Case Report

Neonatal sepsis due to *Salmonella* Typhi and Paratyphi A

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Abstract

Sepsis due to *Salmonella enterica* serovar Typhi and Paratyphi A is rare in neonates. Though described as a mild and unrecognized illness in infants, life-threatening complications and even deaths have been reported. We present five cases of neonatal septicaemia due to *S.* Typhi and *S.* Paratyphi A. The cases were presented because of their interesting clinical presentations and possible modes of transmission. *Salmonella* infections should be considered in the differential diagnosis of sepsis neonatorum, especially in endemic areas.

Key words: enteric fever, neonate, *Salmonella*, sepsis

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Introduction

Enteric fever due to *Salmonella enterica* serovar Typhi and Paratyphi A continues to remain a major cause of morbidity and mortality in developing countries, including India, with the incidence highest in the 5 to19 years age group [1]. Enteric fever in children younger than two years of age and neonates is rare and thought to be a mild, often unrecognized illness [2-4]. However, life-threatening complications and deaths have been reported, especially among young and malnourished infants [5,6]. The majority of the cases of enteric fever in neonates have been due to *S*. Typhi. *Salmonella* Paratyphi A is implicated rarely [7,8].

Salmonella Typhi and *Salmonella* Paratyphi A strains were isolated from five neonatal septicemia cases who were admitted in our hospital between 2004 and 2005. The cases are presented because of their interesting clinical presentations and possible modes of transmission.

Setting

All cases concerned babies delivered at Safdarjung Hospital, Delhi (India), a 1,500-bed, tertiary care centre with a delivery rate of 15,000-18,000/year. Almost 20% of deliveries require nursery admission. The neonatal unit has two nurseries: an intramural nursery for infants born within the hospital and an extramural nursery for infants born outside the hospital. There are 20 to 25 neonates in each nursery at any given time. Each nursery has six intensive care unit (ICU) beds and isolation facilities are available. The following criteria are used for performing sepsis screening, including blood culture of neonates: sepsis in the form of maternal fever, premature rupture of membranes of more than 24 hours duration, unclean vaginal examination prior to admission, mechanical ventilation, umbilical catheterization, and assisted delivery by forceps or ventouse application. Early onset sepsis (EOS) and late onset sepsis (LOS) are defined as clinical sepsis in an infant less or more than 72 hours old. Empirical therapy for suspected EOS consists of ampicillin with gentamicin and that for LOS consists of third-generation cephalosporins with amikacin.

In the present study, follow-up of all neonates presenting with positive blood cultures for *Salmonella* was conducted with respect to their clinical presentation, possible sources of infection, and outcome.

Case 1: A 20-year-old G_2 P_1 L_0 female with 28 weeks' amenorrhea with anemia (Hb 8.5 gm/dl) delivered a male baby vaginally in the labor room. The baby was preterm with a very low birth weight of 1,000 grams and had severe birth asphyxia requiring resuscitation. The Apgar score was 2, 6, and 8 at 1, 5, and 10 minutes respectively. The baby was transferred to the neonatal ICU and was managed conservatively. Presumptive first-line antibiotics were started in view of prematurity, very low birth

weight, use of resuscitation equipment, and respiratory distress. Tube feeds were started on day 3 after the baby stabilized. Blood culture sent on day 1 showed no growth. On day 5, however, the baby became sluggish and developed sclerema and icterus (serum bilirubin 10.0 gram/dl). Phototherapy was started, and a repeat blood culture along with a cerebrospinal fluid sample was sent for culture. Empirical therapy with intravenous cefotaxime and amikacin was started on presumption of LOS. On day 11, the baby developed apnoea and was put on mechanical ventilation. On day 12, the second blood culture (5th day) grew *S.* Paratyphi A. Therapy was changed to parenteral ceftriaxone and amikacin according to the sensitivity profile of the isolate and continued for 15 days. The baby responded and was discharged on the 28th day of delivery. The mother's blood and stool cultures were negative for *Salmonella*.

Case 2: A G3 P1 L1 female was admitted with a history of 38 weeks' amenorrhoea, previous lower section caesarean section (LSCS), fever for 5 days. and diarrhoea. Blood culture performed in a private laboratory had been sterile. She was anemic with a hemoglobin level of 6.2 gm/dl and received packed cells. On admission, she received parenteral ampicillin, gentamicin and metronidazole. On the 6th day of admission, she delivered a male baby with a birth weight of 2.7 kg by LSCS in view of fetal distress due to meconium stained liquor. The baby cried immediately at birth and did not require resuscitation. He was managed conservatively and was transferred to the neonatal ICU for suspected meconium aspiration syndrome after sepsis screen. He was started on parenteral ampicillin and gentamicin. Blood culture of the baby grew *S.* Typhi. Though the baby was asymptomatic, in view of the positive blood culture report, antibiotics were continued for seven days after which the baby was discharged. Stool cultures of both mother and baby were negative for *S.* Typhi.

Case 3: A G2 P1 L1 A1 female with amenorrhoea for 38 weeks and previous LSCS was admitted for delivery. She gave a history of high-grade fever with chills for 4 days' duration which subsided after taking treatment from a private practitioner. On the day of admission, she delivered a very low birth weight (1.2 kg) female baby vaginally. The baby was immediately transferred to the nursery for very low birth weight care and probable clinical sepsis in view of the mother's fever. On admission in the neonatal ICU, sepsis screen including blood culture was sent and the baby was managed conservatively. Sixteen hours after birth, the baby had persistent respiratory distress and the sepsis screen showed positive. The baby was administered parenteral ampicillin and gentamicin. Subsequently, the blood culture grew *S.* Typhi. Antibiotics and conservative management were continued and the respiratory distress settled at 40 hours after birth. Parenteral ampicillin and gentamicin were continued and the baby was discharged on the 10th day of delivery. The mother's stool culture could not be performed.

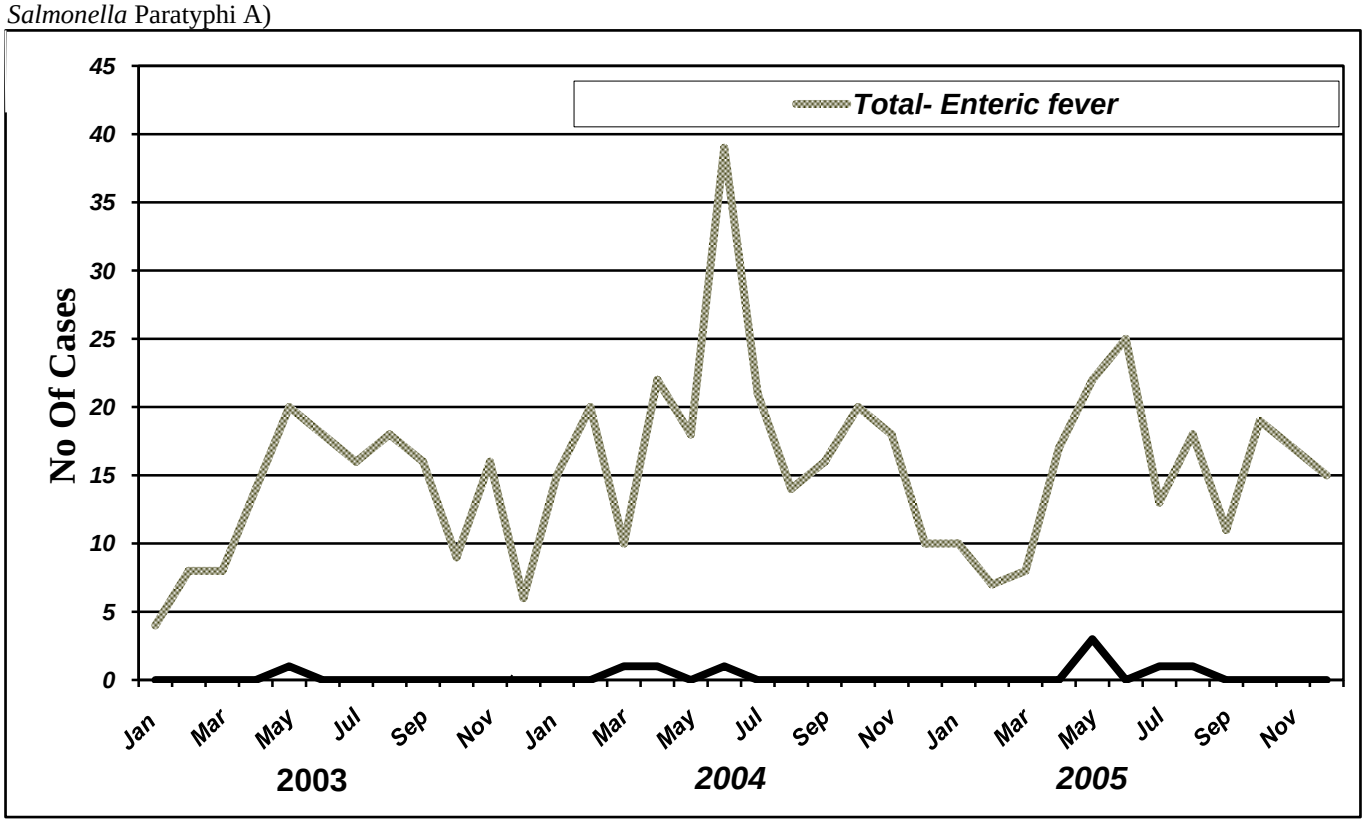
Case 4: A female baby weighing 2.25 kg (low birth weight) was born to a full-term 29-year-old G3 P2 L2 female by vaginal delivery. She gave a history of fever of one day's duration prior to delivery. The Apgar score of the newborn at 1, 5 and 10 minutes was 1, 4 and 7, respectively. The baby was transferred to the nursery because of low birth weight and severe birth asphyxia. The baby had respiratory distress and multiple multi-focal convulsions. She was given intravenous fluids, oxygen, first-line antibiotics, and injection phenobarbitone. Blood and cerebrospinal fluid cultures were sent. Chest X-ray revealed right lower lobe infiltration indicating pneumonia. On day 3, oxygen was omitted and on day 5, oral feeds were started. The blood culture taken on transfer to the neonatal ICU revealed growth of *S.* Typhi. Cerebrospinal fluid culture was sterile. Parenteral antibiotics were continued for 14 days after which the baby was discharged. The mother's blood and stool cultures were negative for *Salmonella*.

Case 5: A full-term male baby weighing 2.8 kg was born by normal vaginal delivery to a 32-year-old female with no significant antenatal history. The baby cried immediately after birth and was vigorous; hence he was shifted with the mother. On day 2, the mother complained that baby was not accepting feeds. On clinical examination, no abnormality was detected; however, a sepsis screen was performed and blood cultures sent. On day 3, the baby started accepting feeds well, the sepsis screen was found to be negative, and the baby was discharged. The blood culture grew *S.* Typhi; however, the mother and baby could not be investigated further.

Investigations

After the blood culture reports became available, an attempt was made to identify the possible sources

Figure 1. Enteric fever cases in pregnant women at Safdarjung hospital, 2003-2005 (Culture positive cases: 9 only one was *Salmonella* Paratyphi A)



of infection. Stool and blood cultures were performed on the mothers of three babies (cases 1, 2, and 4), but the cultures were negative. It was not possible to investigate the mothers of babies 3 and 5. Environmental and staff screening did not yield any evidence of spread within the nursery Susceptibility testing performed by a standard antimicrobial disk-diffusion test per the Clinical Laboratory Standards Institute (CLSI) guidelines [9] revealed that all four isolates of *S.* Typhi were susceptible to ampicillin, co-trimoxazole, chloramphenicol, nalidixic acid, ciprofloxacin and ceftriaxone. *Salmonella* Paratyphi A isolate was resistant to nalidixic acid only.

Discussion

Salmonellosis is normally not considered in the differential diagnosis of neonatal sepsis. However, a literature review of neonatal typhoid fever by Reed *et al*. [10] suggested two major clinical forms of typhoid fever in infants, one of sepsis neonatorum and the other of asymptomatic fecal carrier. In cases of sepsis neonatorum, the patients have severe septicaemia and the presenting signs and symptoms appear to be as varied and non-specific as one might see with other gram-negative bacterial sepsis. Presentation may be at birth to up to 10 days after birth. The incubation period is shorter and is usually only about 48 hours, although it may be up to seven days. Classical signs and symptoms of typhoid fever viz. leucopenia, splenomegaly, rose spots, abdominal distension, bronchopneumonia, and even fever may not be present [6]. Infants are often anorexic, floppy and irritable, and may present with pyrexia, jaundice, dehydration, respiratory distress and diarrhoea, while some present with hypothermia, abdominal distension, seizures and cough [10]. Other presentations reported in the literature include meningitis and brain abscess [11] and neonatal cholecystitis [12]. In the present case series, three babies had sepsis and the major clinical presentations observed included icterus, lethargy and sclerema (one baby), respiratory distress with or without pneumonia (three babies), and two babies were asymptomatic. Though bronchopneumonia constitutes one of the classical clinical features of typhoid fever in adults, it has not been previously reported in neonates.

The second presentation seen in two babies (cases 2 and 5) was asymptomatic disease, possibly with transient bacteremia. Asymptomatic infection with fecal carrier has been reported, and results from colonization of the gastrointestinal tract of the infant

Table. 1. Reports of Culture positive Neonatal Typhoid and Paratyphoid cases from India and other Endemic countries

S.No	Mother's workup	Babies Workup					Reference
		Birth Weight	Clinical presentation	Mode of transmission	Serotype	Outcome	
INDIAN STUDIES							
1	No history available Culture: not done Delivery: Not known	Not known	6th day of life. Also had cyanotic heart disease. Respiratory distress, fever, loose stools	Vertical transfer, with outbreak in orphanage	*Salmonella* Group C1	Death	18
2	Premature rupture of membranes Stool, blood culture: negative Delivery: Vaginal	1820gm	14th day of life Sepsis	Not commented	*S*. Typhi	Discharged	19
3	Not mentioned, Cultures: not done Delivery: Vaginal	1500gm	5th day of life Brain abscess, meningitis	Not commented	*S*. Typhi	Death	11
4	Not mentioned, Culture: not done Delivery: Vaginal	2600gm	5th day of life Diarrhoea, Jaundice, cholecystitis	Horizontal. Contaminated feed	*S*. Typhi	Discharged	12
5	Not significant Blood, stool culture: Negative Delivery: LSCS	4000gm	5th day of life. Sepsis	Horizontal. Contaminated formula feed	*S*. Paratyphi A	Discharged	7
6	Fever, Blood culture: positive Delivery: LSCS	1565gm	At birth. Respiratory distress	Vertical	*S*. Paratyphi A	Death	8
S.No	**Mother's workup**	**Babies Workup**					**Reference**
		Birth Weight	**Clinical presentation**	**Mode of transmission**	**Serotype**	**Outcome**	
INTERNATIONAL STUDIES							
7	8 cases (Africa) Fever -4 culture negative Carrier-1, culture positive Delivery: Vaginal	Not Known	Diarrhea, jaundice , fever, hypothermia	Vertical and contaminated feed	*S*. Paratyphi A -6 *S*. Typhi - 2	Death -4	20
8	One case (Mauritius) Typhoid carrier. Culture positive Delivery :Vaginal	2700gm	Diarrhoea and stool carrier	Vertical	*S*. Typhi	Discharged	15
9	3 cases (Pakistani immigrants) Carrier -1 Fever with culture positive 1 Delivery: vaginal	Not Known	24 hours to 3rd day of life. Fever, seizures, hypothermia, hypoglycaemia, carrier. Neonatal outbreak reported	Vertical	*S*. Typhi	All Discharged	16
10	10 cases (South Africa) All culture negative Fever -3 Delivery- Vaginal, LSCS	Range 1000-3620gm	1st--21 days of life Diarrhea, fever, jaundice , hypothermia, respiratory distress, seizures , carrier	Vertical and contaminated feed.	*S*. Typhi	Death -3	10
OUR STUDY							
11	5 cases All culture negative Fever -2 Delivery- Vaginal, LSCS	Range 1000-2800gm	Icterus, lethargy, sclerema, respiratory distress, bronchopneumonia	Vertical	*S*. Typhi - 4 *S*. Paratyphi A - 2	All discharged	

at birth [10]. These babies may become persistent excreters. The mother must by definition be a carrier or have current typhoid infection with excretion of the organism in the stool. In 1930, Wing and Treppoli [13] first described this mode of transmission in an American housewife who had typhoid fever during pregnancy and eight weeks later delivered a baby who appeared clinically well except for dehydration and positive stool cultures for *S*. Typhi. The mother persistently excreted *S*. Typhi throughout her hospital stay. This mode of transmission with persistent excretion by healthy neonates was later reported by Diddle *et al*. [14], Freedman *et al*. [15] and Chin *et al*. [16]. Stool cultures performed on one of the asymptomatic babies did not confirm fecal carriage in our study.

The different modes by which *S*. Typhi and *S*. Paratyphi A can be transmitted to the neonates include vertical transmission from the mother and transmission from exogenous sources [10]. Vertical transmission may be due to one of the following routes: transplacental spread of the organism when the mother has symptomatic typhoid fever, as a result of *S*. Typhi or *S*. Paratyphi A bacteremia during labour with spread to fecal circulation; or infection by the oral route during birth due to inadvertent fecal contamination of the lower birth canal [10]. Intermittent bacteremia has been described in carriers by Watson [17] and it is possible that labour precipitates bacteremia. Aspiration leading to infection by the oral route has been supported by studies where the same *S*. Typhi phage types were isolated both from mother and baby [16]. Infection due to aspiration has been reported from both the mother with typhoid fever [13] as well from typhoid carriers (both stool and cervical carriage) [15]. Neonatal infection from an exogenous source may occur from top feeds supplemented with contaminated water in endemic areas or from index cases, especially asymptomatic carriers via treating personnel [10].

We speculate that transmission was vertical in the present case series in all the babies, since the organisms were isolated from blood culture immediately after birth. We strongly believe that transplacental spread occurred in three of our babies (case numbers 2, 3 and 4) since one of them was delivered by caesarean section (case 2) and the other two presented with severe sepsis at birth. Furthermore, in these three cases, the mothers were also symptomatic prior to delivery. In the two other babies (cases 1 and 5) delivered by vaginal route, aspiration of birth canal contents seems to be the major mode of transmission, though the transplacental route cannot be ruled out in case 1 since the baby presented with severe birth asphyxia and respiratory distress. Infection from exogenous sources is ruled out in the present series because the neonates were given top feeds in the nursery under strict supervision and sterile precautions, and no simultaneous outbreaks were reported. The majority of the isolates were *S*. Typhi. *Salmonella* Paratyphi A sepsis was observed in only one neonate probably because *S*. Typhi is more common in the general population (ratio *S*. Typhi: *S*. Paratyphi A, 3: 1). No mortality was observed as timely and appropriate therapy was initiated.

Table I summarizes previous reports of neonatal typhoid and paratyphoid cases in India and other countries.

The limitation of our study was the inability to isolate Salmonella from the mothers' blood and stool for various reasons, including rapid turnover of patients in a busy hospital.

A review of the hospital and laboratory records revealed nine cases of *Salmonella* (eight cases of *S*. Typhi and one of *S*. Paratyphi A) infection from cultures of blood and high vaginal swabs in pregnant women in our hospital during 2003-2005 (Figure1) suggesting the occurrence of infection and carriage state in pregnant women. However, enteric fever is rarely considered in the differential diagnosis of fever in pregnancy. There have been reports of outbreaks [21,22] of *S*. Typhi in maternity wards and neonates from mothers with undiagnosed clinical disease and asymptomatic carriage. Thus it can be concluded that in endemic areas, enteric fever must be included in the differential diagnosis of temperature elevation in young women with pregnancy so that neonates can be screened and managed appropriately. In conclusion, *Salmonella* infections should be considered in the differential diagnosis of sepsis neonatorum, especially in *Salmonella* endemic areas.

References

1. Park K (2005) Typhoid fever. Park's Textbook of Preventive and Social Medicine, 18th edn. Jabalpur: Bhanot, 187-190.
2. Kapoor JP, Man Mohan, Talwar V, Daral TS, Bhargava SK (1985) Typhoid fever in young children. Indian Pediatr 22: 811-813.
3. Sudhindra BK (1995) Enteric fever in young children. Indian Pediatr 32: 1127.
4. Mahle WT, Levine MM (1993) *Salmonella* Typhi infection in children younger than five years of age. Pediatr Infect Dis J 12: 627-631.

5. Klonin HK, Minelli E, Adhikari N (1989) Three unusual cases of *Salmonella* infection in infants. Ann Trop Paediatr 9: 240-242.
6. Karande SC, Desai MS, Jain MK (1995) Typhoid fever in a 7-month-old infant. J Postgrad Med 41: 108-109.
7. Randhawa VS, Kumar A, Saili A, Datta V, Agrawal C, Mehta G (2007) Paratyphoid sepsis. Indian J Pediatr 74: 197-198.
8. Raveendran R, Wattal C, Sharma A, Kler N, Garg P, Gujrat K, Khera N (2007) Vertical transmission of *Salmonella* paratyphi A. Indian J Pediatr 74: 784-786.
9. Clinical Laboratory Standards Institute. Performance standards for antimicrobial disk diffusion testing. Wayne, PA: CLSI; 2005 [Fifteenth Informational Supplement (M100--S15)].
10. Reed RP, Klugman KP (1994) Neonatal typhoid fever. Pediatr Infect Dis J 13: 774-777.
11. Mukherjee D, Banerjee I (1996) Neonatal *Salmonella* infection. Indian Pediatr 33: 438-439.
12. Singh UK, Suman S (1999) *Salmonella* cholecystitis in a neonate. Ann Trop Paediatr 19: 211-213.
13. Wing ES, Troppoli DV (1930). The intra-uterine transmission of typhoid. JAMA 95: 405-406.
14. Diddle AW, Stephens RL (1989) Typhoid fever in pregnancy. Am J Obstet Gynecol 38: 300-305.
15. Freedman ML, Christopher P, Boughton CR, Lucey M, Freeman R, Hansman D (1970) Typhoid carriage in pregnancy with infection of neonate. Lancet 1: 310-311.
16. Chin KC, Simmonds EJ, Tarlow MJ (1986) Neonatal typhoid fever. Arch Dis Child 61: 1228-1230.
17. Watson KC (1967) Intravascular *Salmonella* typhi as a manifestation of the carrier state. Lancet 2: 332-334.
18. Sahni M, Bedi S (2005) Enteric fever in infancy. Two cases in an orphanage outbreak. Indian J Community Med 30: 155.
19. Kumar A, Bhargava V (1995) Typhoid fever in a neonate. Indian Pediatr 32: 678-680.
20. Duggan MB, Beyer L (1975) Enteric fever in young Yoruba children. Arch Dis Child 50: 67-71.
21. Duff P, Engelsgjerd B (1983) Typhoid fever on an obstetrics-gynecology service. Am J Obstet Gynecol 145: 113-114.
22. Ayliffe GA, Geddes AM, Pearson JE, Williams TC (1979) Spread of *Salmonella* typhi in a maternity hospital. J Hyg 82: 353-359.

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