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# A Case Report of Thrombocytopenia-associated Multiple Organ Failure Secondary to *Salmonella enterica* Serotype Typhi Infection in a Pediatric Patient: Successful Treatment With Plasma Exchange

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**Abstract:** A high proportion of the patients with *Salmonella enterica* serotype Typhi infection develop severe sepsis. The mortality rate is high despite aggressive antimicrobial therapy in these patients. The case of a 10-year-old boy who developed thrombocytopenia-associated multiple organ failure (TAMOF) secondary to *S. typhi* infection is reported. The patient did not respond to antimicrobial treatment, including ciprofloxacin, in addition to conventional supportive measures, so plasma exchange was performed. The thrombocytopenia and organ failure had resolved after 3 days of plasma exchange therapy. Plasma exchange is suggested to be a life-saving intervention in a child with TAMOF secondary to *S. typhi* infection. **Key Words:** Children, Plasma exchange, *Salmonella enterica* serotype Typhi, Thrombocytopenia-associated multiple organ failure.

Severe sepsis is a frequent reason for hospitalization and mortality in children. Septic shock has a high mortality risk at approximately 63%, and if multiple organ dysfunction syndrome (MODS) develops the mortality increases to approximately 80% (1–3). Despite improved supportive measures and more effective antibiotic therapies, severe sepsis and septic shock are the second leading cause of death in noncoronary intensive care units (1). Although subclinical or atypical presentations are common in *Salmonella enterica* serotype Typhi (*S. typhi*) infections, this microorganism is one of the etiological agents in severe bacteremia especially in developing countries (4). The clinical presentation of *Salmonella* infections is very variable. Although bacteremia caused by *S. typhi* is reported to have a benign clinical course, toxemia and associated complications involving many systems may also occur in young children (1,5). Underlying chronic or immunosuppressive diseases increase the risk of severe clinical presentations.

Although previous studies investigating the improvement of outcome in sepsis have concentrated on the correction of organ dysfunction, it has been shown that systemic thrombosis and thrombocytopenia were the key factors in the prognosis of the cases (6). The recent onset of thrombocytopenia in critically ill patients has been established as an independent risk factor for the development of MODS (6). Thrombosis is also a potential contributor to organ failure in children with critical illness, with or without infection. Many forms of multiple organ failure have been identified to be associated with thrombocytopenia and systemic thrombosis at autopsy series. This thrombotic storm situation causes mortality in cases with sepsis, despite new treatment modalities. Thrombocytopenia-associated multiple organ failure (TAMOF) is a thrombotic microangiopathic syndrome that has been reported in critically ill patients

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**TABLE 1.** *Selected laboratory values of the patient*

| | Normal range | On admission | Prior to plasma exchange | After 3 daily session |
|---|---|---|---|---|
| Hb (g/dL) | 11.7–15.5 | 9.3 | 7.6 | 10.1 |
| WBC ($\times 10^3/\mu L$) | 4.1–11.2 | 13 700 | 3500 | 6600 |
| Platelets ($\times 10^3/\mu L$) | 159–388 | 157 | 59 | 378 |
| aPTT (s) | 27.9–38.1 | 38.3 | 46.3 | 25.7 |
| INR | 0.86–1.20 | 1.3 | 1.5 | 1.3 |
| Fibrinogen (mg/dL) | 144–430 | — | 119 | 217 |
| Antithrombin-3 activity (%) | 71–120 | — | 49 | 122 |
| Thrombin time (s) | 15–22 | — | 26 | 19.6 |
| D-dimer 3 | 0–0.48 | — | 30 | 0.3 |
| ALT (U/L) | 5–40 | 535 | 661 | 57 |
| AST (U/L) | 8–33 | 171 | 251 | 44 |
| Creatinine (mg/dL) | 0.6–1.2 | 2.2 | 1.6 | 0.5 |
| BUN (mg/dL) | 5–18 | 39.3 | 25.9 | 13.3 |
| LDH (U) | 150–400 | — | 1485 | 342 |

ALT, alanine transaminase; AST, aspartate transaminase; aPTT, activated partial thromboplastin time; BUN, blood urea nitrogen; Hb, hemoglobin; INR, international normalized ratio; LDH, lactate dehydrogenase; WBC, white blood cells.

after infection, transplantation, radiation, chemotherapy, autoimmune diseases, and cardiopulmonary bypass (5). It is defined by the clinical triad of new-onset thrombocytopenia, multiple organ failure, and increased lactate dehydrogenase (LDH) levels. Bacterial infections have also been reported as a cause of TAMOF in some studies (5,7), however, the role of *S. typhi* is not known in this catastrophic syndrome.

In the case of sepsis, it is the presence of various bacteria, their cell wall components, secretory products, and toxins that cause cytokine release and activation of the immune, complement, and coagulation systems, and the subsequent development of systemic endotheliopathy (6).

Mortality was reported to be very high in the cases of TAMOF treated with the conventional interventions (5). The use of plasma exchange has been reported to reduce the mortality. We report on a child without any underlying disease who developed *S. typhi* septicemia, presenting with TAMOF and treated with plasma exchange.

## CASE REPORT

A 10-year-old boy was admitted to the infectious disease ward of our hospital with a one month history of fever, arthralgia, and lumbar pain after 7 days of oral ampicillin–clavulanate treatment, with a diagnosis of acute sinusitis. He had lost 3 kg in the previous month, and had had tenderness and erythema of the left wrist for the last two days. He was hospitalized and diagnosed with fever of unknown origin.

Examination on admission revealed that he was lethargic, but woke with verbal and tactile stimuli. Remarkable findings included: fever (38.8°C, axillary), lymphadenopathy (maximum size: 1 cm in diameter in the inguinal region bilaterally), and a dull percussion tone over Traube's region, despite the absence of a palpable spleen. The vital signs, other than body temperature, were within normal limits.

Initial laboratory evaluation showed (normal values in brackets): hemoglobin (Hb) 9.3 g/dL (11.7–15.5 g/dL), white blood cells (WBC) $13.7 \times 10^3/\mu L$ ($4.1–11.2 \times 10^3/\mu L$), platelets $157 \times 10^3/\mu L$ ($159–388 \times 10^3/\mu L$), blood urea nitrogen (BUN) 39.6 mg/dL (5–18 mg/dL), creatinine 2.2 mg/dL (0.6–1.2 mg/dL), uric acid 8.9 mg/dL (2.7–8.5 mg/dL), alanine transaminase (ALT) 535 U/L (5–40 U/L), aspartate transaminase (AST) 171 U/L (8–33 U/L), γ-glutamyl transferase (GGT) 242 U/L (5–40 U/L), and alkaline phosphatase (ALP) 257 U/L (35–129 U/L) (Table 1). Urine analysis and other biochemical tests were found to be within the normal limits. Serological tests for viral hepatitis, toxoplasmosis, rubella, Epstein–Barr virus, cytomegalovirus and measles were all negative. Immunoglobulin (Ig) G antibodies against brucella, shigella, *Borrelia burgdorferi*, respiratory syncytial virus, adenovirus, influenza A and B viruses and parainfluenza 1, 2 and 3 viruses were positive, but IgM and seroconversion of immunoglobulins (evaluated two weeks later) were all negative. Complement 3 and 4 levels were within normal limits, and anti-nuclear antibody and anti-ds DNA were also negative. Abdominal ultrasonography revealed millimetric para-aortic lymph nodes and splenomegaly with a diameter of 119 mm. An increase in the myeloid series without any blastic or atypical cells was seen in the bone marrow examination. Bone marrow smears were negative for plasmodium and leishmania infection.

With a diagnosis of possible sepsis, meropenem, teicoplanin and amikacin were started on the second

day of the hospitalization. Blood, urine, throat and stool cultures were reported to be negative.

On the third day the patient had a tonic-clonic convulsion, was hypotensive (85/50 mm Hg), bradycardic, and had a Glasgow coma score of 8. Acyclovir (1500 mg/m$^2$/day) for probable herpes simplex virus encephalopathy and ciprofloxacin therapy for possible systemic *Salmonella* infection with encephalopathy were added. Fluid replacement was performed, and dopamine for hypotension and isoproterenol for resistant bradycardia were also given. He developed severe thrombocytopenia ($14 \times 10^3$/μL), and his coagulation parameters deteriorated: aPTT 46.3 s (27.9–38.1 s), international normalized ratio (INR) 1.13 (0.86–1.20), fibrinogen 119 mg/dL (144–430 mg/dL), thrombin time 26 s (15–22 s), antithrombin 3 activity 49% (71–120%), D-dimer 3 > 30 (0–0.48)]. Plasma LDH was 1485 U (150–400 U) and peripheral smear revealed no finding of hemolysis. Bilateral pleural effusion was detected in the ultrasonographic evaluation of the chest. An exudative fluid was sampled by needle aspiration from the pleural cavity (1020 g/cm$^3$, protein 2.54 mg/dL, LDH 1162 IU/L, pH 9, glucose 92 mg/dL, fluid LDH/blood LDH ratio 0.7) Polymerase chain reaction was positive for *S. typhi* in blood, bone marrow, and thoracentesis fluid samples by using ST3 (5′-AGA TGG TAC TGG CGT TGC TC-3′) and ST4 (5′-TGG AGA CTT CGG TCG CGT AG-3′) primers (*S. typhi* ATCC 19430 was used as a positive control). Later on *S. typhii* was isolated from the culture of the effusion.

On the fifth day the patient was transported to the Pediatric Intensive Care Unit (PICU) and with the diagnosis TAMOF, plasma exchange was performed in order to normalize the thrombocyte count and prevent cytokine discharge caused by *Salmonella* septicemia. Plasma exchange was applied via a right internal jugular venous catheter using a total plasma volume of 1200 mL with a Fresenius Astec Fontec Plasma Exchanger (Hamburg, Germany). After three sessions of daily plasma exchange, the platelet count increased to $236 \times 10^3$/mm$^3$, the lethargy and seizures resolved, and the liver function tests normalized. The patient became afebrile. The result of electroencephalography was compatible with *Salmonella* encephalopathy and there was no pathologic finding in cranial magnetic resonance imaging with contrast.

On the 11th day of antimicrobial treatment (four days after the last application of plasma exchange), the patient's blood pressure returned to normal and the dopamine infusion was stopped. The patient was discharged from hospital in good health after 14 days of acyclovir, vancomycin and ciprofloxacin treatment.

## DISCUSSION

*Salmonella enterica* serotype Typhi is the most common *Salmonella* isolate in many developing countries, causing an estimated 12.5 million cases annually worldwide, with an incidence of 365 cases per 100.000 persons.

Although the incidence of *Salmonella* infections has declined greatly with the provision of clean water and good sewage systems in developed and developing countries, the emergence of antibiotic resistance and severe clinical presentations cause the disease to remain a serious public health problem. Overall, 10–15% of patients develop severe disease and, despite appropriate antimicrobial treatment, the average reported case fatality rates may be as high as 30–50%. Mortality is mostly due to the occurrence of severe diseases in developing countries where intensive care facilities are too few, and there is an increasing rate of resistance to antibiotics. Currently, fluoroquinolones and third-generation cephalosporins are the drugs of choice for the treatment of *Salmonella* infections, but decreased susceptibility to these antimicrobials has been reported (8).

Severe complications such as disseminated intravascular coagulation (DIC), hemorrhage, pneumonia, splenic or hepatic granulomas, meningitis, encephalomyelitis, multiple organ failure, pleural effusion, hemolytic uremic syndrome, endocarditis and cardiogenic shock can be a manifestation of fatal *S. typhi* infection. Factors affecting severity include the duration of illness before therapy, choice of antibacterial agent, strain virulence, inoculum size, previous exposure or vaccination, and other host factors such as HLA types, AIDS or other immune system diseases. Our patient developed severe thrombocytopenia and multiple organ failure despite ciprofloxacin treatment begun on the third day of hospitalization.

Although infections are among the well known causes of TAMOF, it does not appear that TAMOF secondary to *S. typhi* disease has previously been reported. TAMOF induces poor outcomes in critically ill patients. The mortality rates were close to 100% before recent studies reporting that plasma exchange therapy has consistently shown positive results. Bell et al. (9) reported their experience with 108 patients having thrombotic thrombocytopenic purpura and hemolytic uremic syndrome and demonstrated that the use of plasma exchange therapy might reduce mortality. Plasma exchange is suggested by Darmon et al. in order to reduce multiple organ failure and improve survival (7). It has been thought

that plasma exchange reduces mortality by removing toxic compounds produced by bacteria, cytokines, and hazardous mediators that may impair the coagulation pathway, blood pressure, cardiac function, and membrane permeability. These compounds and mediators are removed by the exchange procedure. Despite aggressive fluid resuscitation, vasoactive agents and antimicrobial therapy, the thrombocytopenia deteriorated and multiple organ failure was observed in our patient. After plasma exchange for only 3 days, resolution of thrombocytopenia and reversal of organ failure was noticed. No complications due to exchange therapy were notified.

In our case, DIC was suggested with thrombocytopenia, decreased anti-thrombin activity and increased D-dimer levels. Aggressive fluid resuscitation, restoration of normal or hyperdynamic circulation, and removal of the nidus of infection and/or causes of systemic coagulation are important determinants of outcome. Plasma exchange is suggested as a nonspecific therapy by several authors to be effective for reversal of DIC (6,10).

## CONCLUSION

Although the medical literature on plasma exchange for adult patients is growing, the use of this intervention in the pediatric age group, especially in *Salmonella* sepsis, is extremely limited. Our patient is the first example of TAMOF caused by *Salmonella* infection who survived after plasma exchange therapy. Plasma exchange should be considered as a rescue therapy in patients with progressive TAMOF, but further controlled, randomized studies involving pediatric patients are needed to advocate it as a routine treatment for sepsis.

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## REFERENCES

1. Balk RA. Severe sepsis and septic shock. Definitions, epidemiology, and clinical manifestations. *Crit Care Clin* 2000;16:179–92.
2. Hardaway RM. A review of septic shock. *Am Surg* 2000;66: 22–9.
3. Stegmayr BG. Is there a future for adsorption techniques in sepsis? *Blood Purif* 2000;18:149–55.
4. Bhan MK, Bahl R, Bhatnagar S. Typhoid and paratyphoid fever. *Lancet* 2005;366:749–62.
5. Nguyen TC, Carcillo JA. Bench-to-bedside review: thrombocytopenia-associated multiple organ failure—a newly appreciated syndrome in the critically ill. *Crit Care* 2006;10: 235.
6. Nguyen T, Hall M, Han Y et al. Microvascular thrombosis in pediatric multiple organ failure: Is it a therapeutic target? *Pediatr Crit Care Med* 2001;2:187–96.
7. Darmon M, Azoulay E, Thiery G et al. Time course of organ dysfunction in thrombotic microangiopathy patients receiving either plasma perfusion or plasma exchange. *Crit Care Med* 2006;34:2127–33.
8. Kumar A, Arora V, Bashamboo A et al. Detection of *Salmonella typhi* by polymerase chain reaction: implications in diagnosis of typhoid fever. *Infect Genet Evol* 2002;2:107–10.
9. Bell WR, Braine HG, Ness PM et al. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Clinical experience in 108 patients. *N Engl J Med* 1991; 325:398–403.
10. Zenz W, Bodo Z, Zobel G et al. Recombinant tissue plasminogen activator restores perfusion in meningococcal purpura fulminans. *Crit Care Med* 1998;26:969–71.