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Case Report

Plasma Exchange as A Rescue Therapy in Weil's Disease with Severe Hyperbilirubinemia, Acute Renal Failure, and Multidrug-Resistant Organism Co-Infection: A Rare Case in Critical Care Setting

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Abstract

Background: Leptospirosis is a zoonotic disease caused by spirochete *Leptospira interrogans*. Additional therapy modality is required in critical Weil's Disease, which does not improve despite standard therapy with antibiotics and renal replacement therapy (RRT). Therapeutic plasma exchange (TPE) has been reported to show positive outcomes in patients with sepsis. However, TPE has not been widely used in treating severe leptospirosis. We report a case of Weil's disease with severe hyperbilirubinemia, acute renal failure, and co-infected with multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA), successfully treated with TPE, intermittent RRT, and definitive antibiotics.

Case Presentation: A 25-year-old male developed Weil's disease with severe hyperbilirubinemia and acute renal failure treated in the ICU. He received empirical antibiotics and intermittent RRT but deteriorated and experienced a septic shock. His serum bilirubin increased to 43.34mg/dL, and the blood culture result showed MDR-PA co-infection. Further, he underwent a single TPE and received definitive antibiotics, resulting in rapid clinical improvement as well as liver and renal function recovery.

Conclusion: Therapeutic plasma exchange as a rescue therapy can be considered for further intensive care support in severe leptospirosis which has not shown improvement despite standard treatment with RRT and antibiotics. However, the use of TPE requires well-designed clinical trials to further establish its efficacy. Leptospirosis can coexist with other pathogens which is adding the therapeutic challenge.

Keywords: *Leptospirosis; Weil's disease; plasma exchange; renal replacement therapy; multidrug-resistant organism*

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INTRODUCTION

Leptospirosis is a zoonotic disease caused by spirochete *Leptospira interrogans*. According to official Ministry of Health (MoH) records, leptospirosis caused an estimated 895 human cases in Indonesia in 2018, with a case fatality rate of 17.8%.[1] The annual morbidity of leptospirosis in the population was recently calculated to be 39.2 per 100,000.[2] The clinical spectrum of leptospirosis ranges from subclinical infection to fulminant infection resulting in septic shock and severe multiorgan failure. Leptospirosis shows a biphasic disease course. The first phase is the septicemic phase in which leptospira can be found in blood and cerebrospinal fluid.

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This phase lasts 4 to 7 days with non-specific symptoms including fever, headache, myalgia, and abdominal pain. An immune phase follows, during which the leptospires are excreted in the urine, and anti-Leptospira immunoglobulin M (IgM) antibodies develop in the blood. At this stage, the patient re-develops the initial symptoms. Five to 10 percent of patients develop Weil's disease, a severe form of leptospirosis that manifests as renal system failure, hepatomegaly, liver impairment, and/or an alteration in the levels of consciousness.

Severe hyperbilirubinemia and acute renal failure have been associated with high mortality in leptospirosis patients.[3] High serum bilirubin can cause toxic damage to kidney and liver cells then worsening multiorgan failure. Treatment of Weil's disease is an antimicrobial agent and supportive care including adequate hydration, advanced respiratory support, and early initiation of renal replacement therapy.[4] Additional therapy modality is required in critical Weil's Disease, which does not improve despite standard therapy with antibiotics and renal replacement therapy (RRT). There have been reports of the use of plasma exchange in sepsis and leptospirosis patients that showed positive outcomes. However, TPE has not been widely used in treating fulminant leptospirosis.

Leptospira may coexist with other pathogens leading to complicated diagnosis, extending the length of treatment, and increasing mortality, therefore identifying the presence of co-infected pathogens is very crucial.[5] Here in, we report a case of Weil's disease with severe hyperbilirubinemia, acute renal failure, and co-infected with multidrug-resistant *Pseudomonas aeruginosa (*MDR-PA), successfully treated with TPE, intermittent RRT, and definitive antibiotics.

CASE REPORTS

A 25-year-old male presented to our emergency departments with a 5-day history of fever and bilateral calf pain. He complained of headache, jaundice, nosebleed, tea-colored urine, and black discoloration of stools. He lives in a flood-prone area and worked as a waiter. He denied recent travel, recent antibiotic exposure, or sick contacts. He took no regular medications.

On examination, the patient was mildly tachycardic (120 beats per minute) with a blood pressure (BP) of 114/80mmHg, respiratory rate of 20 breaths per minute, and temperature of 36.8°C. The patient was alert and oriented. Physical examination findings were icteric sclera, subconjunctival bleeding, the skin appeared jaundiced, the lungs were clear to auscultation, and the abdominal examination revealed no abnormality.

Initial laboratory study results showed anemia (8.5mmol/L), leukocytosis (15,000µL), thrombocytopenia (50,000µL), hypokalemia (3.30mmol/L), and hyponatremia (123.0mmol/L). His serum bilirubin was 41.07mg/dL (direct 24.52mg/dL and indirect 16.55mg/dL), aspartate transaminase (AST) was 20.5IU, alanine transaminase (ALT) was 59.3IU, serum alkaline phosphatase (ALP) was 78.0IU, gamma GT was 86.7µL. Serum creatinine was 10.08mg/dL and blood urea was 346.6mg/dL. Coagulation studies were normal. The leptospiral strip test for IgM antibodies was positive. Hepatitis B surface antigens and anti-human immunodeficiency virus antibody titers were all negative. Results of abdominal ultrasonography and chest radiography were normal, and electrocardiography showed sinus tachycardia at 120 beats per minute.

The patient was diagnosed with Weil's disease and empirical antimicrobial treatment was started with ceftriaxone. Within 12 hours of admission, he became hypotensive with a BP of 81/56mmHg, his temperature rose to 38.4°C, respiratory rate of 40 breaths per minute, his leukocyte increased to 38,600µL, and serum bilirubin 43.34mg/dL. He developed septic shock with an APACHE II score of 25 points (55% estimated non-operative mortality). Therefore, the patient was transferred to the ICU and intubated. Despite receiving adequate intravenous fluids, packed red cell (PRC), and thrombocyte concentrate (TC) transfusions, noradrenaline infusions were started at 0.2 mcg/kg/min for circulatory support. Hemodialysis was started for acute renal failure and sepsis.

Until 3rd day of admission, the patient had undergone second hemodialysis in which blood urea, and creatinine were decreased, but his serum bilirubin and clinical condition had not improved. On the 5th day of admission, the patient's mental state begins to deteriorate (E3M5VETT), and the use of noradrenaline increased to 0.4mcg/kg/min. By the 6th day of admission, plasma exchange was initiated based on clinician judgement. We are working with the Indonesian Red Cross Society to conduct TPE in our ICU. He underwent a single session of TPE with 1.5-liter exchanges using a 5% human albumin solution (body weight 40 kg, hematocrit 40%). After plasma exchange sessions, serum bilirubin was reduced to 14.6mg/dL. His mental state and respiratory function both improved significantly. Respiratory ventilator support and vasopressors were gradually withdrawn (lowered to 0.025mcg/kg/min), and the patient became oriented and alert. Two days after TPE, the patient was extubated and transferred to the intermediate care unit.

Nonetheless, the patient's leukocytes had not improved significantly. Blood cultures and antibiotic susceptibility tests were performed, and the antibiotic was changed to meropenem and amikacin while waiting for the results. After 1 day in the intermediate care unit (9th day since admission), the patient's blood pressure dropped to 75/40mmHg, respiratory rate up to 35breaths per minute, leukocytes rose to 43,700µL, and the patient fell into a septic shock. APACHE II scored 24 points (40% estimated non-operative mortality). The patient was readmitted to the ICU and re-intubated. The culture result showed that he was co-infected with multidrug-resistance *Pseudomonas aeruginosa* (MDR-PA), which is resistant to ceftriaxone, meropenem, cefepime, cefotaxime, ampicillin-sulbactam, amoxicillin clavulanic acid, and erythromycin. The antibiotics were changed according to culture and antibiotic susceptibility tests results using piperacillin-tazobactam 4.5g iv/6hr. After the antibiotic was changed, the leukocytes gradually decreased, and the patient showed clinical improvement. APACHE II score also showed improvement to 18 points (25% estimated non-operative mortality). The piperacillin-tazobactam administration was continued for up to 7 days accompanied by other supportive therapy

and routine hemodialysis. The final laboratory study results were notable for leukocytes 10,500µL, blood urea of 32.4mg/dL, creatinine of 1.21mg/dL, and total bilirubin of 2.02mg/dL The patient was subsequently discharged and scheduled for intermittent hemodialysis.

DISCUSSION

Our patient developed severe sepsis with acute renal failure and multi-organ failure 5 to 6 days after the initial symptoms of Leptospira infection, and this is coinciding with the immune phase of the disease. The patient lives in a flood-prone area which is a risk factor for leptospira infection. The recommended antimicrobial agent is benzylpenicillin (1.5 million units intravenously every 6 hours), ceftriaxone (1–2g IV once daily), or cefotaxime (1g IV every 6 hours) given for a period of 7 days.[3] The patient in this case was given ceftriaxone as the empirical antibiotic. Severe cases with multi-organ involvement should be followed-up in an intensive care unit.

In addition to antimicrobial therapy, renal replacement therapy (RRT) or hemodialysis is the necessary supportive therapy for fulminant leptospirosis with sepsis and acute renal failure. In patients with sepsis, acute renal failure has been associated with prolonged ICU and hospital stays in survivors.[6] Early initiation of RRT has been shown to greatly reduce the mortality associated with Weil's disease.[7] Acute renal failure in leptospirosis typically presents as nonoliguric and hypokalemic.[4] This patient was admitted with high serum creatinine, hypokalemia, and oliguria after several days of hospitalization. Therefore, this patient had been programmed for hemodialysis from the first day of hospital admission. RRT in leptospirosis patients has been known to remove the inflammatory cytokines produced as a reaction to the spirochete.[7] Figure 1 shows the improvement of serum creatinine after the patient underwent routine hemodialysis. However, until the second hemodialysis, the patient's serum bilirubin and clinical condition has not shown improvement

The presence of jaundice is characteristic of Weil's disease, however highly bilirubin values such as those present in our patient are not frequently presented in the literature. Based on the literature review conducted by Edmond et al., there are only four publications on PubMed where bilirubin levels exceed 30mg/dL.[8] Extreme hyperbilirubinemia can have multiple cellular toxic effects, including effects on cellular respiration, membrane integrity, transport function, and direct oxidative damage to tubular cell membranes with subsequent release of vasoactive mediators thereby contributing to persistent renal failure.[9]

TPE as rescue therapy was used as part of our treatment in cases of Weil's disease that did not respond to standard critical care after considering the benefits and risks in the individual patient. The bilirubin level was one of the major parameters on which our TPE decisions were based. There are no definite criteria or evidence-based strategy regarding when to start or stop, the frequency, and duration of the TPE procedure.[10,11] A mild criteria for hyperbilirubinemia with a total serum bilirubin level >5 mg/dL should be considered to perform TPE.[11] The number of TPE sessions is determined based on patient improvement.[11,10] The target of bilirubin reduction after TPE is also unclear. Based on previous reports, TPE could reduce bilirubin levels by 46.53%, 21.20%, and 37.69%.[12]

The guidelines of the American Society for Apheresis (ASFA) until the 8th edition in 2019 recommend TPE in septic patients with multiorgan failure in category III (optimum role of apheresis therapy is not established, decision making should be individualized) grade 2B (weak recommendation, moderate-quality evidence).[13] Although the role of plasmapheresis in the treatment of leptospirosis has not been defined, TPE has been reported as an adjunctive therapy for patients with severe leptospirosis in recent years. Tse et al. reported dramatic improvement in a 39-year-old man with severe leptospirosis complicated by acute renal failure treated with single plasma exchange as

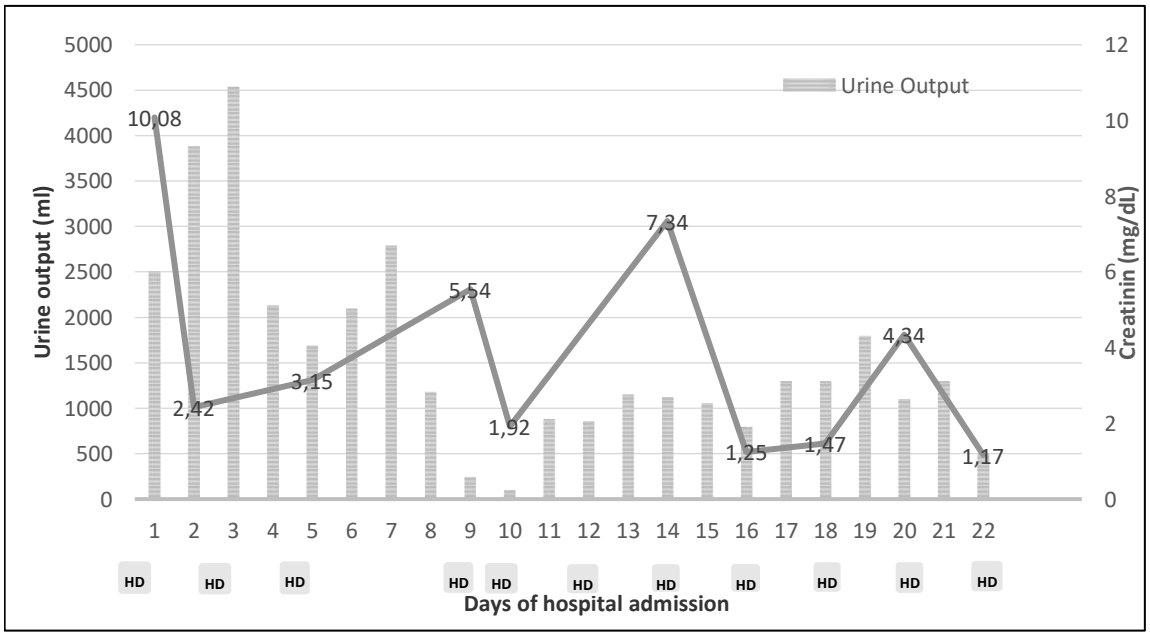

Figure 1. Changes in creatinine serum and urine output

adjunctive therapy.[14] Taylor et al. described a 67-year-old man with severe leptospirosis successfully treated with plasma exchange and showed a significant reduction of serum bilirubin levels.[15] Liu et al., stated that PE is superior in removing bilirubin than the other methods and could reduce blood ammonia.[12] A retrospective single-center pediatric study conclude that TPE and hemodialysis significantly reduced bilirubin and ammonia.[10]

TPE is contraindicated in several conditions, including hemodynamically unstable patients, patients who have an allergy to fresh frozen plasma or replacement colloid/albumin, patients who are allergic to heparin, and unavailability of central line access or large bone peripheral lines. Hypocalcemia and the use of angiotensin-converting enzyme (ACE) inhibitors in the last 24 hours are relative contraindications for TPE. The common complications that can occur during or post-plasma exchange procedure are hypocalcemia or hypomagnesemia, transfusion reactions, fluid and electrolyte imbalance, hypotension, bleeding due to hypofibrinogenemia and thrombocytopenia.[16]

In this report, patients received a single TPE with a centrifugation technique (HAEMONETICS MCS+ 09000 - 220 - E). During the TPE procedure, the patient was hemodynamically stabilized with a ventilator and drug support. Total plasma volume (TPV) was calculated as follows: estimated plasma volume (in liters) = 0.07 × weight (kg) × (1 – hematocrit).[17] The volume of replacement fluid is equal to the volume extracted. We chose 5% human albumin solution (HAS) as a replacement fluid for various reasons. It is essential to use colloid over crystalloid when the volume extracted is more than 1000ml. When compared with fresh frozen plasma (FFP), HAS is easier to obtain, relatively inexpensive, and has minimal side effects such as infection and incompatibility.[18] As demonstrated in Figure 2, the initiation of plasma exchange led to an immediate improvement in serum bilirubin (>50%).

In the septicemic phase of leptospirosis, tissue damage occurs due to systemic inflammation, while in the immune phase, tissue destruction occurs due to immune complex mechanisms. In addition, the use of antibiotics causes the organism to release an excessive amount of endotoxins upon death, which also aids in the immunological pathogenic process (Jarisch-Herxheimer reaction).[19] Plasma exchange eliminates the harmful substances in the bloodstream, such as bilirubin, ammonia, endotoxins, and proinflammatory cytokines which will minimize the tissue damage caused by the mechanism above. TPE also replaces the albumin and helps to maintain the biochemical and homeostatic balance in the body. Removal of serum bilirubin has led to reducing toxic insults to kidney and liver cells. Consequently, improving hyperbilirubinemia with TPE and treating the underlying condition would be the most effective option.[12,20]

As seen in Figure 3, the leukocyte trend of the patient did not show a significant improvement since the start of antibiotic therapy. We started with empiric antibiotic therapy for leptospirosis with ceftriaxone. When the patient showed no improvement in clinical and leukocyte parameters, we took the blood culture and antibiotics susceptibility test. Due to limited facilities, culture findings take longer than expected to be available. While waiting for the culture results, the antibiotics changed to meropenem and amikacin which can cover both anaerobes and pseudomonas.[21] After 5 days, the culture results showed that the patient was co-infected with MDR *Pseudomonas aeruginosa* and had a lot of antibiotic resistance, so we changed the antibiotic to piperacillin-tazobactam as a potent β-lactam/β-lactamase inhibitor.[22] After using piperacillin-tazobactam, the patient's clinical condition and leukocytes gradually improved.

Leptospira may coexist with other pathogens, resulting a complicated diagnosis, extend the length of treatment, and increase mortality, therefore identifying the presence of co-infected pathogens is very crucial.[5] MDR pathogen is a significant cause of infections in hospitals, especially in ICU. This patient experienced MDR-PA hospital-acquired infections (HAI) which certainly poses a therapeutic challenge because effective antimicrobial therapy is very limited.

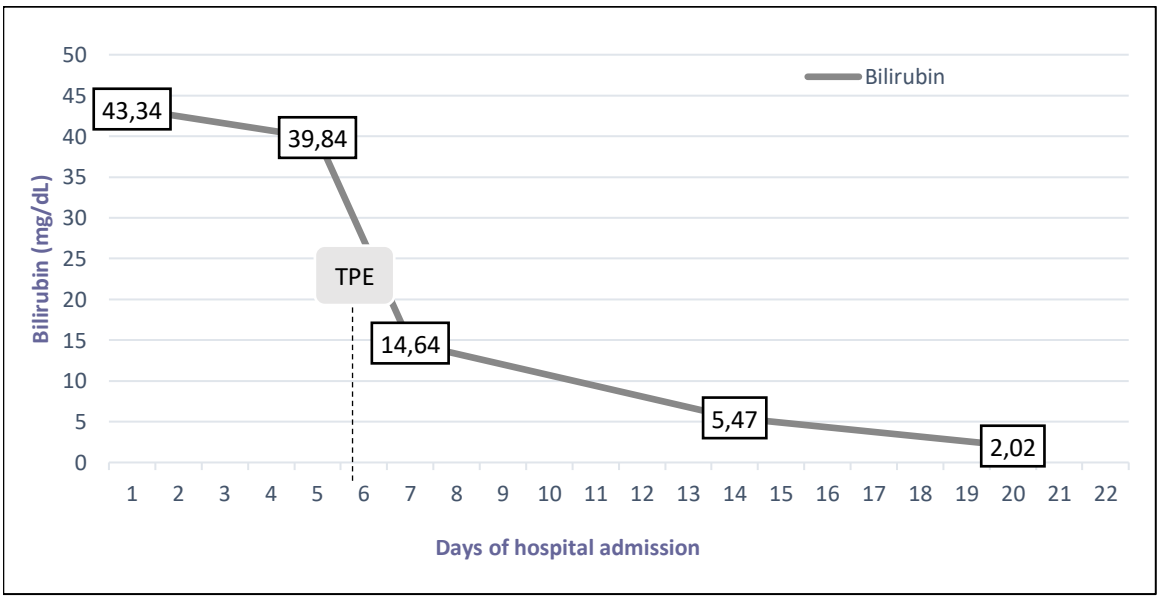

Figure 2. Changes in bilirubin level

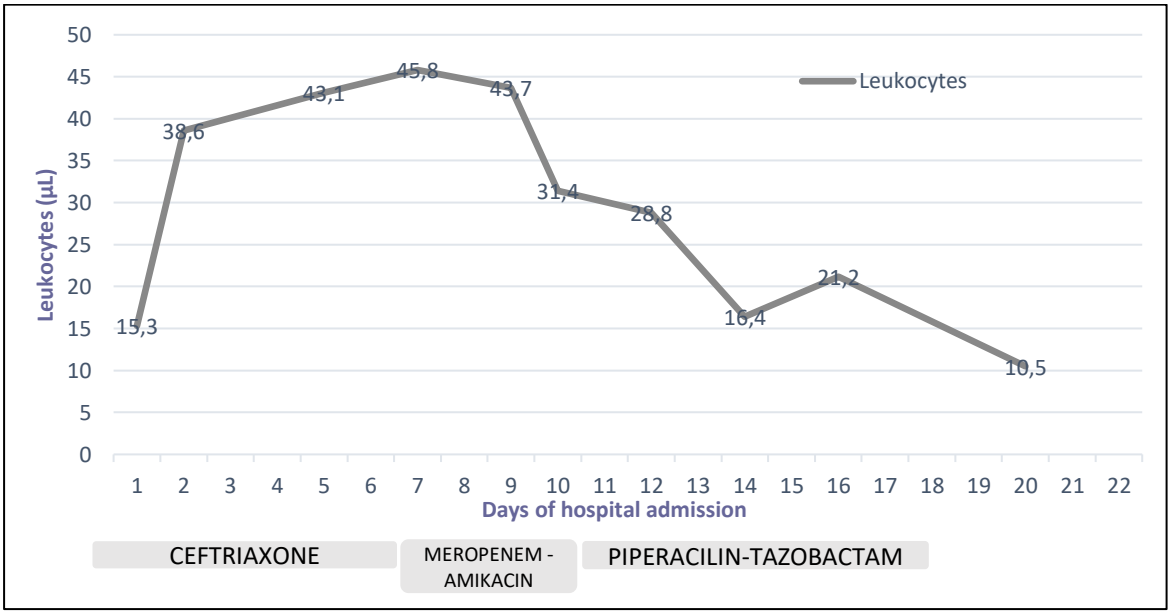

Figure 3. Changes in antibiotics and leukocyte trend

Several factors can explain the cause of this infection such as the use of invasive medical devices (e.g., endotracheal tubes, feeding tubes, and urinary catheters), the use of intravenous antibiotics within the past 60 days, and the duration of hospitalization. The presence of sepsis/septic shock and multiorgan failure are independent factors associated with increased mortality in MDR infections.[23,24,25]

CONCLUSION

In summary, our patient developed Weil's disease with severe hyperbilirubinemia, acute renal failure, and co-infected with multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA). Further, he underwent a single TPE and received definitive antibiotics, resulting in rapid clinical improvement as well as liver and renal function recovery. Based on our experience, we suggest to considered TPE as a rescue therapy for further intensive care support in severe leptospirosis which has not shown improvement despite standard treatment. Co-infection with other pathogens needs to be considered in patients with long hospital stays, especially for those who use invasive medical devices. Improving hyperbilirubinemia with plasma exchange and treating the underlying condition would be the most effective option. However, the use of TPE requires well-designed clinical trials to further establish the efficacy.

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