Clinical Characteristics, Acute Complications, and Neurologic Outcomes of *Salmonella* Meningitis in Saudi Infants and Children

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J Pediatr Infect Dis

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Abstract

Objective This study aimed to clarify the clinical presentations, acute complications, and long-term sequelae of *Salmonella* meningitis in Saudi infants and children.

Methods This retrospective study, conducted from 1999 to 2016, evaluated the neurological complications and long-term outcomes of children 14 years of age and younger diagnosed with *Salmonella* meningitis at King Khalid University Hospital. All affected children had 3 years of follow-up to assess neurologic complications and mortality.

Results Invasive *Salmonella* infection occurred in 141 patients. Of those, 14 (10%) had meningitis. The median age of onset of infection was 4.7 months. The most frequent symptoms at presentation included fever (100%), seizures (71%), diarrhea, and vomiting (43%). Nontyphoidal *Salmonella* species were isolated in all (but one) cerebrospinal fluid samples. Relapse occurred in four patients owing to inadequate antibiotic duration, although the organisms were susceptible to ceftriaxone. The majority of patients (86%) developed acute neurologic complications, including subdural empyema and multiple cerebral infarcts (57%), hydrocephalus (36%), ventriculitis (29%), and cerebral venous sinus thrombosis (21%). Four patients (28.5%) died due to *Salmonella* meningitis complications. Four patients survived with full recovery. Six patients (60%) had long-term neurologic complications. Hydrocephalus, cerebral palsy, developmental delay, and epilepsy occurred in five, four, three, and three patients, respectively.

Conclusion *Salmonella* meningitis results in significant mortality and adverse neurodevelopmental outcomes. The probability of relapse after an apparent recovery should be considered. Consensus on antibiotic treatment for *Salmonella* meningitis is needed.

Keywords
- *Salmonella*
- meningitis
- children
- infants

Introduction

Salmonella spp., which include typhi and nontyphi species, account for a substantial portion of enteric disease burden in Saudi Arabia. According to the Saudi Ministry of Health, in 2017, an estimated 1,452 cases of *Salmonella* caused by nontyphi species causing foodborne illnesses were reported.[1]

Salmonella infections are acquired by the ingestion of contaminated food, especially dairy products. Waterborne infections and person-to-person transmission also occur. Contact with an animal carrying *Salmonella*, including reptiles (iguanas, turtles), accounts for 3 to 5% of all *Salmonella* infections.[2] Only 10% of enteric infections progress to invasive salmonellosis.[3] Children, particularly infants, have an increased risk of *Salmonella* gastroenteritis that progresses

received
March 1, 2019
accepted after revision
July 29, 2019

DOI https://doi.org/10.1055/s-0039-1696977.
ISSN 1305-7707.

to invasive disease.[4] Meningitis caused by *Salmonella* is rarely reported (≤1%) among acute bacterial meningitis in developed countries.[5] However, in Africa, *Salmonella* spp. account for 13% of cases of childhood bacterial meningitis, ranking fourth behind *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis.* In these studies, *Salmonella typhi* accounted for more than half of the cases.[6] *Salmonella* meningitis is associated with a higher degree of relapse rate, significant neurological sequelae, and mortality compared with meningitis caused by the more common gram-negative pathogen, *Escherichia coli*.[3,7] The treatment of *Salmonella* meningitis requires bactericidal agents that are capable of penetrating into the cerebrospinal fluid (CSF) and macrophages. With the emergence of antibiotic resistance, third-generation cephalosporins are recommended for initial empiric therapy.[8] The American Academy of Pediatrics suggests that localized invasive *Salmonella* disease should be treated for at least 6 weeks to prevent relapse, whereas nonfocal infections can be treated for 10 to 14 days.[2] Studies on *Salmonella* meningitis, including its spectrum of complications and outcomes, among infected Saudi infants and children are lacking. Therefore, the present study aimed to clarify the clinical presentations, acute complications, and neurologic outcomes of *Salmonella* meningitis in Saudi infants and children.

Methods

We conducted a retrospective chart review including 3-year neurologic follow-up of cases at King Khalid University Hospital (KKUH). The hospital is the teaching hospital of the College of Medicine of King Saud University. It has 850 beds and serves both as a referral unit for all regions of Saudi and as a district hospital for the north sector of Riyadh area. The pediatric department has 68 inpatient beds.

Cases of *Salmonella* meningitis were identified over a 17-year period from 1999 to 2016. Inclusion criteria were as follows: patients from birth to 14 years of age who had documented positive CSF and/or blood cultures for *Salmonella. Salmonella* meningitis was defined as isolation of *Salmonella* spp. from the CSF. Invasive disease was defined as bacteremia or meningitis (other sites of infections without documented bacteremia were not included).

Cases were identified from both the hospital information technology department and microbiology laboratory records. Consequently, the medical charts of these patients were reviewed to confirm if they indeed had clinical and laboratory parameters consistent with the diagnosis of *Salmonella* meningitis and if they were eligible for inclusion into the study. The decision to obtain cultures was made by the attending pediatrician. *Salmonella* isolates were identified using Analytical Profile Index 20 E (bioMérieux, Marcy l'Etoile, France) and the automated Microscan System (Siemens Healthcare Diagnostics, Deerfield, Illinois, United States) and serogrouped using specific antisera (Welcome, Kansas, United States). The antimicrobial susceptibility testing of the isolates to ampicillin, trimethoprim/sulfamethoxazole, ceftriaxone, and meropenem was assessed using disc diffusion method and later automated Microscan System (Dade Behring). Ciprofloxacin minimum inhibitory concentration was assessed using the E-test method (AB BIODISK, Solna, Sweden). Demographic features, clinical presentations, laboratory data, acute complications at hospitalization, antibiotic therapies, outcomes, and outpatient follow-up data were collected from the medical charts and documented on a standardized form using the medical record database (including electronic health records) at KKUH. Hospital information system was used to follow patients' readmission to the hospital over the 19-year study period. Documentation of subsequent emergency room presentation, inpatient admission, or outpatient follow-up visits was noted to determine any additional sequelae or relapse from the *Salmonella* meningitis episode. Relapse was defined as reemergence of clinical and CSF finding of meningitis within 3 weeks of completion of antibiotic treatment course. All patients with bacterial meningitis at our department have a regular long-term follow-up. All patients who had survived meningitis were regularly followed up by a pediatric neurologist and infectious disease physicians. Motor impairment and sequelae on neurologic examination were determined by pediatric neurologist during follow-up. Patients were assessed for evidence of any long-term neurologic complications at 6 months, 1 year, and 3 years after the acute incident of *Salmonella* meningitis. The outcomes were categorized as follows: (1) death related to *Salmonella* meningitis, (2) adverse neurologic outcomes, and (3) full recovery (e.g., no motor impairment and normal development for age).

The adverse neurologic outcomes were classified as follows: cerebral palsy or any other persistent neuromotor deficits; developmental delay, defined as a child not attaining developmental milestones at the expected age, including motor and speech/language development; hydrocephalus; epilepsy; and sensorineural hearing loss (documented by audiologic test by an otolaryngologist). Patients who died were lost to follow-up, or had not reached the 3-year follow-up time point by January 2016, when the study was concluded, were excluded from the long-term neurologic outcome analysis.

The study was approved by the hospital's ethics committee.

Results

Clinical Features

During the 17-year study period, 1,003 *Salmonella* isolates were isolated from children aged ≤14 years. The majority of the isolates (817) were from fecal samples, 127 from blood, 25 from other body swabs (wound, abscesses, and body fluids), 20 from urine, and 14 from CSF. *Salmonella* serotype D1 (40%) was the most frequently detected, followed by serotype B (26%) and C1 (13%). Nontypable *Salmonella* isolates were recorded in 18% of cases. *Salmonella typhi* was detected in 4% of patients (40 cases). *Salmonella* meningitis occurred in 14 of the 141 (10%) cases of invasive *Salmonella* infection in children at our center. All but one patient with *Salmonella* meningitis were under the age of 12 months, with ages ranging from 1.5 to 9 months (mean age, 4.7 months).

All were previously healthy, full-term infants who were born and lived in Riyadh and had not traveled recently to other countries. None of the patients reported contact with ill family members, although family members were not tested for *Salmonella* infection. No reported direct exposures to common animal vectors for *Salmonella* such as reptiles were documented.

Twelve patients presented to the emergency room and were admitted; two patients were referred to us after partial antibiotic treatment at another local hospital. Two required initial care at the intensive care unit prior to transferring to the general pediatric wards.

Clinical presenting features are summarized in ►**Table 1**. Significant proportion of children had seizures on presentation (79%) and less than half had gastrointestinal symptoms.

The duration of symptoms prior to admission varied from 1 to 10 days (mean, 3 days), with 63% of patients presenting at the hospital within 2 days from symptoms onset. Cultures were collected on admission prior to the administration of intravenous (IV) antibiotics. Despite all patients having positive CSF cultures for *Salmonella* spp., only 8 of the 14 patients had positive blood cultures, and 3 patients had positive stool cultures (patients 3, 7, and 8) for *Salmonella*. Five patients (2, 4, 12, 13, and 14) had peripheral blood leukocytosis ranging from 13,000 to 25,600 cells/mm^3 on admission. CSF analysis did not reveal a distinct pattern (►**Table 2**). The CSF white cell count was elevated in 12 of the 13 patients (patient 8 had clotted sample with only CSF culture results), with a range of 10 to 2,100 cells/mL and neutrophil predominance in 9 patients. The CSF protein level was elevated in 11 of the 12 patients, and glucose level was low in all 12 patients. The isolated serotypes were D1 (28%), B (14%), and G1 (7%), whereas 42.8% of the isolates could not be typed using the recommended sera and were reported as infected with nontyphi *Salmonella* spp. *Salmonella enterica* serotype typhi was identified in one patient (7%). Serial lumbar punctures were performed in all patients 3 to 7 days after admission; all were negative except in patient 1 who had delayed sterilization. The fourth CSF culture for this patient was negative 18 days after admission.

Table 1 Clinical features and progress of *Salmonella* meningitis cases

Characteristics	Cases ($n = 14$) *n* (%)
Fever	14 (100)
Seizure	11 (79)
Lethargy	8 (57)
Bulging anterior fontanel	4 (28)
Diarrhea	7 (50)
Vomiting	6 (43)
Abnormal CSF profile[a]	12 (92)
Underlying immune deficiency[b]	3 (27)
Intracranial complication:	
Subdural empyema	8 (57%)
Multiple cerebral infarct	8 (57%)
Hydrocephalus	5 (36%)
Ventriculitis	4 (28.5%)
Venous sinus thrombosis	3 (21%)
Multiple brain abscesses	1 (7%)
Outcome	
Cure	4 (28.5)
Relapse	5(36)
Death	4(28.5)
Long-term neurologic complication	6 (60)

Abbreviation: CSF, cerebrospinal fluid.
[a]Number of patients who have CSF analysis performed is 13.
[b]Number of patients who underwent immune work-up is 11 patients.

Underlying immunodeficiency was evaluated in 11 patients; patients 3, 9, and 12 were confirmed as having chronic granulomatous disease (CGD), severe combined immunodeficiency (SCID), and interleukin (IL)-12 deficiency, respectively. Human immunodeficiency virus (HIV) testing was performed in eight patients who yielded negative results.

Antibiotic Therapy

Patients received broad-spectrum antibiotics for suspected bacterial infection at first presentation (vancomycin and ceftriaxone). Recommended weight-based dosing of antibiotics for meningitis was used. Results of antibiotic susceptibility testing were available for all patients. All isolates were susceptible to third-generation cephalosporins. Two isolates were resistant to ciprofloxacin (cases 5 and 11); one isolate each from cases 5 and 7 was resistant to ampicillin and nalidixic acid. All patients were initially treated with third-generation cephalosporin (ceftriaxone or cefotaxime). For patients who had complication or relapse, either meropenem (8 patients) or ceftriaxone in combination with ciprofloxacin (2 patients) was administered. Treatment duration ranged from 3 to 12 weeks course of IV antibiotics. Dexamethasone was administered in three patients.

Five infants had relapse of meningitis (36%), four of whom had the first episode diagnosed in another hospital. Duration of relapse occurred within 5 to 14 days of discontinuation of antibiotics. All patients with relapse were initially treated with ceftriaxone monotherapy for 3 weeks (patients 2, 4, 9, 10, and 12). In two of these patients, CSF sterility was documented during the course of the initial 3 weeks antibiotic therapy. Two of the relapsed cases were confirmed to have SCID (patient 9) and IL-12 deficiency (patient 12).

One child (patient 1) had recurrence after 6 weeks of the first episode. The first and second episodes were treated with ceftriaxone (for 4 weeks) and meropenem (for 8 weeks), respectively.

Acute Neurologic Complications

All the patients remained hospitalized for the completion of antibiotic therapy. The mean duration of hospitalization was

Table 2 Demographics, laboratory characteristics, treatments, and acute complications of 14 children with *Salmonella* meningitis

Case no. and year	Age and sex	CSF					Brain imaging	Antibiotic	Acute complication	Outcome
		WBC/mm^3	RBC/mm^3	Glucose/mmol/L	Protein G/L	Gram stain, culture				
1. 1999	3 yr M	12,000 N80%	0		NA	GNB *Sal.* typhi	Subdural empyema	Meropenem Dexamethasone 8 wk	Subdural empyema, recurrent meningitis, vegetative state	Died
2. 2003	6 mo F	790 N60	40	1.8	6.11	GNB *Sal.* group B	Subdural empyema	Ceftriaxone Meropenem 12 wk	Lt frontal subdural empyema Rt side weakness	Survived with sequelae
3. 2004	7 mo M	2100 N80	400	2.9	0.45	NOS *Sal.* group G1	Meningeal enhancement	Ceftriaxone 4 wk	None	Survived, no sequelae
4. 2007	2 mo F	850 N 90	50	3	1.29	GNB *Sal.* group D1	Subdural empyema, sinus thrombosis, arachnoiditis, encephalomalacia including midbrain.	Ceftriaxone 3 wk Mero 12 wk	Bifrontal subdural empyema, massive multiple brain infarcts.	Died
5. 2008	6 mo M	285 N70%	30	0.3	2.8	GNB *Sal.* group B	Ventriculitis, brain abscess, multiple infarcts, hydrocephalus	Ceftriaxone 6 wk	Brain abscess, multiple infarcts, hydrocephalus, VP shunt	Died
6. 2009	6 mo F	1150 N 70	70	0.8	2.4	*Sal.* spp.	Multiple infarct, bifrontal subdural empyema.	Ceftriaxone 6 wk	Rt hemiparesis, Rt facial palsy	Survived with sequelae
7. 2009	5 mo M	10 L100%	40	0.3	1.56	NOS *Sal* group D1	Sagittal sinus thrombosis, ventriculitis, multi-infarcts, subdural empyema	Ceftriaxone 6 wk	Intractable seizure, required EVD	Survived with sequelae
8. 2010	9 mo M	Clotted sample				*Sal.* group D1	Intracranial hemorrhage	Meropenem 2 wk	Septic shock, multiorgan failure, and brain death	Died
9. 2010	2 mo F	900 N80	50	<1	2.7	*Sal.* group D1	Subdural empyema	Meropenem 6 wk Ciprofloxacin 4 wk Dexamethasone	Hydrocephalus	Survived, no sequelae
10. 2011	25 d M	120 L100%	600	2.4	2.4	*Sal.* spp.	Dilated ventricles, intracranial bleeding, infarcts	Cefotaxime and ampicillin, then meropenem 6 wk	Hydrocephalus, seizures	Survived, with sequelae
11. 2012	6 wk	200 N10 L90	50	<0.5	5.6	*Sal.* spp.	Ventriculitis, multiple infarct both thalami and midbrain	Meropenem 8 wk Dexamethasone	Hydrocephalus, seizure	Survived with sequelae
12. 2012	3.5 mo M	1000 N 95	40	2.7	1.45	*Sal.* spp. non-typhi	Normal	Meropenem 6 wk	Normal	Survived, no sequelae

Table 2 (*Continued*)

Case no. and year	Age and sex	CSF					Brain imaging	Antibiotic	Acute complication	Outcome
		WBC/mm^3	RBC/mm^3	Glucose/mmol/L	Protein G/L	Gram stain, culture				
13. 2014	3 mo M	75 N90	225	0.2	8.3	*Sal.* spp.	Subdural empyema, ventriculitis, multiple infarcts, venous sinus thrombosis	Ceftriaxone 6 wk	Empyema required surgery	Survived, with sequelae
14. 2015	8 mo M	150 N85	0	1.2	1.5	GNB *Sal.* spp.	RT frontal subdural empyema	Meropenem 3 wk Ciprofloxacin+ ceftriaxone 10 wk	Subdural empyema, required craniotomy and evacuation	Survived, no sequelae

Abbreviations: CSF, cerebrospinal fluid; EVD, extraventricular drain; F, female; GNB, gram-negative bacilli; L, lymphocytes; Lt, left; M, male; N, neutrophils; NA, not available; NOS, no organisms seen; RBC, red blood cell; Rt, right; *S. typhi*, *Salmonella typhi*; *Sal.* spp., *Salmonella* species; *Sal., Salmonella*; VP shunt, ventriculoperitoneal shunt; WBC, white blood cell.

50 days (range, 14–84 days). All patients underwent brain imaging; either computed tomography (CT) scans and/or magnetic resonance imaging was performed during 2 days to 2 weeks after admission. Twelve patients had abnormal brain imaging, eight patients (57%) had subdural empyema (7 required neurosurgical intervention), and eight patients (57%) had multiple cerebral infarcts including brainstem infarcts (patient 4). Hydrocephalus was seen in five patients (36%), ventriculitis in four (28.5%) patients, venous sinus thrombosis in three (21%) patients, and multiple brain abscesses in one (7%) (patient 5) patient.

Outcomes

Among the 14 patients, there were four (28.5%) deaths secondary to *Salmonella* meningitis complication. Patient 1 developed cerebral palsy and vegetative state. Patient 2 developed relapse of meningitis with massive brain infarcts and died of septic shock. Patient 5 developed brain abscess with multiple infarcts and died after 6 weeks of illness. Patient 8 developed septic shock and multiorgan failure and succumbed to brain death after 12 days of admission. Of the 10 survivors who were followed up to 3 years, 6 patients (60%) had long-term neurologic complications (►**Table 2**). Hydrocephalus requiring ventriculoperitoneal (VP) shunt insertion occurred in five patients (patients 5, 6, 9, 10, 11), cerebral palsy in four patients (patients 1, 2, 7, 13), developmental delay (psychomotor retardation) in three patients (patients 10, 11, 13), and epilepsy in three patients (patients 7,10,11), one of whom required corpus callosotomy due to her/his uncontrolled seizures (patient 7). Three patients developed impaired hearing tests (patients 1, 4, 5). Four patients had complete recovery and were discharged at baseline condition with normal neurologic status and neurodevelopment on outpatient follow-up to 3 years' post-discharge (patients 3, 9, 12, 14). Two patients did not have any acute neurologic complication, one had hydrocephalus that required VP shunt with no long-term sequelae, and one had empyema and required neurosurgical intervention. Two of them were treated with a combination of ciprofloxacin and ceftriaxone for 4 to 8 weeks, one was treated with ceftriaxone alone, and one was treated with meropenem alone.

Discussion

This study highlights the unfavorable outcome of non-typhoidal *Salmonella* (NTS) meningitis in children aged <1 year. A total of 10% of children with invasive *Salmonella* infection at our hospital had meningitis; the majority of patients were infants. In infants, decreased opsonization, complement levels, chemotaxis, and phagocytosis increase the susceptibility to gram-negative bacteria.[9,10] In contrast to enteric fever, which has no clear clinical associations with classic immunodeficiency disorders, invasive NTS is associated with different immunocompromised conditions. In the disorders of oxidative cellular killing, like CGD, NTS is described as the most common cause of bloodstream infection and the third leading cause of all infections.[11]

Furthermore, inherited cytokine deficiencies that are required for intracellular killing, mostly IL-12 and IL-23, are associated with invasive NTS.[12] Upon further workup, three infants in the study were confirmed to have underlying immune defects. All our patients were symptomatic, most presenting with signs of infection such as fever, seizure, and irritability, but gastrointestinal symptoms (vomiting and diarrhea) were also prominent. Unlike infants with other common bacterial causes of sepsis and meningitis such as group B streptococcus or *E. coli*, our patients with *Salmonella* meningitis had positive blood cultures in only half of the cases. Marked CSF pleocytosis with a high proportion of neutrophils was observed in most cases[3,8]; however, in our series of 14 patients, the initial blood and CSF white blood cell (WBC) count results differed from those previously reported. Only five patients had a total WBC count $>11{,}000$ cells/mm^3 and $>70\%$ polymorphonuclear cells. The majority of the patients had WBC count between 4,000 and 9,600 cells/mm^3 and between 40 and 68% polymorphonuclear cells. The 12 patients with elevated WBC count in the CSF had values that ranged from 40 to 12,000 cells/mm^3, while polymorphonuclear cells ranged from 10 to 95%. Our finding showed that the most commonly isolated serotypes in the CSF were serogroups D1 and B. Earlier reports showed that most cases of *Salmonella* meningitis were due to *S. typhimurium* (serogroup B), *S. enteritidis* (serogroup D), and *S. paratyphi* B (serogroup B).[13,14]

Management of *Salmonella* meningitis has not been well defined. Previously used antimicrobial therapy, including ampicillin, chloramphenicol, and cotrimoxazole, had low cure rates ($\sim$40%) along with high concomitant mortality ($\sim$45%).[15] After the administration of third-generation cephalosporins, reports showed that the mortality rate declined to $\sim$10%, but morbidities remained high.[8] However, despite the substantial success of cephalosporins in treating *Salmonella* meningitis, there are some reports on its failure and relapse even after apparent complete clinical and culture response.[8,16–19] The duration of treatment of children in these reports varied from 3 to 8 weeks.[18] The evolving resistance to third-generation cephalosporins is also a cause for concern. In their study on childhood meningitis, Lecour et al reported the case fatality rate for *Salmonella* meningitis in patients treated with cefotaxime as 28.6%, which is similar to that reported in our study.[20] In our cases the disease progressed in 12 patients despite conventional ceftriaxone treatment. Subdural empyema, cerebral infarcts, and venous thrombosis developed while patients were on ceftriaxone. Two patients were treated with a combination of ceftriaxone and ciprofloxacin, and therapy in others was changed to meropenem. The combined use of cephalosporins with other antibiotics appears to have produced promising results. Use of fluoroquinolones, mainly ciprofloxacin in *Salmonella* meningitis, has increased, particularly in cases where there seems to be no clinical response to other antibiotics.[8,18–20] An advantage of fluoroquinolones is the achievable intracellular diffusion. Carbapenems, mainly meropenem, have also been described as therapeutic alternative with good outcome.[7,21,22] These agents have good CSF pharmacokinetic properties, and, like ceftriaxone, meropenem had the lowest minimum inhibitory concentration against *Salmonella* isolates from CSF.[23] Additionally, high cellular-to-extracellular-concentration ratios have also been reported for meropenem.[24] Therefore, carbapenems can be considered as therapeutic alternatives, especially in patients who do not have favorable clinical response or in relapse cases, but more studies with appropriate epidemiological design to support such recommendation are needed.

Use of dexamethasone, as adjunctive therapy, may be considered to reduce the effects of acute inflammatory response to bacterial invasion in the CNS, although the benefits of steroids in meningitis appear debatable.[25]

Salmonella meningitis has a high relapse rate. Using polymerase chain reaction in serial CSF analysis, studies have shown that NTS persists in CSF for at least 3 to 4 weeks.[26] The documented relapse rate of NTS meningitis is up to 60%.[27] The rate of relapse declined, however, with increasing length of antibiotic therapy. Our five patients who experienced relapse supposedly received appropriate treatment with ceftriaxone for 3 to 4 weeks, but meningitis relapsed 5 to 14 days after discontinuing treatment. Duration of treatment with appropriate antibiotic for >4 weeks seems reasonable. The optimal duration is probably 6 weeks.[2]

Overall, *Salmonella* meningitis is associated with a high frequency of complications.[8,14,28] Late presentation, convulsion, prolonged fever, and coma are associated with poor outcomes.[29] The fact that more than half of the patients in this present study developed subdural empyema, multiple cerebral infarcts, and hydrocephalus suggests that it is reasonable to recommend a complete evaluation of patients with documented *Salmonella* meningitis irrespective of clinical improvement. This should include a repeat lumbar puncture to document sterility of the CSF, neuroimaging studies with contrast to identify parenchymal lesions, empyema, hydrocephalus, and hearing and developmental assessments over time. Kavaliotis et al, in their reported series, identified three of five patients who developed abnormalities on brain CT.[15] Performance of early neuroimaging studies in our patients may have contributed to the detection of some treatable complications. Studies completed in developing countries have documented mortality rates ranging from 18 to 58% in children and as high as 89% in neonates with *Salmonella* meningitis.[7,22] High mortality rates in developing countries have been linked to increased comorbid conditions such as malnutrition and acquired immune deficiency syndrome/HIV and delay in the initiation of proper antibiotic therapy. In the present study, 18 (86%) infants suffered at least one complication during the acute phase of meningitis, leading to a complicated clinical course. On follow-up, 6 (60%) of the 10 infants who survived had subsequent motor deficit, epilepsy, hearing deficit, and experienced mild-to-severe sequelae. The 60% incidence of mild-to-severe adverse long-term outcomes in our patients was high, compared with that reported in previous studies.[15,18,19,30,31] One explanation is that the cases in this present study demonstrated more complex involvements of the brain, such as cerebral infarction and ventriculitis.

Additionally, most of the previous studies had short follow-up periods,[29,31,32] which might have underestimated the actual occurrence of disability. As meningitis survivors remain at risk of neurologic sequelae and lifelong impairment,[33,34] there is difficulty in evaluating those cases, particularly during the first 2 years of life. Many of the reports were not very specific on the incidence of neurologic sequelae. In the meantime, there are more survivors with the availability of third-generation cephalosporins and other antibiotic options, and subsequently, more complications may be noted than with the older drugs. While the number of cases in this report was not big, this study does permit us to assess trends in the frequency of an adverse outcome.

There are few limitations of this study. This study was conducted at a single center and may not represent other center findings in Saudi Arabia. The sample size was not large. The follow-up assessment methods included a regular clinical neurologic examination conducted to identify children with gross motor disability, and this might not detect cases with minimal neurologic deficits.

Conclusion

In summary, this study provided additional evidence into the spectrum of relapse, acute complications, and long-term neurologic outcomes in infants with *Salmonella* meningitis in Saudi. Timely recognition of complications and a follow-up plan for neurodevelopmental evaluation of cases are needed. Screening of infants < 12 months with *Salmonella* meningitis for underlying immunodeficiency is warranted. Addition of carbapenem or fluoroquinolone in relapsed cases or where there seems to be no clinical response to third generation cephalosporines would be the best option. New prospective studies from other sites in Saudi on antibiotic selection and evaluation of associated morbidity and mortality of *Salmonella* meningitis in infants are needed.

Conflict of Interest
None declared.

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