CASE REPORT: DIFFICULTY IN DIAGNOSIS AND TREATMENT OF DENGUE HEMORRHAGIC FEVER IN PATIENTS WITH CHRONIC RENAL FAILURE: REPORT OF THREE CASES OF MORTALITY

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Abstract. In 2002, an outbreak of dengue fever (DF) in Taiwan caused mortality in some patients with chronic renal failure (CRF). We report three cases of CRF who died of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) despite an intensive care process. The difficulty in diagnosis and the treatment dilemma attributable to ambiguity in symptoms and signs between CRF and DF may delay the diagnosis, contributing to a high risk of mortality. The narrow window of fluid tolerance in patients with CRF further hampers the success of resuscitation in DHF and DSS. Continuous venous to venous hemodialysis (CVVHD) is helpful in managing a condition with unstable hemodynamics. However, to decrease mortality, the physician must pay great attention to ensure an early awareness of DHF/DSS and deliver a prompt and aggressive treatment of patients of dengue viral infections with chronic renal failure.

INTRODUCTION

Dengue fever (DF), a mosquito-transmitted disease caused by dengue virus, was one of the most important infectious diseases in the last century. Every year, an estimated 50–100 million cases of dengue fever and 250,000–500,000 cases of dengue hemorrhagic fever (DHF) are found.1 The incidence, disease severity, and distribution have been increasing in the past 60 years.2–4 The principal vectors of DF, Aedes aegypti and Aedes albopictus, exist worldwide between the latitudes 35° N and 35° S. Consequently, DF has been a major public health issue in many Southeast Asian countries and a leading cause of hospitalization and death among children.5

Taiwan is located in a subtropical area, and it has been an endemic area of DF since 1870.5 There have been two major outbreaks of DF in recent years in the southern part of Taiwan, especially in Kaohsiung city in 1987 and 2002.5,6 During the 2002 outbreak, 15,453 suspected cases were reported to the Center of Disease Control (CDC), Taiwan; 5,388 patients met the World Health Organization (WHO) criteria for diagnosis of DF and 242 patients met the criteria for DHF in the Kaohsiung area.6 Six patients with chronic renal failure (CRF) with the diagnosis of DHF and dengue shock syndrome (DSS) died during this outbreak in Kaohsiung Medical University Hospital, a 1,200-bed medical center in Kaohsiung City, Taiwan. We found the diagnosis and treatment of these patients were more difficult than for the general population. Here, we report three patients with CRF who died with DHF/DSSTo address the difficulty in diagnosis and clinical management.

CASE REPORT

Case 1. A 69-year-old female patient was diagnosed with CRF in September 2002 through the findings of shortness of breath, nocturia, facial pallor, high blood urea nitrogen (BUN, 73.6 mg/dL), high serum creatinine (8.89 mg/dL), low hemoglobin (6.7 g/dL), and bilateral contracted kidney on sonogram. The etiology of CRF was considered as chronic interstitial nephritis based on the history of herbal drug abuse. She received arterio-venous fistula creation for preparation of long-term hemodialysis. Ten days after the operation, because of the symptoms of nausea, vomiting, diarrhea, and tremor, she was sent to the emergency room. No fever, skin rash, abdominal pain, dizziness, or vertigo was noted, and neither loss of consciousness nor seizure occurred. Urine production was constant, and lower legs were free from edema. At the emergency room, the BUN was 164 mg/dL, and the serum creatinine was 15.6 mg/dL. The venous blood gas showed high anion gap metabolic acidosis (pH: 7.101, pCO₂: 30.9 mm of Hg, HCO₃⁻: 9.7 mEq/L, anion gap: 18). The white blood cell (WBC) count was 4,880/μL, hemoglobin was 6.8 g/dL, and the platelet count was 240,000/μL. She received hemodialysis because of uremic symptoms with severe azotemia and acidosis. Blood transfusion with 1 U packed red blood cells (PRBCs) was given for symptomatic anemia. After admission, she experienced a mild cough and high fever with body temperature of up to 39.1°C, and an upper respiratory tract infection was initially suspected. However, progressive thrombocytopenia (platelet: 12,000/μL), coagulopathy (partial thromboplastin time: not coagulated, control: 29.5 seconds), and marked liver injury took place on Day 5 after admission. The peak level of aspartate aminotransferase (AST) was 20,500 IU/L (reference range, 6–25 IU/L) and alanine aminotransferase (ALT) was 5,320 IU/L (reference range, 0–25 IU/L) on Day 6 after admission. Furthermore, mild upper gastrointestinal bleeding occurred, and bilateral pleural effusions were also noted by chest x-ray on the same day. The hemoglobin was 11.1 g/dL at that time; therefore, she received blood transfusion with 24 units of platelets, 2 units of fresh-frozen plasma (FFP), and desmopressin for bleeding diathesis. On Day 8 of admission, refractory shock and respiratory failure occurred, despite an adequate fluid supply (central venous pressure kept at 10–15 cmH₂O), massive transfusion with blood components (platelet: 60 units, FFP: 8 units, PRBCs: 4 units), and positive inotropic agent
A 64-year-old male patient was diagnosed as having multiple organ failure on Day 9 of admission. Under the suspicion of DF, we performed serologic tests on Day 3 and 9 after admission; IgM and IgG antibodies were positive for dengue virus on Day 9. The clinical course is shown in Figure 1.

**Case 2.** A 64-year-old male patient was diagnosed as having gouty nephropathy with CRF (serum creatinine, 2.1 mg/dL) starting in July 2002. He also had hypertension and congestive heart failure diagnosed in 1996. On September 11, 2002, he was transferred from a local clinic under the impression of DF with presentations of general weakness, abdominal pain, diarrhea, myalgia, headache, and chills. The WBC count at the local clinic was 10,700/µL, hemoglobin was 14.8 g/dL, and the platelet count was 32,000/µL. On arrival at the emergency room, the blood pressure was 163/83 mm of Hg, pulse rate was 93 beats/min, and the respiratory rate was 28 times/min. Petechiae over both legs and tarry stool were noted. The platelet count at the emergency room dropped below the detectable level, and hemoglobin was 13.9 g/dL. Severe liver function impairment (AST: 1,576 IU/L, ALT: 1,046 IU/L), acute renal failure (BUN: 82 mg/dL, serum creatinine: 6.4 mg/dL), and coagulopathy (partial thromboplastin time: 97.5 seconds, control: 29 seconds) were noted. After blood transfusion (platelet: 72 units, FFP: 8 units, PRBCs: 2 units), he was admitted to the infection ward. Unfortunately, marked metabolic acidosis (pH: 7.156, pCO2: 22.2 mm of Hg, HCO3−: 7.9 mEq/L) and massive gastrointestinal bleeding with shock occurred after admission. Multiple packs of blood components transfusion for massive bleeding, coagulopathy, and thrombocytopenia, desmopressin for bleeding diathesis, and proton inhibitor for suspected peptic ulcer bleedings were all given at that time, but these treatments proved to be in vain. The next day, dyspnea and ascites developed. Despite multiple packs of blood components transfusion (platelet: 36 units, FFP: 8 units, PRBCs: 6 units), desmopressin, and positive inotropic agents (dopamine: 19 µg/kg/min, norepinephrine: 10.7 µg/min) monitored by central venous pressure, refractory shock and respiratory failure worsened progressively with generalized tonic-clonic seizure activity. Two days after admission, he died of refractory shock with multiple organ failure. His serum IgM and IgG antibodies for dengue virus were positive. The clinical course is shown in Figure 1.

**Case 3.** A 53-year-old male hypertensive patient had a history of diabetes mellitus for 23 years, and CRF was diagnosed by a serum creatinine level of 5.9 mg/dL in September 2002. On October 25, 2002, he was admitted to the nephrology ward because of deterioration of renal function with fluid overload presenting as dyspnea on exertion, cough, and decreased urine amount. However, no fever, chilliness, sore throat, nausea, vomiting, or abdominal pain was mentioned. After admission, he was referred for hemodialysis for severe azotemia (BUN: 170 mg/dL, serum creatinine: 11.4 mg/dL), metabolic acidosis (pH: 7.116, pCO2: 30.4 mm of Hg, HCO3−: 9.4 mEq/L), and fluid overload. However, fever, hematocrit decreased (hemoglobin increased from 9.0 to 15.3 g/dL in 4 days), hypoalbuminemia (serum albumin: 2.4 g/dL; reference range: 3.5–5.0 g/dL), and thrombocytopenia (platelet: 13,000/µL) were noted after admission. Bilateral pleural effusion, thickened gall bladder wall, and ascites were also detected by abdominal sonography. In addition, severe liver function impairment (peak AST: 8,720 IU/L, ALT: 2,061 IU/L) with jaundice (peak total bilirubin: 6.0 mg/dL; reference range: 0.2–1.0 mg/dL) and coagulopathy (partial thromboplastin time: 67.3 seconds, control: 32.1 seconds) occurred at that time. Under the impression of DHF, we checked the serum IgM and IgG antibodies for dengue virus, and the results were positive. On Day 2 after admission, tarry stool and hematemesis occurred, and the gastrointestinal endoscope revealed diffuse gastric erosion and hemorrhagic gastritis. On Day 4 after admission, respiratory failure caused by pleural effusion and pulmonary edema occurred. This patient was treated with ventilator support, fluid monitoring, blood components transfusion (PRBCs: 16 units, FFP: 18 units, platelets: 84 units), hemodialysis, and continuous veno-venous hemodialysis, proton pump inhibitor, and desmopressin. The endotracheal tube was removed on Day 12 of admission and, gastrointestinal

![Figure 1](image1.png)  
**Figure 1.** Clinical course of Case 1. The 69-year-old woman was admitted for HD because of a uremic condition, but fever developed later with progressive decrease of platelet counts, hemocoagulation, and elevation of AST/ALT. Bleeding diathesis occurred on Day 6; refractory shock developed on Day 8. After vigorous resuscitation, the patient died on Day 9 after hospitalization, and IgM and IgG antibodies for dengue virus were positive. HD, hemodialysis; GI, gastrointestinal; H2, histamine 2; Hb, hemoglobin; PLT, platelet.

![Figure 2](image2.png)  
**Figure 2.** Clinical course of Case 2. The 64-year-old male patient was diagnosed with DF and advanced CRF at hospitalization. Severe thrombocytopenia with platelet count under detectable limits, hemocoagulation, and elevation of AST/ALT were noted at emergency room. After admission, despite vigorous resuscitation for bleeding diathesis and circulatory collapse, 2 days later he died of refractory shock with multiple organs failure. Serum IgM and IgG antibodies for DV were positive. See Figure 1 for abbreviations.
bleeding subsided 19 days after admission. However, liver function impairment and thrombocytopenia persisted. Twenty-seven days after admission, respiratory failure recurred with fever; a chest x-ray showed air space lesion over both upper lung fields. Despite mechanical ventilator support, adequate fluid supply, blood transfusion (PRBCs: 10 units, FFP: 9 units, platelet: 36 units), desmopressin, antibiotics, and positive inotropic agent (dopamine: 17 μg/kg/min, noradrenaline: 5.33 μg/min), this patient died of respiratory failure 30 days after admission. The clinical course is shown in Figure 3.

**DISCUSSION**

Dengue viral infection may manifest from self-limited febrile illness to life-threatening diseases.\(^3\) Classic DF frequently presents with fever, headache, myalgia, bone or joint pains, nausea, vomiting, and skin rash. Other signs and symptoms include a flushed face, sore throat, cough, cutaneous hyperesthesia, and taste aberrations.\(^2,3\) DHF is defined as an acute febrile illness with minor or major bleeding, thrombocytopenia (≤ 100/μL), and evidence of plasma leakage documented by hemoconcentration (hematocrit increased at least 20%), pleural or other effusions, or hypoalbuminemia.\(^7\) DSS is defined as DHF with signs of circulatory failure, including narrow pulse pressure (≤ 20 mm of Hg), hypotension, or frank shock.\(^7\) DHF commonly begins with a sudden rise in temperature and develops on the third to seventh day of illness.\(^5\) Secondary infection and patients with chronic disease are risk factors for DHF.\(^8\) The three mortalities we reported all met the criteria of DHF, and Cases 1 and 2 further met the criteria for DSS.

In consideration of diagnosis in DF, the symptoms of DF are nonspecific. Early recognition of the warning signs of DHF (intense continuous abdominal pain, persistent vomiting, and restlessness or lethargy) and early treatment are of prime importance in reducing the mortality rate.\(^6\) For patients with CRF, the presentations of DF are not obvious, and diagnosis is more difficult. The warning signs are even similar to the presentation of uremia. In the diagnostic criteria of DHF, hemoconcentration, pleural or other effusions, and hypoalbuminemia are easily ignored in uremia. As in Case 1, the initial presentation was explained by uremia, and the treatment regimen only focused on uremic problems. Although fever was noted after admission, she did not have other typical symptoms of DF, except for complaining of a cough. We suspected that she might have had DF on Day 3 of admission after the manifestation of a progressively decreasing platelet count. On Day 6 after admission, gastrointestinal bleeding and bilateral pleural effusion developed. However, uremic patients could have gastrointestinal bleeding and pleural effusion, especially at the initial stage of dialysis. The evidence to support the diagnosis of DHF rather than uremia included severe thrombocytopenia, severe liver function impairment, and hemoconcentration (hemoglobin change from 8.7 to 11.2 g/dL in 2 days). If physicians are not aware of these changes, correct diagnosis will be delayed. In Case 3, the initial presentation also resembled uremia with fluid overload; there was no fever. The clues to a suspicion that he might have DHF were fever, abnormal liver function test, thrombocytopenia, and hemoconcentration (hemoglobin increase from 9.0 to 15.3 g/dL in 4 days). In this case, diagnosis of DHF will be delayed if the physician does not notice the changes in hemoglobin and platelets. Diagnostic delay correlates with increased mortality.\(^2\)

Even if physicians have made early and accurate diagnoses of DF, the treatment of DF in patients with CRF is still difficult. Because no specific antiviral treatment of dengue virus exists, the only treatment is supportive care, such as rest, adequate fluid intake, and antipyretics.\(^2,10\) For treatment of DHF/DSS, the three most important issues are fluid supply, electrolyte balance, and bleeding control.

Because of capillary leakage, the problem of fluid loss is more severe than blood loss in DHF/DSS, and the strategy of treatment must focus on the restoration of volume status and maintenance of blood pressure.\(^10\) In patients with DSS, if fluid is inadequate, prolonged shock will lead to refractory shock, and mortality will occur.\(^11\) However, if too much fluid is given, acute pulmonary edema occurs. Therefore, how to monitor the fluid status and provide the optimum fluid intake is very important in patients with DSS. Urine output, central venous pressure catheter, and chest x-ray are all monitoring tools for evaluation of fluid status. Among these tools, urine output is a good, simple indicator. However, in CRF, especially in dialysis patients, the urine output cannot be an indicator for the monitoring of fluid status. If patients without CRF have fluid overload during the treatment period, we may use diuretics to correct fluid status, but in patients with renal failure, the diuretics may only have a limited effect, and eventually dialysis may be required. This makes it more difficult to maintain the balance on fluid supply. Therefore, we recommend more frequent evaluation of fluid status and careful monitoring of the fluid supply in patients with CRF complicated with dengue viral infection. In particular, a central venous pressure (CVP) catheter is necessary for patients with DHF/DSS. Re-evaluating Case 3, we did not delay the diag-

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**FIGURE 3.** Clinical course of Case 3. The 53-year-old man received HD after admission because of diabetic nephropathy at stage of CRF with fluid overloading. Thrombocytopenia, hemoconcentration, and elevation of AST/ALT were noted at admission, and the IgM and IgG antibodies for Dengue virus were positive. The patient recovered from bleeding diathesis, respiratory failure, and shock but presence of thrombocytopenia and impaired liver function persisted. A second episode of respiratory failure and circulatory collapse developed on Day 27 of hospitalization, and he died on Day 30 despite vigorous resuscitation. See Figure 1 for abbreviations.
nosis and, even with intensive monitoring of fluid status, shock developed, which shows the difficulty in treating these patients. Concerning the fluid solution for resuscitation of DSS, there are controversies between crystalloid or colloid solutions. The WHO recommends immediate volume replacement with isotonic solutions but plasma or colloid solution for profound or persistent shock. One double-blind, randomized comparison of three kinds of intravenous fluids for initial resuscitation of Vietnamese children with DSS showed that Ringer lactate is beneficial, and it is thus indicated for children with moderately severe DSS. Dextran 70 and 6% hydroxyethyl starch also have similarly beneficial effects in children with severe shock. However, another study showed that the longest recovery times occurred in patients resuscitated with Ringer lactate in comparison with the other three kinds of fluids (normal saline, gelatin, and dextran). Ringer lactate also contains potassium and lactate, and they may theoretically carry the risk of hyperkalemia and worsen tissue acidosis by lactate accumulation if not metabolized normally. Therefore, this treatment must be used with caution in patients with CRF. Dextran 70 has been reported as the preferred solution for acute resuscitation in DSS, but it may induce severe anaphylaxis. Starch is an effective colloid solution and is preferred in children with severe DSS. However, the safety of starch is not well established in patients with CRF. Therefore, these three kinds of intravenous fluids seem unlikely to be applied to patients with CRF. More research is needed to find the most suitable fluid in patients with CRF with DSS.

During the treatment of DHS/DSS, in addition to the requirement of a large amount of fluid, the acid-base and electrolyte balances are important issues. The patients with CRF have greater chances of developing acidosis and electrolyte imbalance, especially at a shock status. The majority of these imbalances can only be corrected by dialysis, such as hyperkalemia occurring in oliguric renal failure. However, it is difficult to perform hemodialysis in patients in a shock state without further compromising the hemodynamics. In this case, continuous renal replacement therapy (CRRT) should be considered. In Case 3, we used continuous veno-venous hemodialysis (CVVHD) for correcting fluid overload and electrolyte imbalance in the intensive care unit, and this treatment enabled this patient to overcome the first critical episode.

Coagulopathy and severe thrombocytopenia are other important complications in DHF that will cause severe bleeding and mortality. Among these varieties of severe bleeding, gastrointestinal bleeding is the most common. Pulmonary and brain hemorrhage are other potentially fatal complications. For the treatment of gastrointestinal bleeding, blood transfusion is still the mainstay of management, and endoscopic injection therapy is not effective as adjuvant treatment. The three cases we reported all had gastrointestinal bleeding, and Case 3 also had pulmonary hemorrhage. Many patients with CRF, in addition to coagulopathy and severe thrombocytopenia, also have platelet dysfunction in quality. This bleeding diathesis will make the situation of bleeding difficult to stop. As seen in Cases 1 and 2, active gastrointestinal bleeding may present before death. In Case 3, it took 18 days to stop gastrointestinal bleeding in the first critical period, but the patient still died of respiratory failure because of pulmonary hemorrhage. To improve the bleeding diathesis in uremic patients, desmopressin has been suggested for temporary correction of bleeding time. Desmopressin (1-deamino-8-D-arginine vasopressin), also called DDAVP, can shorten the prolonged bleeding time, release endothelial hemostatic factors, and promote the adhesion of platelets to the vascular subendothelium; therefore, it is used to improve platelet function in von Willebrand disease and hemostasis in uremic patients. Furthermore, because desmopressin also has the effect of water retention, it seems reasonable to restore body volume in DHF/DSS. The implications of desmopressin in DHF have been reported; further studies are needed for validation of that effect. Each of our three patients received desmopressin, but all died.

In conclusion, we report three cases of CRF morality of DHF/DSS to explore the difficulty in diagnosis and dilemma of treatment in such patients. For the general population, the mortality of DHF is 1–5%. The difficulty in diagnosis and the treatment dilemma in patients with CRF cause a high risk of mortality, which may be attributed to the overlap in symptoms and signs between CRF and DF. Where a high index of clinical suspicion is paramount in making a diagnosis, a travel and vector exposure history should be obtained where appropriate, especially for patients with CRF.

Received August 7, 2006. Accepted for publication December 18, 2006.

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REFERENCES


