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Cerebral infarction in perinatal and childhood bacterial meningitis

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Summary

Background: Cerebral infarction is an important neurological complication of childhood bacterial meningitis, but little is known about its epidemiology and outcomes.

Aim: To determine the predictive factors, clinical features, causative pathogens, and outcomes of cerebral infarction secondary to perinatal and childhood bacterial meningitis.

Design: Retrospective analysis

Methods: Over the period 1986–2001, 166 perinatal and childhood patients were identified as having culture-proven bacterial meningitis, of whom 14 had cerebral infarction at admission. The clinical and CSF data of patients with and without cerebral infarctions on admission were compared.

Results: Cerebral infarction patients accounted for 10% (14/166) of bacterial meningitis cases, mostly in the first year of life (11/14, 79%). *Salmonella* species ($n=4$) and *Streptococcus pneumoniae* ($n=4$) were the most frequent causative pathogens, accounting for 57% (8/14) of episodes. Single infarctions were found in four patients and multiple infarctions in 10. At 1 year follow-up, outcome was good in three, but poor in 11. Significant differences between the two patient groups at admission included age bands, presence of seizures, hydrocephalus, disturbed consciousness on admission, and CSF lactate concentration.

Discussion: There was a high prevalence of cerebral infarctions when the disease was caused by *S. pneumoniae* and *Salmonella* species. Occurrence was highest in the first year of life, and the prognosis in this patient group is poor. Risk factors associated with cerebral infarction in our patients included age 28–365 days, seizures, hydrocephalus, disturbed consciousness on admission, and high CSF lactate concentrations.

Introduction

Cerebral infarction is an important neurological complication of child bacterial meningitis, often associated with poor outcome.[1–5] However, little information has been collected about its epidemiology and the therapeutic outcomes of cerebral infarction in perinatal and childhood bacterial meningitis.[6] Currently, there is no consensus on the classification, evaluation, outcome measurement, or treatment of ischaemic stroke in children.[7] In this study, we examined the clinical characteristics of 16 perinatal and childhood bacterial meningitis patients. We chose to study and compare (i) the localization of cerebral infarctions; (ii) the association between cerebral infarctions and other neurological complications; (iii) the predicting factors strongly associated with cerebral infarctions; and

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(iv) outcomes in perinatal and childhood bacterial meningitis with or without cerebral infarctions.

Methods

Over a period of 16 years (1986–2001), 166 perinatal and child patients, all aged < 5 years, at Chang Gung Memorial Hospital (CGMH)-Kaohsiung, were retrospectively identified as having had acute bacterial meningitis. Among these 166, 14 were recorded as suffering from cerebral infarction secondary to bacterial meningitis at the time of admission. CGMH-Kaohsiung, the largest medical centre in southern Taiwan, is a 2482-bed acute-care teaching hospital, which provides both primary and tertiary referral care of patients. Southern Taiwan consists of two cities and three counties (Kaohsiung Municipality and County, Tainan City and County, and Pingtung County) with a population of approximately 5 441 000, as of October 1998.[8] The annual population growth for Taiwan is reported to be 0.75%.[8]

The criteria for a definite diagnosis of perinatal and childhood bacterial meningitis include: (i) isolation of bacterial pathogens in one or more CSF cultures; and (ii) typical CSF findings including leukocyte counts $> 0.1 \times 10^9$/l with predominant polymorphonuclear cells, and/or CSF protein concentrations >1.5 g/l, and/or CSF glucose divided by blood glucose value < 0.5.[9] Cranial computed tomography (CT) scans and/or magnetic resonance imaging (MRI) studies were done in all patients identified as having acute bacterial meningitis at the time of admission. Cranial ultrasonographies in our neonatal and infantile patients are done every week, and our standard is to follow-up MRI if: (i) clinical deterioration, the presence of focal neurological signs, or persistent disturbed consciousness was found; (ii) the electroencephalogram reading showed a predominantly unilateral abnormality; and (iii) cranial ultrasonographies revealed ventriculitis or subdural empyemas. Cerebral infarction secondary to bacterial meningitis was defined as new-onset cerebral infarction demonstrated by brain CT scan or MRI. In this study, the definition of cerebral infarction is modified from the adult cerebral vascular disease criteria of the WHO.[10] Patients were considered to have multiple infarctions if at least two were identified.

The initial levels of consciousness on admission of these 166 patients were based on the Adelaide Paediatric Coma Scale, with slight modification, and were classified into two groups: (i) oriented (score ≥ 9) and 2) clouded consciousness, stupor or coma (score 3–8).[11] In our institution, a combination of ampicillin and a third-generation cephalosporin was the mainstay of initial empirical antimicrobial treatment for most patients with perinatal and childhood bacterial meningitis during the period of study. The ultimate choice for antibiotics was guided by the final culture results. Patients with increased intracranial pressure (IICP) were given intravenous mannitol. Corticosteroids were given to patients who suffered clinical deterioration during hospitalization.

Therapeutic outcomes, evaluated at least one year after completing treatment, were classified as normal, mildly abnormal (i.e. minimal monoparesis, hemiparesis, mild motor or language delay, controlled seizures, transient or permanent hearing loss, and subdural effusion), severely abnormal (i.e. blindness, hydrocephalus, institutionalization, quadriplegia, severe mental retardation, microcephaly and uncontrolled seizures), and death.[2,11,12] For the purpose of analysis, death and severely abnormal were defined as 'poor outcomes', while normal and mildly abnormal were considered 'good outcomes'.

We compared the clinical features and CSF parameters of perinatal and childhood bacterial meningitis with or without cerebral infarctions on admission. Data included age, gender, and clinical manifestations. For comparing two patient groups, the χ^2 test or Fisher's exact test was used. The Wilcoxon rank sum test was used to compare the CSF glucose, total protein, lactate, and WBC counts, and glucose ratios between two patient groups. Stepwise logistic regression was used to evaluate the relationships between clinical factors and therapeutic outcomes, with adjustments made for other potential confounding factors. Variables with a zero cell count in a 2-by-2 table were eliminated from the logistical analysis; only variables with a strong association with treatment failure ($p < 0.05$) were included in the final model. All statistical analyses used SAS.

Results

Fourteen patients had cerebral infarctions at the time of admission (Table 1). The 14 patients included eight males (aged 2 months to 2 years, mean 10.6 months) and 6 females (2 months to 3 years, mean 9.3 months) (Figure 1). Beside bacterial meningitis, two patients had other underlying conditions: juvenile chronic myeloblastic leukemia in one, and congenital hydrocephalus after a neurosurgical operation in the other.

Table 1 Clinical details and Neuroimaging findings of patients with cerebral infarction

Patient	Sex/age	Clinical manifestations	Neuroimaging findings	
			Other findings	Infarct locations
1	M/8 months	Fever, seizure, clouded of consciousness, feeding intolerance, left hemiparesis	Gyral enhancement; subdural empyemas	Right frontotempoparietal and basal ganglia
2	F/3 months	Fever, seizure, feeding intolerance, clouded consciousness	Hydrocephalus	Bilateral basal ganglia
3	M/2 years	Fever, oculomotor palsy, neck stiffness, clouded of consciousness, feeding intolerance	Gyral enhancement; hydrocephalus	Left frontotemporal
4	M/7 months	Fever, seizure, bulging fontanelle, clouded consciousness, feeding intolerance	Gyral enhancement; subdural empyemas	Bilateral frontal
5	F/3 years	Fever, clouded consciousness, feeding intolerance, diarrhea	Gyral enhancement, exudates in basal cistern	Bilateral basal ganglia, right thalamus, frontal and pontine
6	M/12 months	Fever, seizure, feeding intolerance, diarrhoea, clouded consciousness	Gyral enhancement, exudates in basal cistern	Bilateral basal ganglia infarctions
7	M/2 years	Fever, abducen nerve palsy, clouded consciousness, neck stiffness	Hydrocephalus	Right thalamus and pontine
8	F/2 months	Fever, focal seizure, clouded consciousness		Bilateral occipital; left transverse sinus and sagittal sinus thrombosis
9	F/3 months	Fever, seizure, bulging fontanelle, diarrhoea, clouded consciousness	Hydrocephalus; subdural empyemas	Bilateral basal ganglia, right thalamus, and left cerebellar
10	M/2 months	Clouded consciousness	Hydrocephalus	Bilateral basal ganglia
11	M/4 months	Fever, seizure, neck stiffness, clouded consciousness	Hydrocephalus	Bilateral temporal
12	F/2 m	Fever, seizure, bulging fontanelle	Hydrocephalus	Left parietooccipital and thalamus
13	F/12 months	Fever, seizure, clouded consciousness	Gyral enhancement	Left parietal
14	M/13 months	Fever, seizure, bulging fontanelle, clouded consciousness	Gyral enhancement	Left occipital

Except for cerebral infarction, the other clinical features of the 14 patients are listed in Tables 1 and 2. Fever was observed in all but one, and all but one were in a state of disturbed consciousness. Hydrocephalus was seen in seven patients, six of whom had poor outcomes. Seizure occurred in 10, nine of whom had generalized seizures and one, a focal seizure. The other clinical manifestations included cranial nerve involvement, and neck stiffness or bulging fontanelle.

The neuroimaging findings for these 14 patients are listed in Table 1. Cerebral infarctions involved the arterial system in 13 patients and both the arterial and venous systems in the other one. Single infarctions were found in four patients, and multiple infarctions in the other 10 (Figures 2 and 3). The single infarctions were found in the left frontoparietal region, left parietal lobe, left occipital lobe, and right thalamus, respectively. Hydrocephalus was found in seven cases. There was one congenital obstructive hydrocephalus, and six with communicating hydrocephalus. Other neuroimaging findings included gyral enhancement and exudates in the basal cistern or sylvian fissures.

The pathogens isolated from the CSF cultures in these 166 patients are listed in Table 2. Regarding the causative pathogens of the patients with cerebral infarctions, *Salmonella* species (4 patients) and

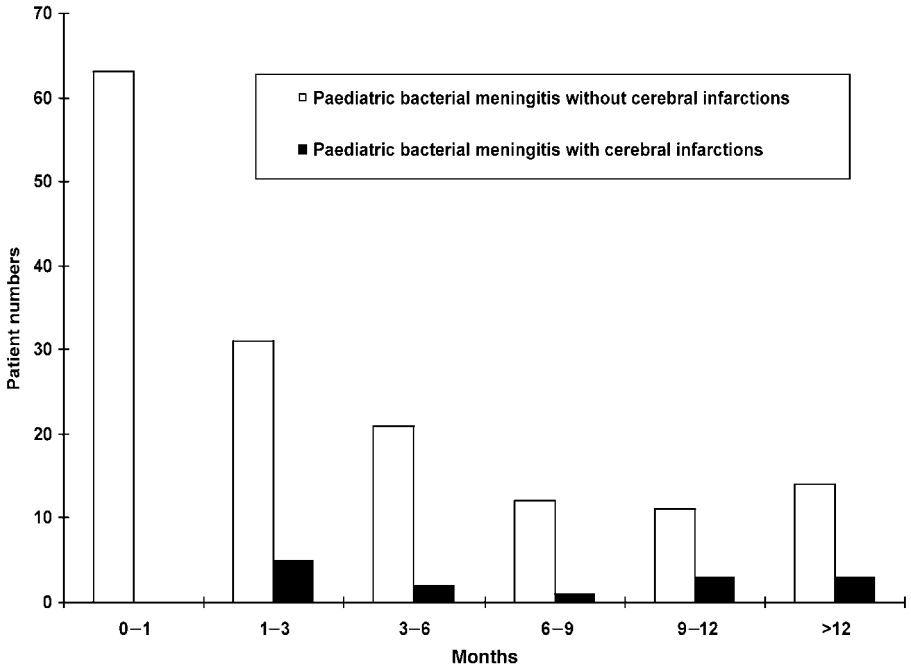

Figure 1. Age distribution of patients with and without cerebral infarctions.

Table 2 Comparisons of clinical features and CSF parameter between perinatal and childhood bacterial meningitis with or without cerebral infarctions on admission

	With cerebral infarctions ($n=14$)	Without ($n=152$)	p
Sex (M/F)	8/6	90/62	0.880
Age (days)	317.9 ± 323.2	191.8 ± 355.2	0.20
*Age bands**			
Neonates	0	63	0.008†
Infants	11	75	
Children	3	14	
Clinical features			
Fever	13	141	1.00
Seizure	10	62	0.027†
Disturbed consciousness**	13	76	0.002†
Hydrocephalus	7	22	0.004†
Neck stiffness	2	14	0.628
Cranial nerve involvement	2	16	0.651
Bulging fontanelle	4	38	0.754
*CSF parameters****			
Glucose (mmol/l)	1.55 ± 1.47	1.68 ± 1.48	0.60
Glucose/blood glucose ratio	0.24 ± 0.24	0.29 ± 0.4	0.61
Total protein (g/l)	7.31 ± 11.8	3.07 ± 4.81	0.21
Lactate (mmol/l)	12.37 ± 7.4	6.29 ± 4.75	0.02†
White cell count ($\times 10^9$/l)	6.36 ± 15.42	3.58 ± 1.88	0.58
Outcome			
Good	3	97	0.002†
Poor	11 (3 deaths)	55 (17 deaths)	

*Neonates, age < 28 days; infants, aged 29–365 days; children, > 365 days old. **Disturbed consciousness included those who with clouded consciousness, stupor or coma (score on Adelaide Paediatric Coma Scale of 3–8). ***Not all patients were tested; †Statistically significant.

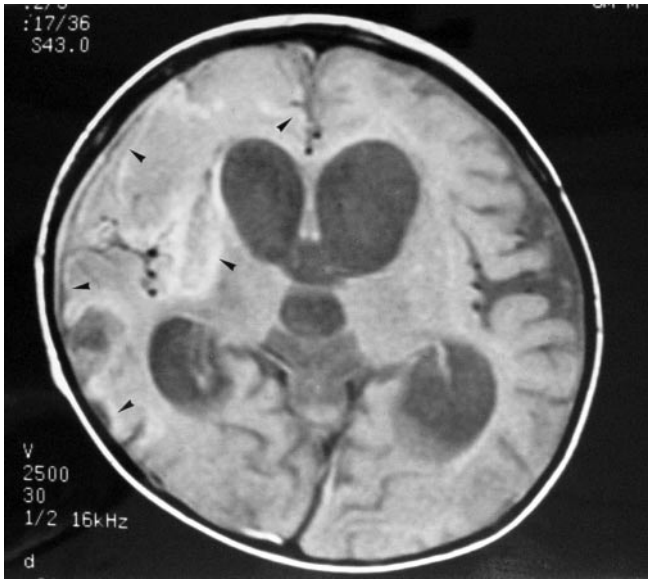

Figure 2. MRI axial view T1WI shows hyperintensity changes in right frontotemporoparietal region and putamen (arrows).

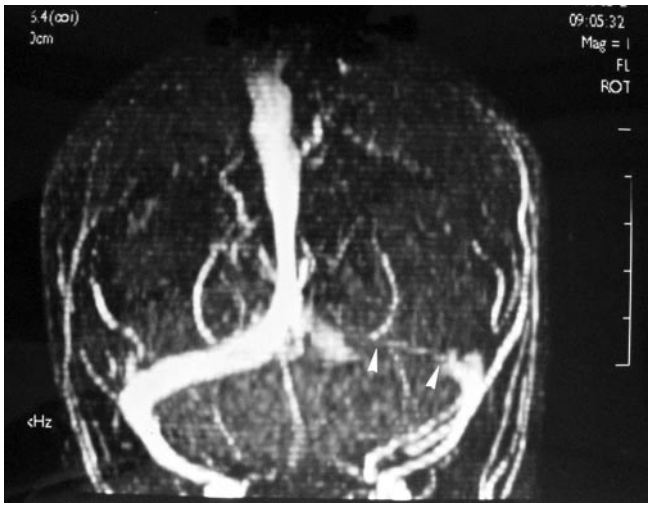

Figure 3. Two-dimensional time-of-flight MR venogram shows nonopacification of left transverse sinus (arrows).

Streptococcus pneumoniae (4) were the most frequent. They were followed by *Enterobacter cloacae* (2), *Escherichia coli* (1), *Haemophilus influenzae* (1), *H. parainfluenzae* (1), and *Neisseria meningitidis* (1). Among these 14 strains, six were identified as antibiotic-resistant. These included Gram-negative bacilli in five cases (*E. cloacae* 2; *E. coli* 1; *Salmonella* spp. 1; and *H. influenzae* 1), which were resistant to β-lactam antibiotics (ampicillin, piperacillin, ticarcillin, and third-generation cephalosporins); and penicillin-resistant *S. pneumoniae* in the remaining case.

The CSF glucose level of the 14 cases ranged from 0 to 3.79 mmol/l (mean ± SD 1.42 ± 1.25), with the glucose ratio ranging from 0 to 0.56 (mean ± SD 0.22 ± 0.226), total protein from 0.25 to 39.1 g/l (mean ± SD 6.52 ± 11.12), lactate from 1.39 to 24.2 mmol/l (mean ± SD 11.39 ± 7.64), and white blood cell (WBC) count from 0.009 to 29.2×10^9/l (mean ± SD 7.08 ± 15.03). Blood cultures were done for all 14 patients, and were positive in nine.

Comparisons of clinical features and CSF parameters between perinatal and childhood bacterial meningitis with or without cerebral infarctions on admission are listed in Table 1. Significant differences included age bands ($p = 0.008$), disturbed consciousness on admission ($p = 0.002$), presence of seizure ($p = 0.027$) and hydrocephalus ($p = 0.004$), and CSF lactate concentration ($p = 0.02$). In stepwise multiple logistical regression analysis, the results revealed that after analysis for all the above variables, only the presence of disturbed consciousness on admission ($p = 0.033$) and hydrocephalus ($p = 0.022$) were independently associated

Table 3 Causative organisms, 1986–2001

Causative organisms	With cerebral infarctions ($n=14$)	Without ($n=152$)
Gram-negative bacilli ($n=64$)		
Escherichia coli	1*	27**
Salmonella species	4***	10†
Pseudomonas aeruginosa	0	8
Enterobacter cloacae	2††	3
Other Gram-negative bacilli	0	9
Haemophilus species ($n=18$)		
Haemophilus influenzae	1†††	15
Haemophilus parainfluenzae	1	1
Streptococcus species ($n=59$)		
Group B Streptococci	0	32
Streptococcus pneumoniae	4	15
Other streptococci	0	8
Staphylococcus species ($n=9$)		
Staphylococcus aureus	0	5
Coagulase-negative *Staphylococcus*	0	4
Neisseria meningitidis ($n=5$)	1	4
Mixed infection ($n=4$)	0	4
Other pathogens ($n=7$)	0	7

*Resistance to trimethoprim-sulfamethoxazole, ampicillin, piperacillin, and ticarcillin. **Eighteen strains had resistance to trimethoprim-sulfamethoxazole, ampicillin, piperacillin, and ticarcillin. ***One strain had resistance to ampicillin and chloramphenicol. †Six strains had resistance to ampicillin and chloramphenicol. ††Both strains had resistance to one or more third-generation cephalosporins (ceftazidime, moxalactam, or ceftriaxone). †††Resistance to ampicillin, piperacillin, ticarcillin, and more than one third-generation cephalosporins.

with cerebral infarctions. Regarding the causative pathogens, *Salmonella* spp. and *S. pneumoniae* were the two most common pathogens causing cerebral infarctions ($p=0.001$, Fisher's exact test). When age was taken into account, in stepwise logistical regression analysis, *Salmonella* spp. and *S. pneumoniae* remained the two most common pathogens causing cerebral infarctions.

Six patients (1, 3, 5, 6, 9, and 13) had combined steroid and antibiotic therapy, and all had poor outcomes. Two cases received surgical intervention, one (patient 10) of which for hydrocephalus and the other (patient 1) for subdural empyemas, but both had poor outcomes. The overall mortality rate was 21%. At follow-up of one year or more, three (patients 4, 8, and 11) displayed good outcomes, but the other 11 (patients 1–3, 5–7, 9, 10, and 12–14) had poor outcomes. The mean lengths of hospitalization for those with good and poor outcomes were 20.6 and 37.5 days, respectively. Of the three with good outcomes, two (patients 8 and 11) completely recovered, and the other had mild hemiparesis (patient 4). Of the 11 with poor outcomes, three had quadriparesis with assisted gait (patients 1, 3, and 10), three had wheelchair or bed-bound quadriplegia (patients 2, 9, and 12), two uncontrolled seizures (patients 13 and 14), and three died (patients 5–7).

Discussion

Differences in the relative prevalence of causative pathogens of perinatal and childhood bacterial meningitis complicated by cerebral infarctions vary with geography and climate as well as time period.[13–16] *S. pneumoniae* was the common causative pathogens in developed countries while *Salmonella* spp. were more common in developing countries.[13,15] In our study, *S. pneumoniae*, and *Salmonella* spp. were the common causative pathogens, accounting for 57% (8/14) of our cases.

Cerebral infarction is a common complication found in perinatal and childhood bacterial meningitis, and its frequency varies according to different study series.[1,6] In one early brain CT study of cerebral infarction in childhood bacterial meningitis in the US, for the 1975 to 1979 period, cerebral

infarctions accounted for 27% (13/49) of episodes.[6] In our study, cerebral infarction accounted for only 8% (14/166) of the complications of perinatal and childhood bacterial meningitis at the time of admission, with occurrence highest in the first year of life.

Although the exact causes in this age group are not known, the immature brain is less resistant to hypoxic-ischaemic brain damage than its adult counterpart, and is selectively vulnerable to focal ischaemia.[17] There are specific differences between infant and adult strokes in the blood-brain barrier, inflammatory response, biochemistry, and vascular perfusion and reperfusion.[9] Previous studies of vascular lesions in childhood bacterial meningitis have focused on its aetiology and pathology, using diagnostic measures such as cerebral angiography,[18–20] autopsy,[21] and cranial Doppler ultrasonography.[22] One study of autopsies in childhood bacterial meningitis[21] demonstrated that neutrophils extended into the perivascular spaces of the cortex. Neutrophils and lymphocytes were found beneath the intima of small- and medium-sized subarachnoid arteries. Focal necrosis and mural thrombi occurred in veins. Cerebral angiography in childhood bacterial meningitis[18–20] has revealed cerebrovascular abnormities, such as arthritis, thrombosis, thrombophlebitis, and vascular narrowing, resulting in severe abnormalities in cerebral blood flow, which accompany bacterial meningitis in childhood.

The study using transcranial Doppler sonography in newborns and infants with bacterial meningitis to evaluate the predictive value of neurological sequelae shows that the mean cerebral blood flow is significantly higher in patients without neurological sequelae. The pulsatility index was significantly higher in patients with neurological sequelae when compared to healthy controls.[22] In our study, cerebral infarctions occurred in both the arterial and venous systems.

Several mechanisms are involved in the development of cerebrovascular complications in perinatal and childhood bacterial meningitis.[13–16,23,24] In addition, the presence of hydrocephalus might stretch already-compromised vessels and lead to further ischaemia; satisfactory circulation can be restored on relief of hydrocephalus with resulting improvements in neurological status and prevention of cerebral ischaemia. In our study, hydrocephalus was a statistically significant risk factor associated with cerebral infarctions in perinatal and childhood bacterial meningitis.

Seizures complicating bacterial meningitis have been previously shown to have an adverse effect on mortality and morbidity, and these studies also demonstrate increased mortality among patients who were convulsive during the course of bacterial meningitis.[25,26] Seizures occurred in 71% (10/14) of our patients with cerebral infarctions, and it is a statistically significant risk factor associated with cerebral infarctions in our study. Although a rapid deterioration of consciousness should raise suspicion of ventricular dilation, cerebral infarctions and the severity of bacterial meningitis may play a much more significant role than hydrocephalus in altering the level of consciousness, and disturbed consciousness on admission was a risk factor associated with cerebral infarction in our study.

Regarding CSF parameters, the only factor associated with cerebral infarction was high lactate concentration. Patients with cerebral infarctions had higher CSF protein concentrations, higher CSF WBC counts, and lower CSF glucose concentrations than those who did not have cerebral infarctions, but not significantly so.

Multiple-antibiotic-resistant strains accounted for 43% (6/14) of the episodes, and their presence posed a therapeutic challenge in the selection of appropriate empirical antibiotic treatment. The use of steroid therapy in combination with antibiotics for improving the outcome or decreasing the neurological sequelae of bacterial meningitis in perinatal and childhood patients remains controversial.[27,28] We found no evidence for the effectiveness of dexamethasone in cerebral infarctions caused by perinatal and childhood bacterial meningitis.

Therapeutic regimens for bacterial meningitis should both eradicate bacterial pathogens and treat neurological complications such as hydrocephalus and seizures. In this study, we found a high prevalence of cerebral infarctions when the disease was caused by *S. pneumoniae*, and *Salmonella* spp., with occurrence highest in the first years of life. Poor outcomes were also found in this special group of patients. Risk factors associated with cerebral infarction in our patients included infants, the presence of seizure hydrocephalus, and disturbed consciousness on admission, and high CSF lactate concentrations.

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