia, and psychomotor retardation, these data were not included in this study. A limited discussion of children with CBM through 31 January 1999 was presented in an earlier report (5).

Case definitions

Pleocytosis was defined as a CSF white blood cell count of ≥ 10 white blood cells/mm^3 because up to 32% of children with bacterial meningitis have CSF white blood cell counts < 100/mm^3 (5). CSF white blood cell count was not adjusted for red blood cell counts (7, 23). CBM was defined as either: (1) a CSF culture positive for an organism considered not to be a contaminant, or (2) a negative CSF culture with pleocytosis plus either a CSF latex agglutination test positive for *Streptococcus pneumoniae* or *Haemophilus influenzae* type b or a blood culture positive for an organism considered not to be a contaminant. CLN was defined as a negative CSF culture with pleocytosis plus negative CSF latex agglutination tests for both *S. pneumoniae* and *H. influenzae* type b.

Laboratory procedures

CSF was cultured on IsoVitalex-enriched chocolate and blood agar. All CSF samples were tested within 24 hours for *H. influenzae* type b and *S. pneumoniae* antigens using latex agglutination (Directigen, Becton Dickinson Microbiology Systems, Lutherville, MD, United States); latex agglutination was not performed for *Neisseria meningitidis* as part of this study. Aliquots of CSF were stored at 2°C to 8°C until weekly transfer to –70°C for storage. Blood cultures were obtained at the discretion of the admitting physicians. The initial procedures included culture in brain–heart infusion broth with subcultures on chocolate and MacConkey agar at 24 hours and within the next 7 days if turbidity developed. Automated blood cultures (BACTEC, Becton Dickinson Microbiology Systems, Lutherville, MD, United States) were introduced into two hospitals in May 1997 and into the third hospital in January 1998.

Statistical analysis

Data were collected on standardized forms and double entered into an Access (Microsoft, Seattle, WA, United States) database. Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS-PC version 10, Chicago, IL, United States). Proportions were compared using two-tailed χ^2 with Yates' correction or Fisher's exact tests. The Student *t*-test was used to compare group means. Nonparametric variables were compared using the Mann-Whitney test. Univariate and multivariate logistic regression models were used to determine the odds ratios for mortality risk factors. A significance level of $P < 0.05$ was used to reject the null hypothesis.

RESULTS

From October 1996 through December 2005, 493 children with CBM and 528 children with CLN were identified. Latex agglutination results were available for 1 002 (98.1%) CSF specimens. The most common cause of CBM was *H. influenzae* type b followed by *S. pneumoniae* (Table 1). Bacterial cultures of CSF or blood were positive in 135 (63.4%) of the 213 children with confirmed *H. influenzae* type b and in 131 (77.1%) of the 170 children with *S. pneumoniae* meningitis (Table 2). The *H. influenzae* type b latex agglutination test was positive in eight children with CSF or blood cultures positive for other organisms: *Streptococcus* spp. (n = 3), *Staphylococcus aureus* (n = 2), or different gram-negative organisms (n = 3). The *S. pneumoniae* latex agglutination test was positive in samples from two children with positive CSF or blood cultures for other organisms (*H. influenzae* type b and *Streptococcus agalactiae*).

In these cases, diagnosis of the etiologic agent was based on culture results. Serum C-reactive protein may be a useful test to distinguish bacterial and viral meningitis, but serum samples were not collected as part of this study.

Blood cultures were obtained on 345 (70.0%) children with CBM and 394 (74.6%) children with CLN. Of the children with CBM with both CSF and blood culture results, 24% were positive on both CSF and blood, 34% were positive only on CSF culture, and 16% were positive only on blood culture. Discordant results between positive CSF and blood cultures were found in four children. Three children were CSF culture positive for *H. influenzae* type b but had positive blood cultures for group A *Streptococcus*, *Enterobacter*, or an unidentified gram-negative organism; the fourth child had *S. aureus* cultured from CSF and an unidentified gram-negative organism cultured from blood. In these four children, the organisms identified in the CSF cultures were considered to be the etiologic agent.

Males constituted 57.0% of all patients; 53.3% of patients lived in Guatemala City, with no significant differences in sex or origin between the confirmed bacterial and CLN groups. Median age at presentation was 6.1 months (interquartile range, 2.8–11.5); mean age was 10.4 months (standard error, 0.4). There were no significant differences in age between the confirmed bacterial and CLN groups. However, 32% of children with CLN were < 3 months of age, compared with only 21% of children with bacterial meningitis ($P < 0.001$). A higher percentage of children with bacterial meningitis were 6 to 11 months of age than were children with CLN (32% versus 22%, respectively; $P < 0.001$). More than 75% of children with meningitis due to *H. influenzae* type b, *S. pneumoniae*, or *N. meningitidis* were less than 12 months of age (Figure 1). In Guatemala, there is no striking seasonal pattern for meningitis. However, a significantly higher percentage of meningitis caused by enteric organisms (*Salmonella* and *Escherichia coli*, 43.9%) occurred in April and May, the beginning of the rainy season, than did meningitis caused by other CBM organisms (19.2%; $P = 0.004$) or CLN (17.2%; $P = 0.001$); no seasonality was noted for other pathogens.

The distribution of CSF white blood cells was different for the CBM and CLN groups (Figure 2). Laboratory parameters at admission, clinical profile at admission, and sequelae at dis-

TABLE 1. Mortality by etiology of meningitis, Guatemala, 1996–2005

Etiology	No.	%	% died
Culture- and latex-negative	528	51.7	14.9[a]
Haemophilus influenzae type b	213	20.9	17.1[b]
Streptococcus pneumoniae	170	16.7	39.5[c]
Other gram-negative[d]	20	2.0	15.0
Escherichia coli	18	1.8	35.3[e]
Staphylococcus spp.	18	1.8	27.8
Streptococcus spp.	16	1.6	18.8
Neisseria meningitidis	14	1.4	21.4
Salmonella	11	1.1	72.7
Pseudomonas	10	1.0	40.0
Enterococcus spp.	3	0.3	0.0
Total	1 021		21.0[f]

[a] Outcome is unknown in six cases that were discharged against medical advice.
[b] Outcome is unknown in three cases: one was discharged against medical advice and two did not have discharge status recorded.
[c] Outcome is unknown in three cases that were discharged against medical advice.
[d] Includes three *Enterobacter*, three *Acinetobacter*, two *Klebsiella*, one *Burkholderia*, one *Chryseobacterium meningocepticum*, one *Haemophilus parainfluenzae*, one *H. influenzae* non-type b, and eight unidentified Gram negatives.
[e] Outcome is unknown in one case that was discharged against medical advice.
[f] Based on 1 008 cases (outcome is unknown in 13 cases).

TABLE 2. Comparison of cerebrospinal fluid (CSF) culture, blood culture, and latex agglutination results for *Haemophilus influenzae* and *Streptococcus pneumoniae*

H. influenzae type b							*S. pneumoniae*						
Culture		Latex[a]			Total		Culture		Latex			Total	
CSF	Blood	+	–	ND	No.	%	CSF	Blood	+	–	ND	No.	%
+	+	29	2	1	32	15.0	+	+	31		1	32	18.8
+	–	40	2		42	19.7	+	–	36		2	38	22.4
+	ND	45		4	49	23.0	+	ND	46	1	2	49	28.8
+	Other[b]	3			3	1.4							
–	+	8		1	9	4.2	–	+	8	4		12	7.1
–	–	59			59	27.7	–	–	30			30	17.6
–	ND	19			19	8.9	–	ND	9			9	5.3
Total		203	4	6	213	100			160	5	5	170	100

[a] Abbreviations: Latex = latex agglutination test; + = positive; – = negative; ND = not done.
[b] One *Enterobacter*, one group A S*treptococcus*, one unidentified gram-negative organism.

FIGURE 1. Cumulative proportion of children with meningitis by age and etiology: culture- and latex-negative meningitis (CLN); *Haemophilus influenzae* type b (Hib); *Streptococcus pneumoniae* (Spn); all other gram-negative and gram-positive organisms (Other)

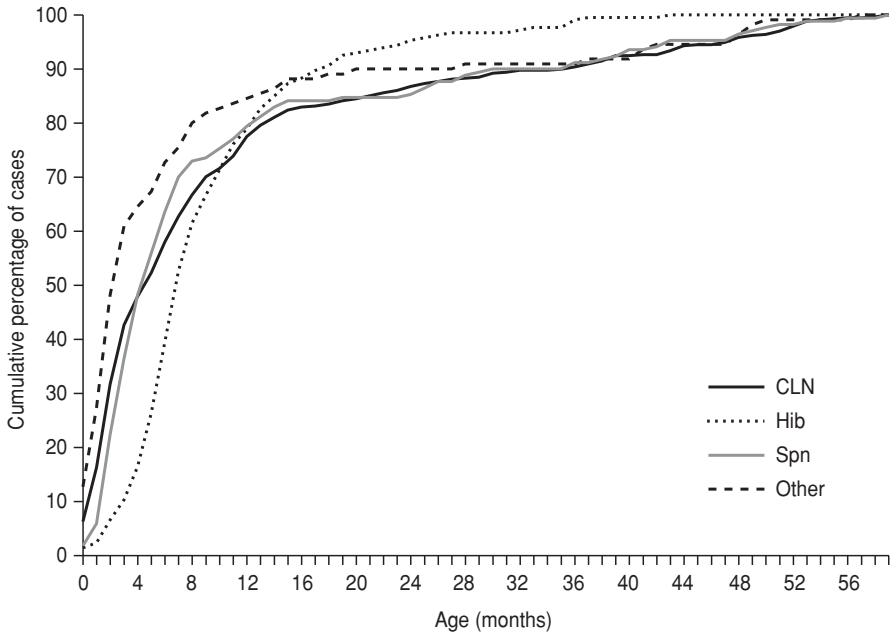
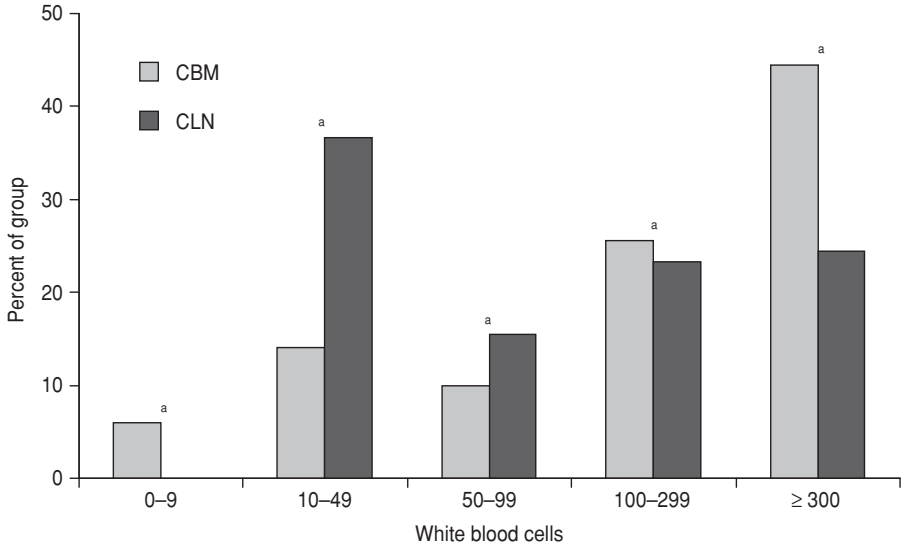


FIGURE 2. Cerebrospinal fluid white blood cells in children with confirmed bacterial meningitis (CBM) and culture- and latex-negative meningitis (CLN)



[a] Difference between CBM and CLN, $P < 0.01$.

charge are shown in Table 3. A clinical diagnosis of concurrent encephalitis was found in five children with CLN. When the data were analyzed for the subset of the CLN group with a CSF white blood cell count of ≥ 100 cells/mm^3, CSF glucose, protein, white blood cell counts, and percent of children who were comatose or in shock at admission were no longer significantly different from those in the CBM group. Among the 182 CBM survivors and 205 CLN survivors studied between October 2000 and December 2005 from whom information was available, clinically observed sequelae were present at discharge in a higher percentage of the CBM than of the CLN group (78.6% versus 46.8%; $P < 0.0001$).

The 172 (32.6%) children with CLN who died or developed sequelae (convulsions, cerebral vascular accidents, cranial nerve paralysis, or hydrocephalus) were ill for significantly more days before admission than the 356 (67.4%) children with CLN who survived without sequelae (5.4 versus 4.0 mean days, respectively; $P = 0.002$); however, no significant differences were found between these two groups in mean CSF white blood cells (1 122 versus 411 units; $P = 0.07$), mean CSF protein levels (197 versus 165 mg/dL; $P = 0.314$), and mean CSF glucose (48 versus 51 units; $P = 0.575$). Receipt of antibiotics before admission was more common in children with CLN who died or developed severe sequelae (55.2%) than in children with CLN who survived without sequelae (37.6%; $P < 0.001$). No significant differences in mean CSF white blood cell count, neutrophils, glucose, or protein were found between children with CLN who had received antibiotics and those who had not received antibiotics before admission. CBM patients diagnosed by latex only ($n = 116$) were significantly more likely to have received antibiotics than the 374 culture-positive CBM patients (56.9% and 30.7%, respectively; $P < 0.001$); information on antibiotic use was unavailable for three CBM patients.

The case-fatality rate was significantly higher for children with CBM than for children with CLN (27.6% and 14.9%, respectively; $P < 0.001$; see Table 1). Children with bacterial meningitis confirmed by culture had significantly higher mortality than children with meningitis confirmed by latex only (31.6% and 14.7%, respectively; $P < 0.001$). The time from hospitalization to death was shorter in chil-

TABLE 3. Laboratory parameters and clinical profiles on admission and sequelae at discharge for children with confirmed bacterial (CBM) versus culture- and latex-negative (CLN) meningitis

	Confirmed bacterial		CLN		
	n	Value	*n*	Value	*P* value[a]
Laboratory parameters at admission					
CSF WBC,[b] mean cells/mm^3 (SE)[c]	489	1 702 (274)	528	643 (183)	< 0.001[d]
CSF WBC, no. ≥ 300 cells/mm^3 (%)	489	217 (44.4)	528	129 (24.4)	< 0.001[d]
CSF neutrophils, mean cells/mm^3 (SE)	471	1 511 (250)	508	465 (142)	< 0.001[d]
CSF glucose, mean mg/dL (SE)	490	22 (1)	525	50 (2)	< 0.001
CSF glucose, no. < 40 mg/dL (%)	491	393 (80.0)	528	207 (39.2)	< 0.001
CSF protein, mean mg/dL (SE)	483	261 (16)	514	175 (15)	< 0.001[d]
CSF protein, no. > 45 mg/dL (%)	490	456 (93.1)	523	417 (79.7)	< 0.001
Peripheral WBC, mean cells/mm^3 (SE)	491	13 899 (351)	525	14 650 (319)	0.091
Peripheral neutrophils, mean cells/mm^3 (SE)	491	9 854 (299)	525	9 596 (268)	0.578
Clinical profile at admission					
Time ill before admission, mean days (SE)	245	5.03 (0.25)	248	4.72 (0.22)	0.345
Antibiotics before arrival, No. (%)	490	181 (36.9)	528	229 (43.4)	0.041
Comatose at admission, No. (%)	244	78 (32.0)	248	56 (22.6)	0.019[d]
Convulsions at admission, No. (%)	246	150 (61.0)	247	91 (36.8)	< 0.001
Shock at admission, No. (%)	246	77 (31.3)	248	50 (20.2)	0.005[d]
Concurrent sepsis, No. (%)	493	125 (25.4)	528	144 (27.3)	0.522
Concurrent pneumonia, No. (%)	493	146 (29.6)	528	150 (28.4)	0.679
Sequelae at discharge[e]					
Convulsions, No. (%)	185	119 (64.3)	209	72 (34.4)	< 0.001
Cerebral vascular accident, No. (%)	185	71 (38.4)	209	29 (13.9)	< 0.001
Cranial nerve paralysis, No. (%)	185	32 (17.3)	209	10 (4.8)	< 0.001
Hydrocephalus, No. (%)	185	28 (15.1)	209	22 (10.5)	0.09

[a] *P* values are calculated with the Mann-Whitney-Wilcoxon test or χ^2 where applicable.
[b] CSF = cerebrospinal fluid; WBC = white blood cells.
[c] SE = standard error.
[d] When data were analyzed for a subset of the CLN group with a CSF WBC count of ≥100 cells/mm^3, these variables were no longer significantly different from values in the CBM group.
[e] Data on deafness were not collected in a standardized fashion.

TABLE 4. Predictors of mortality in multivariate logistic regression for children with confirmed bacterial (CBM) or culture- and latex-negative (CLN) meningitis, Guatemala, October 2000 to December 2005

	All meningitis (*N* = 456)		CBM (*N* = 230)		CLN (*N* = 226)	
Factor[a]	OR[b] (95% CI)[c]	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
CSF glucose < 10 mg/dL	2.1 (1.1–4.1)	0.026	2.9 (1.2–6.7)	0.014	[d]	
Peripheral neutrophils < 2 000 cells/mm^3	3.0 (1.2–7.3)	0.019	[d]	[d]		
Coma at admission	4.2 (2.1–8.4)	< 0.001	4.1 (1.6–10.2)	0.003	3.1 (1.1–8.4)	0.025
Shock at admission	3.3 (1.7–6.6)	0.001	4.8 (1.9–12.0)	0.001	4.4 (1.6–12.0)	0.003
Concurrent sepsis	2.5 (1.3–4.7)	0.005	3.5 (1.5–8.1)	0.004	[d]	
Concurrent pneumonia	2.6 (1.4–4.6)	0.002	3.7 (1.6–8.6)	0.003	[d]	

[a] Other variables included in model were age in months, sex, season, hospital, cerebrospinal fluid (CSF) protein > 200, CSF white blood cells, CSF neutrophils, peripheral white blood cells, number of days of symptoms before admission, convulsions at admission, and antibiotics before admission. Both CBM and CLN were included in the "all meningitis" category.
[b] OR = odds ratio.
[c] CI = confidence interval.
[d] Variable excluded (*P* > 0.10) during backward stepwise conditional logistic regression modeling.

dren with CBM than in those who died with CLN (4.0 ± 0.6 and 8.2 ± 1.4 days, respectively; $P = 0.001$). Among survivors, the time from hospitalization to discharge was significantly longer for children with CBM (16.1 ± 0.9 days) than for children with CLN (13.8 ± 0.5 days; $P = 0.03$).

CSF glucose < 10 mg/dL, peripheral neutrophils < 2 000 cells/mm^3, coma or shock at admission, and concurrent sepsis or pneumonia were independent risk factors for mortality in children with CBM after adjustment for other variables in multivariate logistic regression (Table 4). However, only coma and shock at admission were strong predictors of mortality in children with CLN.

DISCUSSION

Bacterial meningitis results in high mortality (27.6%) and serious sequelae in Guatemalan children. The case-fatality rates in children with bacterial meningitis range from 7% to 56% in other countries (1, 2, 15–22, 24–27), with higher rates in developing countries apparently due to delays in diagnosis and initiation of optimal therapy (15, 22). Although the case-fatality rate was lower for children with CLN, nearly 15% died and many (47%) had serious sequelae (1–5, 11–22).

The potential causes of CLN include partially treated bacterial meningitis, viruses, fungi, parasites, and noninfectious disorders (drug-induced, systemic disease and malignancies). The most common viral causes include nonpolio enteroviruses, herpes simplex virus, arboviruses, and mumps in unvaccinated populations (28–31). Except for herpes simplex, most viruses cause self-limiting illness, although arboviruses can be associated with neurologic sequelae. The case-fatality rate in Guatemalan children with CLN was much higher than would be expected for enterovirus or mumps virus infections. Also, mortality in children with CLN was associated with coma and shock, suggesting that many of the severe cases were probably of bacterial etiology.

Finally, antibiotic use before admission was significantly higher in children with CLN who died or had sequelae, suggesting that prior antibiotic use may have interfered with isolation of bacterial agents from these children. Alternatively, nearly half the children with CLN who died had not received antibiotics before culture; these infections may have been due to bacteria that are not easily cultured or to severe viral (e.g., dengue) infections.

Most of our nonsevere CLN cases were likely of viral etiology. The mean CSF white blood cell count for the children who survived CLN without sequelae is within the reported range for childhood viral meningitis (6, 10, 32, 33). Although the mean CSF protein in this group is elevated compared with previously reported values for childhood viral meningitis (6, 12, 32), the mean is generally lower than is reported for bacterial meningitis (6, 7, 9).

Comparisons of our data with previously reported values must be done with caution because the prior studies were based on meningitis occurring in wider age ranges. Children in the CLN group with higher CSF white blood cell counts (≥ 100 cells/mm^3) were more similar to the CBM group in terms of CSF parameters and clinical profile at admission, also suggesting that many of the children with severe CLN had meningitis of undiagnosed bacterial etiology.

The most frequently identified risk factors for meningitis-associated mortality include shock, coma, low CSF glucose, low neutrophil and leukocyte counts, and convulsions and seizures (22, 24, 25, 27, 34). In this study, coma and shock at admission each constituted a significant independent mortality risk factor for both CBM and CLN in multivariate logistic models. Low CSF glucose (< 10 mg/dL), concurrent sepsis, and concurrent pneumonia were also associated with mortality for CBM. In addition, the average time to death for children with CLN was approximately twice as long as for children who died with CBM. These data further support that many of the children who died with CLN likely had inadequately treated bacterial meningitis or already had severe complications at presentation.

Although antibiotic use before admission was associated with a bad outcome in the CLN group, there were no differences in CSF parameters between children with CLN with and without antibiotics before admission. Information on antibiotic use may be inaccurate because many people are unaware of the type of medication they have taken and because the data were collected from medical charts rather than from interviews.

In this study, 98% and 97% of children with meningitis caused by *H. influenzae* and *S. pneumoniae*, respectively, had positive CSF latex agglutination tests. Of these, 62% (*H. influenzae*) and 76% (*S. pneumoniae*) were confirmed by CSF or blood culture. Therefore, in countries with limited capacity for diagnostic testing by culture, the latex agglutination test may be a feasible alternative. However, the high cost of this test may limit its widespread use in developing countries.

Because follow-up data beyond discharge were not collected, long-term outcomes and persistent sequelae in this population remain uncharacterized. Future studies should investigate the true long-term sequelae from meningitis in Guatemalan children and the importance of early diagnosis and therapy, especially given the high rate of serious sequelae present at discharge.

H. influenzae type b and *S. pneumoniae* caused 37.6% of the CBM in this population and case-fatality rates were 17.1% and 39.5%, respectively. These vaccine-preventable diseases pose a significant health threat to Guatemalan children. *H. influenzae* type b conjugate vaccine became available in 1999 for infants served by the Social Security health care system in Guatemala City and was introduced for the approximately two-thirds of other children served by public clinics in April 2005. Conjugate pneumococcal vaccines have not yet been introduced in this population. Further studies are needed to determine the impact of these vaccines on preventing confirmed bacterial meningitis as well as CLN. When this study was conducted, we did not have the capability to do viral cultures, and CSF samples were not stored in a manner that would allow optimal polymerase chain reaction testing. Herpesvirus, enterovirus, and arboviral diagnostic testing have recently been introduced in Guatemala, which will allow for more thorough investigation of possible viral etiologies in future investigations.

Acknowledgments. The authors thank the residents, physicians, and patients who contributed to the surveillance of patients, and Stacy Kopka and Tina Proveaux for assistance with manuscript preparation. This study was funded in part by grants from GlaxoSmithKline and a subcontract from The Johns Hopkins University

with funds provided by The Boards of the Global Alliance for Vaccines and Immunizations and the Vaccine Fund as well as independent funds. Support for Erica L. Dueger was provided by a grant from a Fogarty International Research Scientist Development Award (Grant KO1 TW06659). Portions of this project were funded by Cooperative Agreement U50/CCU021235-05 between Universidad del Valle de Guatemala and the Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado.

REFERENCES

1. Al Khorasani A, Banajeh S. Bacterial profile and clinical outcome of childhood meningitis in rural Yemen: a 2-year hospital-based study. J Infect. 2006;53:228–34.
2. Goetghebuer T, West TE, Wermenbol V, Cadbury AL, Milligan P, Lloyd-Evans N, et al. Outcome of meningitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in children in The Gambia. Trop Med Int Health. 2000;5:207–13.
3. Grimwood K, Anderson P, Anderson V, Tan L, Nolan T. Twelve year outcomes following bacterial meningitis: further evidence for persisting effects. Arch Dis Child. 2000;83:111–6.
4. Weightman NC, Sajith J. Incidence and outcome of pneumococcal meningitis in northern England. Eur J Clin Microbiol Infect Dis. 2005; 24:542–4.
5. Asturias EJ, Soto M, Menendez R, Ramirez PL, Recinos F, Gordillo R, et al. Meningitis and pneumonia in Guatemalan children: the importance of *Haemophilus influenzae* type b and *Streptococcus pneumoniae*. Rev Panam Salud Publica. 2003;14:77–84.
6. Chavanet P, Schaller C, Levy C, Flores-Cordero J, Arens M, Piroth L, et al. Performance of a predictive rule to distinguish bacterial and viral meningitis. J Infect. 2006;54: 328–36.
7. Nigrovic LE, Kuppermann N, Malley R. Development and validation of a multivariable predictive model to distinguish bacterial from aseptic meningitis in children in the post-*Haemophilus influenzae* era. Pediatrics. 2002; 110:712–9.
8. Bonsu BK, Harper MB. Differentiating acute bacterial meningitis from acute viral meningitis among children with cerebrospinal fluid pleocytosis: a multivariable regression model. Pediatr Infect Dis J. 2004;23:511–7.
9. Negrini B, Kelleher KJ, Wald ER. Cerebrospinal fluid findings in aseptic versus bacterial meningitis. Pediatrics. 2000;105:316–9.
10. Jaeger F, Leroy J, Duchêne F, Baty V, Baillet S, Estavoyer JM, et al. Validation of a diagnosis model for differentiating bacterial from viral meningitis in infants and children under 3.5 years of age. Eur J Clin Microbiol Infect Dis. 2000;19:418–21.
11. Bottner A, Daneschnejad S, Handrick W, Schuster V, Liebert UG, Kiess W. A season of aseptic meningitis in Germany: epidemiologic, clinical and diagnostic aspects. Pediatr Infect Dis J. 2002;21:1126–12.
12. Tang RB, Chen SJ, Wu KG, Lee BH, Hwang B. The clinical evaluation of an outbreak of aseptic meningitis in children. Zhonghua Yi Xue Za Zhi (Taipei). 1996;57:134–8.
13. Lee KY, Burgner D, Lee HS, Hong JH, Lee MH, Kang JH, et al. The changing epidemiology of pediatric aseptic meningitis in Daejeon, Korea from 1987 to 2003. BMC Infect Dis. 2005;5:97.
14. Lee BE, Chawla R, Langley JM, Forgie SE, Al-Hosni M, Baerg K, et al. Paediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of aseptic meningitis. BMC Infect Dis. 2006;6:68.
15. Peltola H. Burden of meningitis and other severe bacterial infections of children in Africa: implications for prevention. Clin Infect Dis. 2001;32:64–75.
16. Roca A, Sigauque B, Quintó L, Mandomando I, Vallès X, Espasa M, et al. Invasive pneumococcal disease in children < 5 years of age in rural Mozambique. Trop Med Int Health. 2006;11:1422–31.
17. Peltola H. Spectrum and burden of severe *Haemophilus influenzae* type b diseases in Asia. Bull World Health Organ. 1999;77:878–87.
18. Campbell JD, Sow SO, Levine MM, Kotloff KL. The causes of hospital admission and death among children in Bamako, Mali. J Trop Pediatr. 2004;50:158–63.
19. Ferreccio C, Ortiz E, Astroza L, Rivera C, Clemens J, Levine MM. A population-based retrospective assessment of the disease burden resulting from invasive *Haemophilus influenzae* in infants and young children in Santiago, Chile. Pediatr Infect Dis J. 1990;9: 488–94.
20. Peltola H. *Haemophilus influenzae* type b disease and vaccination in Latin America and the Caribbean. Pediatr Infect Dis J. 1997;16:780–7.
21. Odetola FO, Bratton SL. Characteristics and immediate outcome of childhood meningitis treated in the pediatric intensive care unit. Intensive Care Med. 2005;31:92–7.
22. Lovera D, Arbo A. Risk factors for mortality in Paraguayan children with pneumococcal bacterial meningitis. Trop Med Int Health. 2005;10:1235–41.
23. Bonsu BK, Harper MB. Corrections for leukocytes and percent of neutrophils do not match observations in blood-contaminated cerebrospinal fluid and have no value over uncorrected cells for diagnosis. Pediatr Infect Dis J. 2006;25:8–11.
24. Casado-Flores J, Aristegui J, de Liria CR, Martinon JM, Fernandez C. Clinical data and factors associated with poor outcome in pneumococcal meningitis. Eur J Pediatr. 2006;165: 285–9.
25. Farag HF, Abdel-Fattah MM, Youssri AM. Epidemiological, clinical and prognostic profile of acute bacterial meningitis among children in Alexandria, Egypt. Indian J Med Microbiol. 2005;23:95–101.
26. King BA, Richmond P. Pneumococcal meningitis: clinical course and resource use in Western Australian children. J Paediatr Child Health. 2004;40:606–10.
27. Wasier AP, Chevret L, Essouri S, Durand P, Chevret S, Devictor D. Pneumococcal meningitis in a pediatric intensive care unit: prognostic factors in a series of 49 children. Pediatr Crit Care Med. 2005;6:568–72.
28. Rotbart HA. Viral meningitis. Semin Neurol. 2000;20:277–92.
29. Roos KL. *Mycobacterium tuberculosis* meningitis and other etiologies of the aseptic meningitis syndrome. Semin Neurol. 2000;20:329–35.
30. Hasbun R. The acute aseptic meningitis syndrome. Curr Infect Dis Rep. 2000;2:345–51.
31. Connolly KJ, Hammer SM. The acute aseptic meningitis syndrome. Infect Dis Clin North Am. 1990;4:599–622.
32. Dalal I, Tzhori S, Somekh E, Mandelberg A, Levine A, Ballin A. Cytokine profile in cerebrospinal fluid of children with echovirus type 4 meningitis. Pediatr Neurol. 2003;29: 312–6.
33. Landry ML. Frequency of normal cerebrospinal fluid protein level and leukocyte count in enterovirus meningitis. J Clin Virol. 2005;32:73–4.
34. Chang YC, Huang CC, Wang ST, Liu CC, Tsai JJ. Risk factors analysis for early fatality in children with acute bacterial meningitis. Pediatr Neurol. 1998;18:213–7.

Manuscript received on 3 October 2007. Revised version accepted for publication on 9 April 2008.

Meningitis negativa a pruebas antigénicas y de cultivo en niños guatemaltecos

RESUMEN

Objetivo. Comparar los casos infantiles de meningitis bacteriana confirmada (MBC) y meningitis negativa a pruebas de látex y de cultivo (MNLC).

Métodos. Se evaluaron los niños de 1 a 59 meses de edad ingresados en tres grandes hospitales de referencia de la Ciudad de Guatemala entre el 1 de octubre de 1996 y el 31 de diciembre de 2005 con signos clínicos de infección bacteriana. Se realizaron cultivos bacterianos y pruebas de aglutinación antigénica con látex en muestras de líquido cefalorraquídeo (LCR).

Resultados. La tasa de letalidad fue significativamente mayor en los 493 niños con MBC que en los 528 niños con MNLC (27,6% y 14,9%, respectivamente; $P < 0{,}001$). Los niños con MBC tuvieron menor probabilidad de recibir antibióticos y mayor de sufrir convulsiones, choques o entrar en coma al ser ingresados que los niños con MNLC. Se observó un mayor porcentaje de manifestaciones clínicas de secuelas al alta hospitalaria en los 182 niños sobrevivientes con MBC que en los 205 sobrevivientes con MNLC estudiados entre octubre de 2000 y diciembre de 2005 (78,6% y 46,8%, respectivamente; $P < 0{,}0001$). Los factores de riesgo de muerte en los niños con MBC fueron: glucosa en LCR < 10 mg/dL, neutrófilos periféricos < 2 000 células/mm^3, coma o choque al ingreso, y sepsis o neumonía concurrentes; solo el coma y el choque al ingreso predijeron la muerte en niños con MNLC.

Conclusiones. Las altas tasas de letalidad y de secuelas indican que muchos niños con MNLC pueden haber tenido meningitis bacteriana. Las estadísticas basadas solamente en los casos confirmados de meningitis subestiman la verdadera carga de enfermedad prevenible mediante vacuna. Se deben emprender estudios adicionales para determinar las etiologías de la MNLC en esta población.

Palabras clave Meningitis viral, meningitis bacteriana, meningitis aséptica, Guatemala.