Case Series

Complicated enteric fever: a case series

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ABSTRACT
Enteric fever is endemic in Indian subcontinent. Authors are presenting 3 rare cases of complicated enteric fever. The first case is a case of enteric fever which was complicated by ARDS leading to respiratory failure. The second case is a case of enteric fever which was complicated by severe thrombocytopenia and the third case is a case of enteric fever which was complicated by severe encephalopathy. In this study authors have discussed and compared the similar cases found in India and other parts of the world. The physicians who are taking care of the patients of enteric fever should be aware of the above complications.

Keywords: ARDS, Enteric fever, Encephalopathy, Thrombocytopenia

INTRODUCTION
Enteric fever is characterized by severe systemic illness with fever and abdominal pain.\(^1\)

The organism classically responsible for the enteric Fever is *Salmonella enterica* Serotype *typhi*.

The other *Salmonella* serotypes Paratyphi A, B or C can cause a similar syndrome.\(^2\)

The term Enteric fever refers to both Typhoid fever and Paratyphoid fever and the terms can be used interchangeably. It is a very common cause of fever in young adults and children in developing countries specially in SE Asia and Southern Africa (more than 100 cases per 100,000 person years).\(^3\)

Here authors presenting a case series of complicated enteric fever involving Respiratory system in the form of ARDS, Hematologic system in the form of severe thrombocytopenia and Neurologic system in the form of encephalopathy.

CASE SERIES

Case 1

Enteric fever with ARDS

A 18 year old girl was admitted with complaints of High grade fever for 7 days associated with body ache and she had shortness of breath for 1 day. She was being treated at an outside hospital with oral antibiotics and other supportive medication. On Examination she was awake, lethargic, febrile and tachypneic. Her BP was 90/60mmHg, Pulse rate was 144/minute, regular. Respiratory rate was 60 breaths per minute. Her temperature was 1000 F. She had Spo2 of 80% on room air. Her chest showed crepts in infrascapular zones. S1S2 was normal in CVS, there was no murmur. Her Abdomen was soft with no palpable organomegaly. Her CNS examination was normal. She was admitted and investigated. Her CBC showed Hb 9.0gm/dl, TLC 9300/cmm N81% and Platelets 2.45 lacs/cmm. Her QBC for MP was negative. RFT showed RBS 98mg/dl, Urea 18mg/dl, Creatinine 0.7mg/dl, Sodium 139meq/lit and...
Potassium 3.5 meq/lit. LFT showed Bilirubin 0.5 mg/dl, SGOT 78 mg/dl, SGPT 43 mg/dl, ALP 123 mg/dl, A/G ratio 1.4 mg/dl. Her ABG showed compensated metabolic acidosis with Pao2/Fio2 120.75. Her Chest X-ray showed bilateral diffuse patchy opacity suggestive of ARDS? Pulmonary edema. Her ECG showed sinus tachycardia. Her USG of Whole abdomen showed Hepatomegaly with Bilateral mild Pleural effusion and Ascites with Grade 1 Renal parenchymal disease. Dengue serology was non-reactive. Her Salmonella typhi antibody IGM was positive and IgG was equivocal. Echo showed normal study. Her CT scan of chest showed Patchy confluent consolidation involving both Lung fields with relative sparing of anterior segments and bilateral mild pleural effusion. Her serum PCT was 1.16 mg/ml.

She was admitted into ICU. The provisional Diagnosis of the patient was Septicaemia with shock with ARDS. She was started with higher antibiotics (Meropenem and Teicoplanin) along with IV Fluids and other supportive medications. She required Vasopressor support of nor adrenaline and she was initially started on NIV support.

She was electively intubated and ventilated in view of persistent Respiratory distress.

On day 3rd she had persistent high-grade fever. Her repeat CBC showed Hb 9.8 gm/dl, rise in TLC count to 15700/cmm with N77% and platelets 2.40 lacs/cmm. Her CXR remained more or less same. Her serum PCT raised to >100 ng/ml

In view of persistent high-grade fever and further rise in serum PCT she was also added with Colistin. Antimalarial was also added empirically.

On day 5th the patients fever decreased, her Chest x ray showed slight improvement. Her TLC count became normal. Her nor Adrenaline infusion was started to taper down. However, she had fall in Haemoglobin to 6.7 gm/dl. She did not have any malena or any obvious blood loss. She was advised for one unit of PRC transfusion, however the family refused for blood transfusion due to Religious reasons.

Her blood culture showed the growth of Salmonella typhi which was sensitive to most of the antibiotics including amoxyclav, Cephalosporins, Aminoglycosides, Quinolones and Carbapenems. Her antibiotics were de-escalated, Antimalarial stopped. She was started on Weaning from Ventilator support.

On day 7th she had worsening of respiratory status. Her Chest X ray showed worsening of pulmonary oedema. She had further fall in haemoglobin to 6.3 gm/dl leading to further worsening of respiratory status.

Patients family still refused for any blood transfusion despite repeated counselling for the need of blood transfusion.

On day 9th the patient had spontaneous rise in hemoglobin to 6.7 gm/dl. Her Chest X ray started improving, however she developed diarrhoea. C difficile toxin was negative in stool. It was managed with probiotics and raccadotril.

On day 11th she was further weaned off ventilator support and extubated.

On day 13th she was shifted toward where she recovered of her symptoms completely. Her haemoglobin also raised spontaneously to 8.8 gm/dl at the time of Discharge on the Day 16th of admission. She was discharged on haematinics along with iron rich diet.

**Case 2**

**Enteric fever with severe thrombocytopenia**

The patient was a 21 year male resident of Sahadol MP was admitted with complaints of fever with chills for 10-12 days with generalised weakness and mild headache.

On Examination he was febrile and dehydrated. His BP was 110/80mmHg and PR was 90/m regular. His systemic examination was unremarkable.

He was admitted and investigated. CBC showed Hb 13.1 gm/dl, TLC was 2100/cmm with N79%, L20%, E 0%, M04%. Platelet count was 0.20 Lacs/cmm. Peripheral smear showed Normocytic Normochromic RBC with Leukopenia with few reactive lymphocytes and markedly reduced platelets on smear. QBC for MP was negative. His Chest X-ray showed prominent BV markings. USG of whole abdomen showed mild splenomegaly. LFT showed Bilirubin 0.7 mg/dl, SGOT 315 U/L, SGPT 74 U/L, Alk Phos 192U/L, AGR 1.0. RFT showed Serum creatinine 1.0 mg/dl, serum sodium 128mEq/L, serum potassium 4.8 mEq/L. His serum Salmonella Typhi antibody was positive for IgM and Negative for IgG.

He was managed with IV fluids, IV antibiotics (Cefoperazone/Subactum) and other supportive medications.

On day 2 his CBC was repeated which showed Hb 11.8 gm/dl, TLC 2000/cmm and platelet count was 0.10 Lacs/cmm. He was transfused with 4 units of Random donor platelets.

On day 3 he had persistent high grade fever. His repeat CBC showed Hb 11.6 gm/dl, TLC 2400/cmm and Platelet count of 0.30 Lacs/cmm. In view of persistent high grade fever his antibiotics was changed to Piperaclin/Tazobactum.

On day 4 his CBC showed Hb 11.6 gm/dl, TLC was 4100/cmm and platelet count was 0.50 Lacs/cmm.
On day 5 his fever settled. His blood culture showed the growth of Salmonella typhi which was sensitive to both cefoperazone/sulbactum and piperacilin/tazobactum.

On day 6 he was discharged on IV antibiotics along with other supportive medications.

He was reviewed in OPD after 7 days. He had recovered of all of his symptoms. He was advised for repeat CBC and SGOT however he did not turn up in OPD for follow up.

**Case 3**

**Enteric fever with encephalopathy**

A 27-year male resident of Korba Chhattisgarh was admitted with complaints of fever with chills for 10-12 days, nausea and pain in abdomen off and on for 8-10 days, burning and frequency of urine for 8-10 days. He was treated at outside hospital with oral and IV antibiotics (Cefoperazone/Sulbactum) including antimalarial. He had persistent fever hence came to our hospital. On examination he was alert and oriented. He was febrile. His BP was 130/90mmHg and PR was 90/mnt. His systemic examination was unremarkable.

He was admitted and investigated and started treatment with a provisional diagnosis of UTI with enteric fever. His CBC showed Hb 14.4gm/dl, TLC 8500/cmm with N82%, L12%, E01% and platelet count 2.50Lacs/cmm. QBC for MP was negative. His urine R/E showed WBC 1-2/hpf. S. typhi antibody was negative for both IgG and IgM. Chest X ray showed clear lungs field. LFT showed Bilirubin 1.9mg/dl, SGOT 136 U/L, SGPT 124 U/L, Alk Phos 210 U/L and AGR 0.6. RFT showed RBS 86mg/dl, Creatinine 0.8mg/dl, Sodium 127mEq/L, Potassium 5.2mEq/L. His USG of whole abdomen showed mild hepatomegaly with GB wall oedema and moderate splenomegaly. He was started treatment with IV antibiotics (Meropenem) along with other supportive medications however he had persistent high-grade fever. His urine culture showed no growth. He was further investigated. His viral markers were non-reactive. Echo showed no vegetation. CT scan of chest was normal and CT scan of Abdomen showed mild hepatomegaly with splenomegaly with minimal thickening of ileocecal region? Inflammatory.

On day 4th of admission, he developed slurring of speech along with persistent high-grade fever. He did not have any focal neurological deficit, however he had mild neck stiffness. MRI of brain showed normal study. CSF analysis was also normal. On day 5th the patient’s Blood culture showed the growth of Salmonella typhi which was sensitive to Cephalosporins, Quinolones, Aminoglycosides and Carbapenems.

The patients antibiotics deescalated to Ceftriaxone and Amikacin, however the patients neurological status further deteriorated. He became drowsy and was started on RT feed along with other supportive treatment. His EEG was done which showed epileptiform discharges arising from right parietal region for which Levitiracetam was started. His fever had become low grade now. He was also added with Azithromycin.

In view of possible enteric encephalopathy he was also given steroids.

On day 8th the patient became afebrile, however he remained dull with slurred speech.

Gradually he regained alertness but he had tremors of all four limbs with abnormal movements of lips which settled slowly over a period of next 7 days.

The patient had full comprehension of commands however he was unable to produce voice. His Pan endoscopy was done which showed normal movements of the vocal cords.

He was referred to speech therapist for voice training. His Oral exercises were started with guided lip and tongue movements along with daily counselling.

He had started walking with support. Gradually his coordinated oral movement started as better chewing and swallowing with regular oral exercises.

He started producing voice in the form of incomprehensible sounds and he slowly progressed to produce vowels, consonants, words and small sentences with slurred voice.

He was discharged and was on regular OPD follow up. He had regained his normal phonation and able to perform independent activities gradually over a period of 12 weeks.

**DISCUSSION**

The enteric fever is a febrile illness with onset of symptoms 5 to 21 days after ingestion of the causative organism in the contaminated food or water.1

The microorganism Salmonella typhi crosses to small bowel after surviving exposure to gastric acid in the stomach. During the course in the small bowel they penetrate the epithelium and enter into the lymphoid tissue and proliferates and disseminate via the lymphatic or the haematogenous route. Eventually the organism resides within the tissue macrophages in the liver, spleen and the bone marrow.4

Enteric fever is a multisystem disease which most commonly involves the gastrointestinal and neurological system. First case is a case of young female who presented with Enteric fever which was complicated by ARDS and respiratory failure.
ARDS is rarely reported in association with Enteric fever despite the fact that sepsis is a common manifestation and endotoxemia has been described in this condition.5

Agrawal PN et al, from PGI Chandigarh in India has also reported a case of young female patient with Enteric fever whose clinical course was complicated by hypotension, Thrombocytopenia, encephalopathy and ARDS. She recovered with prompt ventilator support.6

A similar case of ARDS complicating enteric fever was reported from Kandy, Sri Lanka by De Silva HJ et al.7

Another case of Enteric fever which was complicated by arthritis and ARDS was reported by Dhakad U et al, from KGMC Lucknow, UP India.8

The probable mechanism for ARDS in a patient of Enteric fever could be that in case of severe sepsis the high load of pro inflammatory cytokines such as TNF, IL-1, IL-6, and IL-8 can lead to acute lung injury which further progresses to ARDS leading to respiratory failure.9

Case 2 is a case of enteric fever which was complicated by leucopenia and severe thrombocytopenia.

Serefhanog In K et al, from Turkey reported a case of Enteric fever that presented with isolated thrombocytopenia which recovered to normal within the first week of ceftriaxone therapy.10

A similar case was also reported from Bangladesh in 2016 by Al Reesi M et al, where the recovery of platelets was slow but achieved normal platelet counts without platelet transfusion.11

Subhan M, Sadiq W et al, from Pakistan reported a case of Enteric fever that presented with leucopenia and thrombocytopenia that recovered with treatment of enteric fever.12

Another interesting case was reported by Shiv charan et al, when a 50-year-old female was presented with fever and gum bleeding and was found to have severe thrombocytopenia. Later on, the blood culture grown Salmonella typhi. The thrombocytopenia recovered in the first week of ceftriaxone therapy.13

Khosla SN, Anand A et al, studied the Haematological profile in 20 culture proven cases of Enteric fever. They found anaemia, leucopenia, eosinopenia, thrombocytopenia and sub clinical DIC. The Bone marrow findings showed Myeloid maturation arrest, decrease in the number of erythroblasts and megakaryocytes with increased phagocytic activity of histiocytes.14

This case also had leucopenia and severe thrombocytopenia, however we had transfused random donor platelets as the platelets had decreased to 10,000/cmm. It was followed by gradual recovery.

The cause for leucopenia and severe thrombocytopenia could be due to bone marrow infiltration by the Salmonella typhi and then gradual recovery upon the use of appropriate antibiotics.

Third case is a case of enteric fever complicated by encephalopathy.

Sejvar J et al from Malawi (Mozambique) studied 303 cases of Typhoid fever from Mar-Nov 2009 and concluded that 43% had a constellation of UMN findings including hyperreflexia, spasticity and sustained clonus. Other neurological features included ataxia (55%), Parkinsonism like features (20%) and tremors in 10%.15

This case also had features of ataxia and tremors.

Another study of 232 patients of Enteric fever was done in Rajasthan, India between 1999-2001. They found that 27.1% of patients had neurological symptoms, out of which 42.8% had delirium state and 57.2% had specific neurological complications in the form of encephalitis (25%), Psychiatric manifestations (19.44%), Cerebellar ataxia (19.44%) and meningitis in 13.89%. They also found that the mortality rate among the patients of Enteric fever with neurological manifestations was 6.35%.16 In another study of Enteric fever by RS Wadia, NR Ichaporia et al, found Cerebellar ataxia as the commonest neurological manifestation second only to toxic delirium. The cerebellar ataxia usually appeared in the second week and lasted a mean of 9.4 days. In 90% of cases it improved completely within a month.17

In this case also the neurological symptoms appeared in the second week however the resolution took 3 months for complete recovery.

Another case of complicated enteric fever was reported by OP Kalra, NK Agrawal et al, where the patient developed acute cerebellar syndrome during the second week of illness and took six weeks for complete recovery after treatment with appropriate antibiotics.18

RK Nair, SR Mehta, S Kumavelu et al, reported a case of 18 year male who was admitted with features of acute psychosis and later on found to have enteric fever.19

An extensive study of neuropsychiatric manifestations in 959 cases of enteric fever was done by Osuntokun BO et al. It showed toxic delirium in 57% of cases, 3.5% had varying depth of coma, 3.1% had bilateral pyramidal sign, 1% had transient extra pyramidal sign and 1% had peripheral neuropathy, mononeuritis multiplex and post typhoid schizophreniaiform psychosis.20

All of the above studies showed that a patient of Enteric fever can develop wide variety of neurological signs and symptoms.
India is endemic for enteric fever. The physicians who are taking care of the patients of enteric fever should be aware of the above complications.

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