

# *Salmonella enterica* serovar Panama meningitis in exclusive breastfeeding infants

## Report of 4 cases, clinical features and therapeutic challenges

Narcisse Elenga, MD, PhD<sup>a,\*</sup>, Emma Cuadro, MD<sup>a</sup>, Laurence Long, MD<sup>a</sup>, Falucar Njuieyon, MD<sup>a</sup>, Elise Martin, MD<sup>a</sup>, Rémi Kom-Tchameni, MD<sup>a</sup>, Antoine Defo, MD<sup>a</sup>, Sitraka H. Razafindrakoto, MD<sup>a</sup>, Yajaira Mrsic, MD<sup>a</sup>, Fanny Henaff, MD<sup>a</sup>, Aba Mahamat, MD, PhD<sup>b</sup>

### Abstract

**Rationale:** The pathway of Nontyphoid *Salmonella* meningitis, especially in exclusive breastfeeding infants, has not been well characterized.

**Patient concerns:** We analyzed data related to nontyphoid *Salmonella* meningitis in 4 infants.

**Diagnoses:** No diarrhea was observed and the coproculture was negative for all patients.

**Interventions:** Early diagnosis and treatment with combination of third-generation cephalosporins plus quinolones for a minimum of 3 weeks is necessary to avoid severe sequelae and death.

**Outcomes:** The first 3 patients had a good evolution, whereas the last patient had multiple brain abscesses and hydrocephalus requiring treatment with a ventriculoperitoneal shunt.

**Lessons:** The highlights of our study are that all infants were exclusively breastfed, no diarrhea observed and the negative coproculture for all the 4 patients, which is relatively rare for *Salmonella* infection.

**Abbreviations:** 3GC = third-generation cephalosporin, CSF = cerebrospinal fluid, DNA = deoxyribonucleic acid, HIV = human immunodeficiency virus, PCR = polymerase chain reaction.

**Keywords:** case reports, exclusive breastfeeding, infant, meningitis, *Salmonella panama*

## 1. Introduction

Nontyphoid *Salmonella* meningitis remains a threat for infants below 2 years of age in both developing and developed countries. However, the pathway of such infections, especially in exclusive breastfeeding infants, has not been well characterized. *Salmonella enterica* subsp. *enterica* serovar Panama was isolated for the first time as part of a food-borne outbreak among soldiers stationed in Panama in 1934.<sup>[1]</sup> Since then, *Salmonella panama* was isolated from food, animals, and water. It belongs to serogroup D1 and causes gastroenteritis in humans. This serotype especially has

been associated with invasive diseases such as bacteremia and meningitis in children.<sup>[2]</sup> Infections usually occur after eating contaminated food or consumption of contaminated breast milk. In French Guiana, nearly 50% of *Salmonella* serotypes isolated from human infections belong to serotypes rarely encountered in metropolitan France. Moreover, nearly 2/3 of them have also been isolated from patients.<sup>[3]</sup>

Here, we analyzed data related to nontyphoid *Salmonella* meningitis in infants in our center in order to clarify the comprehensive features of nontyphoid *Salmonella* meningitis, including clinical characteristics, acute complications, and long-term outcome.

## 2. Patients and methods

Cayenne Hospital is as a referral center for primary care facility situated in Cayenne the main city of in French Guiana. From 2011 to 2016, we identified 4 cases of *Salmonella* meningitis referred to the Paediatrics and Surgery Unit. Medical records of the 4 pediatric cases admitted with spontaneous *Salmonella* meningitis were reviewed. The entry criteria for diagnosis were the isolation of *Salmonella* species in cerebrospinal fluid (CSF) culture, which further supported infection based on pleocytosis (>30/ $\mu$ L) with predominant neutrophilia and hypoglycorrhachia. Other following informations were retrieved: clinical presentations, demographic features, laboratory data, acute complications at hospitalization, antibiotic therapy, and long-term outcomes.

Moreover, for each case, family *Salmonella* contact exposure was investigated through bacteriological analysis of water, breast milk, and feces.

Editor: Cheng-Hsun Chiu.

Consent: For each case report, the parents have written a documented and informed consent. They gave their written consent for the case report to be published.

Conflict of interest statement: The authors have no funding and conflicts of interest to disclose.

<sup>a</sup> Department of Pediatrics, <sup>b</sup> Department of Infectious Diseases, Cayenne Regional Hospital, Rue des Flamboyants, BP 6006, 97306 Cayenne Cedex, French Guiana, France.

\* Correspondence: Narcisse Elenga, Department of Pediatrics, Cayenne Regional Hospital, Rue des Flamboyants, BP 6006, 97306 Cayenne Cedex, French Guiana, France (e-mail: elengafr@yahoo.fr)

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Medicine (2017) 96:19(e6665)

Received: 11 September 2016 / Received in final form: 7 March 2017 /

Accepted: 29 March 2017

<http://dx.doi.org/10.1097/MD.0000000000006665>

## 2.1. Biological methods

Hemoculture and coproculture were used as complementary examinations for the isolation of *Salmonella*. Identification of *Salmonella* spp. was based on conventional techniques as well as automated instruments including Vitek-2 (bioMérieux, Marcy-l'Étoile, France), API 20 NE method (bioMérieux) or recently mass spectrometry (Microflex, Bruker Daltonics, Bremen, Germany).

The EvaGreen real-time polymerase chain reaction (PCR) assay has been used for identification of *S. enterica* subsp. *enterica* serovar Panama.<sup>[4]</sup> Total deoxyribonucleic acid (DNA) was extracted from the *Salmonella* spp. isolated strains with the Wizard Genomic DNA purification kit (Promega, Fitchburg, WI). The DNA was resuspended in a rehydration buffer provided with the Wizard kit. The Singleplex PCR was performed in a reaction volume of 50 µL containing DNA (2 µL for the InstaGene matrix or 1 µL diluted 10-fold for Wizard). This molecular characterization of *S. enterica* serotype was performed at the Enteric Bacterial Pathogens Unit of the Institut Pasteur, Paris, France.<sup>[3]</sup>

## 2.2. Ethical consideration and regulatory

Patients' medical records were retrospectively reviewed, and all data collected were anonymized in standardized forms according to procedures of the Commission Nationale de l'Informatique et Libertés (the French information protection commission). Moreover, all the participants have signed informed consent, before participating in the study.

## 3. Results

We have reviewed 4 medical charts of 4 infants admitted for *Salmonella* meningitis in our center. They did not receive any treatment before admission to the hospital. All the 4 cases met the diagnosis criteria of *Salmonella* meningitis (isolation of *Salmonella* in the CSF, pleiocytosis, and hypoglycorachia). Data about the acute phase of *Salmonella* meningitis were summarized in

Table 1. Human immunodeficiency virus (HIV) infection and other risk factors for invasive disease were absent in our cases. Our 4 patients had an atypical clinical presentation: all had fever with vomiting, between 1 and 7 days before diagnosis. None of them had presented diarrhea. Two of them presented seizures before admission to hospital. All had signs of septic shock at admission. Neurological signs like lethargy, irritability, and bulging anterior fontanel were present in all patients. Biological signs were not different from other bacterial meningitis. No diarrhea was observed and the coproculture was negative for all patients. The laboratory findings were listed in Table 1. The clinical strains of *S. panama* were isolated from the CSF of all the infants. The investigation of the family *Salmonella* contact exposure was negative for all the patients.

During hospitalization, all the children had a brain magnetic resonance imaging and computerized tomography scan to detect acute intracranial complications and to diagnose ventriculitis. Table 1 summarizes the acute complications and outcomes in our patients with *Salmonella* meningitis. The 3 first patients had a less severity of the disease with a good evolution, whereas the last patient had multiple brain abscesses and hydrocephalus requiring treatment with a ventriculoperitoneal shunt. He also had deafness and lack of eye tracking. We have noted no deaths.

## 4. Discussion

Lumbar puncture is easily performed in children, but sometimes the clinical presentation of meningitis may be atypical and delay its completion. The highlights of our study are that all infants were exclusively breastfed, no diarrhea observed and the negative coproculture for all the 4 patients, which is relatively rare for *Salmonella* infection.

Several studies<sup>[5,6]</sup> have reported cases with digestive infection in the previous days and a positive coproculture for salmonella. In all patients, we were able to make an etiological investigation of the source of salmonella (coproculture among parents and siblings, study of consumed water). This etiological research was negative. None of these families amounted turtles or snakes. We

**Table 1**

**Summary table of clinical characteristics, laboratory, and long-term outcome.**

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Admission features				
Year of occurrence	2011	2012	2013	2016
Sex	F	F	F	M
Breastfeeding	Yes	Yes	Yes	Yes
Age at onset, mo	3	6	6	7
Medical background				
Immune deficiency	No	No*	No	No
Sickle cell disease	No	No	No	No
Born from a HIV-infected mother	No	No	No	Yes
Duration of fever before diagnosis, d	7	7	1	5
Temperature on admission, °C	39	39	39	38.5
Diarrhea	No	No	No	No
Vomiting	Yes	Yes	Yes	No
Seizures before admission	No	No	Yes	Yes
Seizures at hospital	No	No	Yes	Yes
Lethargy	Yes	Yes	Yes	Yes
Irritability	Yes	Yes	Yes	Yes
Poor feeding	Yes	Yes	Yes	Yes
Bulging anterior fontanel	Yes	Yes	No	No
Septicshoc	No	Yes	Yes	Yes

(continued)

**Table 1**  
**(continued).**

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Antibiotic before hospitalization	No	No	No	Yes
Duration of hospitalization, days	19	21	22	47
Dosing of Quinolone/3GC, mg/kg/d	45/300	45/300	45/300	45/300
Duration of treatment, d	19	21	21	45
Condition at discharge				
Survival	Yes	Yes	Yes	Yes
Disability	No	No	No	Yes
Ongoing seizure	No	No	Yes	Yes
Focal motor weakness	No	No	No	Yes
Relapse	No	No	No	No
Acute complications and outcomes				
Level of consciousness				
Coma in hospital	No	No	Yes	Yes
Intracranial complications				
Subdural collection	No	No	No	No
Intracranial focal infection	No	No	No	Yes
Empyema	No	No	No	No
Brain abscess	No	No	No	Yes
Cerebral infarction	No	No	No	Yes
Ventriculitis	No	No	No	No
Hydrocephalus	No	No	No	Yes
Long-term outcome development				
Delayed	No	No	No	Yes
Motor disability				
Severe	No	No	No	Yes
Moderate	No	No	No	No
Mild	No	No	No	No
Normal	Yes	Yes	Yes	No
Hearing problems	No	No	No	Yes
Epilepsy	No	No	Yes	Yes
Microcephaly	No	No	No	No
Hydrocephalus	No	No	No	Yes
Visual deficit	No	No	No	Yes
Speech language	No	No	No	Yes
Abnormal	No	No	No	Yes
Normal	Yes	Yes	Yes	No
Biological data				
Peripheral blood data				
Total WBC, G/L	7.7	9.0	3.3	3.6
Neutrophils, G/L	6.31	5.94	0.36	1.34
Lymphocytes, G/L	0.89	2.70	2.44	2.05
Platelet, G/L	306	182	239	101
Hemoglobin level, G/dL	10.6	9.3	7.3	10.4
Ferritin, µg/L	6.1			
CRP, mg/L	140	212	191	270
Hemoglobin electrophoresis	AA	AA	AA	AA
IgG level, G/L	6	5	6	7
IgA level, G/L	0.6	0.9	0.8	0.7
HIV	Negative	Negative	Negative	Negative
CSF data				
Total WBC, µL	450	498	70	840
PMN, µL	252	149	25	647
Glucose, mmol/L	0.4	0.2	1.9	<0.1
Protein, G/L	1.53	1.26	1.93	2.92
Coproculture	Negative	Negative	Negative	Negative
Hemoculture	Positive	Positive	Positive	Positive
Gram coloration	GN	GN	GN	GN
Gram-negative bacterium identified	<i>S. panama</i>	<i>S. panama</i>	<i>S. panama</i>	<i>S. panama</i>

3GC = third-generation cephalosporins, CSF = cerebrospinal fluid, GN = gram-negative, PMN = polymorphonuclea, WBC = white blood cells.

\* Full immunological investigation including congenital or acquired immunodeficiency.

could not find *Salmonella* in pet-reptiles. In French Guiana, domestic reptiles (snakes, turtles, etc.) are common in houses and their presence near habitations is a usual situation.<sup>[3]</sup> Exposure to domestic reptiles was involved in the contamination of infants by *Salmonella*.<sup>[3,7]</sup> Our investigations have not allowed us to find source of salmonella in these infants who were exclusively breastfed. However, a reptilian source of contamination has previously been investigated in French Guiana, and the overall frequency of carriage was 23.2%.<sup>[3]</sup>

Furthermore, some questions remain unanswered and in particular, scarcity of such infections in infants could be related to a low inoculum? None of the patients had an immune deficiency. The diagnosis of meningitis is easy with lumbar puncture performed in infants with septic shock. The serotype identification of *Salmonella* was made in the National Reference Center for *Salmonella* in France. *S. enterica* subsp. *enterica* serovar Panama was isolated for all of the patients. This serotype is known to cause invasive diseases such as meningitis in children.<sup>[1,2]</sup>

The currently recommended first-line treatment of *Salmonella* meningitis is a combination of third-generation cephalosporins (3GC) with quinolones for a minimum of 3 weeks.<sup>[8]</sup> This protocol was conducted for the 4 patients. The evolution was favorable in 3 of them. The fourth patient had a dramatic neurological outcome, though the delay between the onset of fever and diagnosis of meningitis was similar in all patients. No patient was immunosuppressed. But the patient who has had a dramatic outcome was born from HIV-infected mother. It is well described now that children born from HIV-infected mothers are at a high risk of developing bacterial infections.<sup>[9]</sup> Although *Salmonella* meningitis is rare in children, it remains a serious infection. Our study confirms the literature findings.<sup>[10]</sup> Early diagnosis and antibiotic treatment are necessary for a better therapeutic response and to prevent progression toward sequelae or death. A long-term effects monitoring for early developmental assessment for survivors is vital.

For all the 4 patients, a follow-up on psychomotor development with research of sensory disturbances was set up. We have noted no death among the 4 children and 1 patient had a severe neurologic outcome according to our monitoring.

## 5. Conclusion

*Salmonella* meningitis is rare in infant but is severe with a high risk of sequelae in survivors. Early diagnosis and treatment with combination of 3GC plus quinolones for a minimum of 3 weeks is necessary to avoid severe sequelae and death. The long-term monitoring for survivors is useful to improve the functional prognosis.

## Acknowledgments

The authors would like to thank M. Limmois and the other members of the department of Bacteriology for data collection and Dr François-Xavier Weill, MD, PhD, Research Director, Enteric Bacterial Pathogens Unit, Institut Pasteur, Paris, France for his advice and corrections.

## References

- [1] Leeder FS. An epidemic of *Salmonella panama* infections in infants. *Ann N Y Acad Sci* 1956;66:54–60.
- [2] Keddy KH, Sooka A, Musekiwa A, et al. Clinical and microbiological features of *Salmonella meningitis* in a South African population, 2003–2013. *Clin Infect Dis* 2015;1(61 suppl 4):S272–82.
- [3] Gay N, Le Hello S, Weill FX, et al. *Salmonella* serotypes in reptiles and humans, French Guiana. *Vet Microbiol* 2014;14:167–71.
- [4] Fabre L, Le Hello S, Roux C, et al. CRISPR is an optimal target for the design of specific PCR assays for *Salmonella enterica* serotypes Typhi and Paratyphi A. *PLoS Negl Trop Dis* 2014;8:e2671.
- [5] Tuan DQ, Hung PH, Mai PX, et al. *Salmonella meningitis*: a report from National Hue Central Hospital, Vietnam. *Jpn J Infect Dis* 2015;68:30–2.
- [6] Costa Orvay JA, Hervás A, Hurtado A, et al. Meningitis due to *Salmonella* after food poisoning in an infant fed with formula milk. *An Pediatr* 2013;79:270–1.
- [7] Pawlak A. Reptile-associated salmonellosis as an important epidemiological problem. *Postepy Hig Med Dosw* 2014;68:1335–42.
- [8] Guillaumat C, Dang-Duy TL, Levy C, et al. *Salmonella* meningitis in newborns and infants. The importance of fluoroquinolones. *Arch Pediatr* 2008;15(suppl 3):S161–6.
- [9] Slogrove A, Reikie B, Naidoo S, et al. HIV-exposed uninfected infants are at increased risk for severe infections in the first year of life. *J Trop Pediatr* 2012;58:505–8.
- [10] Wu HM, Huang WY, Lee ML, et al. Clinical features, acute complications, and outcome of *Salmonella meningitis* in children under one year of age in Taiwan. *BMC Infect Dis* 2011;11:30.