SCRUB TYPHUS EMERGING THREAT

COMPLICATIONS

# Renal Failure Associated with Scrub Typhus

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Scrub typhus is a zoonotic re-emerging disease of the day caused by Orientia tsutsugamushi (*O. tsutsugamushi*). An estimated one million cases occur annually. Because of reports of *O. tsutsugamushi* strains with difficulty in diagnosis, non specific clinical presentation and reduced susceptibility to antibiotics various complications are inevitable. Mortality rates in untreated patients range from 0-30%. Complications may include atypical pneumonia, overwhelming pneumonia with adult respiratory distress syndrome (ARDS)-like presentation, myocarditis, acute renal failure and disseminated intravascular coagulation (DIC). No significant morbidity or mortality occurs in patients who receive appropriate treatment (1-4).

Acute renal failure associated with scrub typhus infection is not so uncommon as previously thought. The possibility of scrub typhus should be borne in mind when patients present with fever and varying degrees of acute renal failure, particularly if an eschar exists, along with a history of environmental exposure in an endemic area. Prompt diagnosis and the use of appropriate antibiotics can rapidly alter the clinical course of the disease and prevent the development of serious or fatal complications, with clinical features of multiple organ dysfunctions, including shock, fever, acute respiratory failure, acute renal failure, and acute hepatitis (5). Acute renal failure by definition means a clinical syndrome in which a sudden deterioration in renal function results in the inability to maintain the fluid and electrolyte homeostasis (6). Several hypotheses have been proposed to explain the mechanism by which *O. tsutsugamushi* infection causes acute renal failure. First, it is assumed that the pathophysiology of acute renal failure is associated with prerenal azotemia due to renal hypoperfusion in cases of shock or volume depletion. According to Dumler et al, prerenal azotemia is the main pathophysiology of renal failure caused by the decrease of effective renal blood flow due to increased vascular permeability in patients with murine typhus accompanied by systemic vasculitis (7). Hypoalbuminemia is commonly noted to occur in patients with rickettsial disease. This has been reported to be due to the leakage of plasma albumin into the perivascular space because of widespread vascular damage (7). Additionally, acute tubular necrosis might cause renal failure because of the direct invasion of *O. tsutsugamushi* into a renal parenchyma. Walker and Mattern, and others (8, 9) reported that histopathological findings were suggestive of multiple interstitial nephritis in patients with renal failure accompanied by murine typhus. Neither acute glomerulonephritis, nontraumatic rhabdomyolysis with myoglobinuria, or DIC have so far been documented to contribute to the development of acute renal failure. Little is known about whether the development of renal failure is associated with DIC or acute glomerulonephritis. Further clinical studies are therefore warranted to examine the pathophysiology of acute renal failure in patients with scrub typhus. Because scrub typhus causes systemic vasculitis, it can cause meningitis, interstitial pneumonia, acute pulmonary edema, hepatitis, and acute renal failure in untreated cases (8, 10). Hematuria and proteinuria may occur because of renal invasion in 10 to 20% of patients with scrub typhus.

History of endemic area, clinical manifestations suggestive of scrub typhus & presence of Eschar helps to establish dignosis of scrub typus induced ARF. Manifestations such as pneumonitis, meningoencephalitis, jaundice and myocarditis can develop along with acute renal failure in pateints with the prolonged clinical course of untreated illness (11). Establishing the diagnosis and initiating prompt antimicrobial drug therapy are important because death rates for untreated scrub typhus patients are 1%-30% (10). In almost all severe complicated cases which include encephalitis, interstitial pneumonia, renal failure and hepatitis the pathology is due to vascular injury (12).

Acute renal failure is not a common entity, but it is known to be one of the serious complications seen in patients with scrub typhus, spotted fever, or murine typhus (9, 13). Fever, headache, and rash are potential indicators for rickettsial disease and are known to be useful clues for the diagnosis of scrub typhus (7). After a detailed history and through clinical examination including monitoring of vital signs like blood pressure, pulse rate, respiratory rate, and body temperature, investigations required are; CBC (Mild lymphocytosis), urinalysis for microscopic gross

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hematuria, proteins, casts, or WBCs and urine out put , urine for eosinphils, specific gravity, functional excretion of sodium ( 6).Other Investigations are Chest X ray, sonographic evaluation of abdomen, arterial blood gas analysis, serum biochemistry like [Na+], [K+], [$Cl^-$], blood urea nitrogen, and creatinine levels, Liver function tests like, total protein level, albumin, aspartate transaminase, alanine aminotransferase, and other tests like creatine phosphokinase, lactate dehydrogenase, myoglobin, fibrin degradation products, and a D-dimer concentration (3). Serologic tests like rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibody, and cold agglutinin, human immunodeficiency virus, hepatitis B virus, and hepatitis C virus antibodies, and the VDRL, Antistreptolysin O and complement levels , and finally diagnostic renal biopsy. Immunohistochemical (IHC) staining, immunofluorescent staining, and electron microscopic examination (EM), identify the presence of *Orientia tsutsugamushi* coccobacilli within the tubule (2,14,15).

Once it is confirmed *O. tsutsugamushi* is the causative agent for renal failure immediately one should commence the treatment with two loading doses of Doxycycline 2.2mg/kg/ dose,,12 hours apart followed by Doxycycline 2.2mg/kg/ day in 2 divided doses orally or intravenously: a maximum of 300mg/dose; tetracycline 25-40 mg/kg/24 hours in 4 divided doses; a maximum of 2 g/24 hours; or Chloromphenicol intravenously 50- 100mg/kg/24 hours in 4 divide doses which must be monitored to maintain a serum level of 10- 30 mcg/L.

Therapy must be continued for a period of 5 days or until the patient has been afebrile 2- 4 day to avoid the relapse, especially in patients who were treated early. Patients treated with regimens usually become afebrile within 48 hours, and thus the entire period of therapy usually lasts for < 10 days (14).

In addition to the above specific measures, other supportive measures including the life saving one has to be addressed as well, like correction of intravascular volume, hyperkalemia, hypocalcemia, hyponatremia, metabolic acidosis, hypertension, and maintenance of input output chart. Neurological symptoms and anemia has to taken care of simultaneously if any (6).

Acute renal failure associated with scrub typhus infection is not rare as previously thought. The possibility of scrub typhus should be borne in mind when patients present with fever and varying degrees of acute renal failure, particularly if an eschar exists, along with a history of environmental exposure in an area, where scrub typhus is endemic. Prompt diagnosis and the use of appropriate antibiotics can rapidly alter the clinical course of the disease and prevent the development of serious or fatal complications. The diagnosis can be confirmed using immunofluorescence techniques, which show that *Orientia tsutsugamushi* had an IgM titer of 1:80 or greater. Such patients responded very well to doxycycline therapy and recover completely.

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