Jaundice in patients with tropical infections

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Jaundice and encephalopathy is a common presentation of many tropical infections. The hepatic involvement in tropical infections can vary from mild, transient elevation in enzymes to acute liver failure (ALF). (1-5) Paracetamol use in patients with fever and jaundice could accentuate the injury or may result in delayed resolution; however, this aspect has never been addressed in the studies. Malarial hepatopathy is the best-known example of hepatic involvement in tropical infections (6) but similar manifestations can also be seen in other tropical infections like dengue fever, typhoid fever, leptospirosis, amoebic liver abscesses, and other bacterial and fungal infections. (7)

Apart from hepatotropic (Hepatitis A to E) viruses that can cause acute liver failure, a variety of non--hepatotropic viruses, bacteria, protozoa and fungal infections can affect the liver leading to a clinical picture dominated by jaundice fever, and encephalopathy.(1) Tropical infections such as malaria, typhoid fever, leptospira, dengue are common, and present with jaundice and altered sensorium mimicking ALF.

Table 1: Important tropical causes of jaundice and fever

- Hepatitis with fulminant hepatic failure
  - Hepatotropic viruses A or E
  - EBV
  - HSV
- Bacterial sepsis
- Malaria (P falciparum/ P Vivex)
- Typhoid fever
  - Salmonella typhi
  - S paratyphi
- Leptospirosis
- Scrub typhus and other Rickettsial infections
- Dengue (with warning signs) / Dengue Hemorrhagic fever
- Amoebiasis
  - Hepatitis
  - Liver abscess
- Brucellosis
- Macrophage activation syndrome
- Fungal infections (Candida / Aspergillus)

Clinical Approach

Approaches to a febrile patient with jaundice/deranged liver functions starts with a careful history and physical examination. This is aimed at ruling out other features like pain and other systemic .manifestations which often give clues to alternative diagnosis. (1) Usually patients present with a short febrile illness and the jaundice appears or is noted by the relatives or the clinician. Patient may be completely unaware of the jaundice. An important discriminator from acute viral hepatitis is persisting jaundice. In acute viral hepatitis resulting from usual hepatotropic viruses, jaundice follows fever but by the time the patient presents to the clinician, the fever has subsided. If the patients presents with ongoing fever with jaundice, one must rule out alternative causes. In endemic countries, tropical infections are important but one must never forget that fever with jaundice, vomiting and abdominal pain could be a clinical manifestation of acute onset cholangitis. (8) This possibility should always be ruled out in the beginning. Jaundice can mask anaemia in patients with haemolysis due to infections. (6) This fact should always be considered. Presence of hepatomegaly or splenomegaly, which is a common feature in tropical infections, is an important soft pointer against the diagnosis of ALF. (9) Hepatomegaly may be seen early in uncomplicated acute viral hepatitis, where as in acute liver failure, the liver shrinks due to sever apoptosis and collapse of reticulin network. Jaundice only due to haemolysis tends to be mild (Sr Bilirubin rarely exceeding 3-4mg/dl). The same is true for tropical infections.(10) Liver enzymes are raised disproportionate to serum bilirubin and usually show a dominant cholestatic picture.(1) Coagulation parameters are usually preserved in patients with tropical jaundice. (1,6) Severe coagulopathy may indicate a co-infection with hepatotropic viruses or development of disseminated intravascular coagulation (DIC). (6) presence of multi organ dysfunction should alert the physician to the possible diagnosis of a tropical infection.

While clinically approaching such patients, one must rule out surgical causes of jaundice. Multiorgan dysfunction is are in acute viral hepatitis unless it is complicated by fulminate hepatic failure. Presence of a normal sized liver or hepatomegaly along with splenomegaly would indicate a tropical infection. (1,6). When in doubt hepatic enzymes and serum bilirubin can help. Clinical picture mimicking acute hepatic failure with preserved coagulation parameters points towards a diagnosis of tropical infections. Table 1 lists the important tropical infections which can present with acute onset fever and jaundice.

Malarial Hepatopathy

Hepatic dysfunction in malaria has been recognized since many years (11,12) a clinical picture simulating acute liver failure can be caused by Malaria.(13,14) Majority cases have either isolated infection with Plasmodium falciparum (15) or a mixed infection (16) Rarely it is seen with P. vivax alone.(17) In severe malaria incidence of jaundice may vary from 8 to 37%.(18,19)

Jaundice in Malaria is multifactorial in origin.(19) The rupture of hepatocytes during the primary schizogony results in cellular damage but this does not result in significant hepatic dysfunction.(6) Hemolysis after RBC lysis due to severe infestation by P. falciparum can

raise bilirubin. Cytoadherence and sequestration of parasites within small vessels leads to microvascular obstruction with resultant ischemia leading to liver dysfunction.

Other mechanisms suggested are occlusion of portal venous branches by parasitized red blood cells, (20) endotoxemia due to severe systemic infection, (21) intrahepatic cholestasis due to reticuloendothelial blockage and hepatic microvillus dysfunction (22) and apoptosis and oxidative stress.(23)

Co-infection with viral hepatitis E or A and other tropical infections can accentuate jaundice.(24-26) Disseminated intravascular coagulation can also contribute to hepatocellular dysfunction seen in severe malarial infection.(27) Hepatitis may result from ant-imalarial drug-induced liver injury.(19)

"Malarial hepatopaty" is characterized by a rise in serum bilirubin along with the rise in serum glutamate pyruvate transaminase levels to more than three times the upper limit of normal. (28)

Clinical presentation that is confused with liver failure has been described as type B presentation. (12) These patients usually present with acute onset fever along with jaundice which is usually severe and is associated with coma, renal failure and DIC. Examination reveals anemia but in the presence of jaundice, it may be mised. Systemic examination reveals hepatomegaly and often significant splenomegaly. Severe impairment of the sensorium is not unusual in severe malaria, however this may be multifactorial. Cerebral malaria, hypoglycemia, hypoxia and/or uremia due to renal involvement may also contribute to the altered mental status or encephalopathy in severe falciparum infection. Asterixis are almost never seen in isolated malarial involvement but may be seen if concomitant viral hepatitis is present.(29)

True hepatic encephalopathy is considered rare in malaria. Electroencephalogram (EEG) in these patients may reveal delta waves, pseudo periodic burst suppression and triphasic waves. (19) Most of these patients have elevated Serum bilirubin with conjugated fraction crossing 50% mark.(30) Liver enzymes are elevated 3–5 times the normal but may be elevated much beyond this. INR is usually normal, even in patients with marked elevation of enzymes and is elevated only with DIC.(6,19) This is one of the major differences from ALF. Ultrasonography will find hepatomegaly with or without splenic enlargement again differentiating it from ALF.

In endemic and hyperendemic areas, malarial hepatopathy must be excluded in all cases diagnosed to have ALF, because of difference in treatment. Presence of persistent fever, disproportionate anemia, oligo/anuria, firm splenomegaly and normal increased liver span are some of clinical findings that will point towards Malarial hepatopathy.

Dengue fever

Dengue Hemorrhagic Fever (DHF) is a common seasonal arthropod-borne viral fever in India. (31) Dengue virus is a non-hepatotropic virus, but a wide spectrum of liver dysfunction is frequently seen along with this infection which includes liver failure. (32)

Jaundice in dengue infection by itself is a poor prognostic factor (33). Liver involvement clinically manifests as hepatomegaly or biochemically as raised liver enzymes not unlike acute viral hepatitis. Severe dengue can have presentation like fulminant hepatic failure and is associated with increased mortality. (34) Clinically incidence of jaundice varies from 2–25% of cases.(35)

Hepatic involvement is frequent in (60–90%) dengue-infected patients. (36) Most of cases have mild disease with only 10% developing a rise in transaminases more than ten times the upper limits of normal.(37) Usually the SGOT levels are more than SGPT levels.(38) Jaundice an important predictor of severe dengue infection.(39) Clinical picture akin to Acute liver failure (ALF) occurs less frequently and is seen mainly in children.(40-43)

Liver injury in dengue fever is due to the direct cytopathic effect , destruction of virus-infected cells by the host immune response and is accentuated by a non-specific effect of shock and hypotension.(44) Drugs like Paracetamol and herbal drugs are other possible contributors. Rarely there may be coinfection with other hepatitis viruses. (45)

Liver histology shows hepatocytes necrosis at zone two and councilman bodies.(46) It is still unclear if the virus multiplies in the hepatocytes. Higher incidence of severe liver injury in patients with complicated dengue may suggest a role for host immune responses in the causation of liver injury as well.(46) Persistant jaundice with persistant cytopenias is an important indicator of haemophygocytosis. Clinical syndrome mimicking acute liver failure due to dengue would manifest as jaundice with altered sensorium, associated hemorrhagic manifestations, thrombocytopenia, raised enzymes (AST > ALT) and evidence of capillary leak syndrome. (48) Altered sensorium in these cases is either due to hepatic encephalopathy or multiple organ involvement. (32)

Typhoid fever

Enteric or Typhoid fever is common in India in epidemic as well as sporadic forms. (49) Hepatitis and jaundice have been frequently reported.(50) Its incidence varies from 0.5 to 7.6%. (51) Presence of Jaundice in typhoid fever may confuse the clinician as it is more commonly associated with malaria and viral hepatitis. Fulminant hepatic failure in typhoid fever is usually due to coinfection with hepatitis A virus. (52) Hepatic involvement in typhoid is postulated to be secondary to hepatocytes damage by endotoxins. Clinically there is hepatomegaly and biochemical abnormalities include raised transaminases as well as alkaline phosphatase. (53) Hepatic encephalopathy is less commonly encountered.(54) Since a wide variety of neuropsychiatric abnormalities have been described in Typhoid fever.(55,56) it is not unusual to have jaundice and altered sensorium unrelated to hepatic encephalopathy in Typhoid fever.

Jaundice usually appears during the second week of illness and improves slowly with recovery. (57) Presence of significant hepatomegaly can alert a physician while considering the diagnosis of ALF.(58) Neuropsychiatric manifestations are also common in the third week of fever there by complicating clinical presentation. There is biochemical evidence of hepatic dysfunction even in the absence of jaundice in around 21–60% patients.(51) Histologically reticuloendothelial

cell hyperplasia has been recorded.(51) The bacteria proliferate in the hepatocytes producing hepatic damage by cytokines. (57) Typhoid nodules are non specific collection of cells. Some areas also demonstrate cloudy swelling, ballooning degeneration, moderate fatty change and mononuclear cell infiltrate.(59) Intact bacilli have also been demonstrated in the parenchyma of the liver by immunohistochemistry and have been cultured from liver biopsy.(51,60) Rise in conjugated fraction of bilirubin is mainly due to canalicular occlusion by swollen hepatocytes later leading to rupture of bile canaliculi. This also results in reflux of bile into the hepatic sinusoids with elevation of conjugated bilirubin. (58) A & B. The incidence of gastrointestinal hemorrhage and ileal perforation is also higher in icteric patients as compared to non-icteric typhoid patients.(51) Mortality is also higher in jaundices patients with typhoid fever as compared to non jaundiced ones.

Leptospirosis

Weil's disease is a spirochetal infection caused by Leptospira interrogans. Infection occurs in persons working or wading through contaminated water, especially during rainy season. (1) The disease has an average incubation period of 10 days. It is a biphasic illness with mild first phase and severe second phase. Initial presentation is usually like a non specific febrile illness. In the second phase of illness development of hepatorenal dysfunction is commonly seen along with pulmonary involvement in the form of hemorrhage.(60) Severe manifestations are commonly noted during second week (4–9 days into the illness). The pathology is like infectious vasculitis resulting in centrilobular necrosis of the liver and renal tubular dysfunction (interstitial nephritis and acute tubular necrosis).

Liver involvement usually presents with tender hepatomegaly and jaundice. Jaundice is accentuated by additional haemolytic component. Bilirubin levels are very high. Where as liver enzymes may be normal or just mildly raised (2–3 times normal levels). A raised serum bilirubin level with normal aminotransferases is highly suggestive of leptospirosis rather than hepatitis.

Presence of coexisting ARDS, myocarditis, rhabdomyolysis, thrombocytopenia, DIC, hemorrhage into the skin and internal organs, uveitis, and digital gangrene can point to the diagnosis of leptospirosis. Characteristic conjunctival suffusion often with uveitis, severe muscle tenderness and non-oliguric renal failure with hypokalemia are other clinical clues to the diagnosis.

Aseptic meningitis, confusion, hallucination and psychosis may complicate the illness.(61) Occasional patient may develop encephalitis. Convalescence from meningitis or encephalitis may be prolonged and involve periods of physical, muscular weakness and mental exhaustion for months. Latter may give a false suggestion of hepatic encephalopathy. Diagnosis is made with serology with the microscopic agglutination test (MAT) as the gold standard with either a four fold rise in titres or a single titre of >1:800 being diagnostic.(62)

Sepsis induced multiorgan dysfunction

Bacterial sepsis is know to produce a syndrome of jaundice and encephalopathy as a part of multi-organ involvement in critically ill patients in ICU. Sepsis may be secondary to a variety of infections including cholangitis, pyogenic or amoebic liver abscesses, any systemic bacterial infection, Toxic shock syndrome, malaria, typhoid, leptospirosis and so on. (64-66) Acutely oncoming jaundice is commonly a harbinger of sepsis, multisystem organ failure (MSOF). Hepatic dysfunction may also be a reflection of transient hypotension (shock liver), right-sided heart failure, the metabolic breakdown of red blood cells, or pharmacologic toxicity. Jaundice is associated with a significant increase in morbidity and mortality. Encephalopathy in these conditions is due to associated hypoxia, electrolyte disturbance or even hypoglycemia. Hemolysis, Massive transfusion, Hypotension/"shock liver", Disseminated intravascular coagulation, Soft tissue trauma and hematoma resorption, /MSOF and Medications/ hepatotoxins may contribute in causation of jaundice in a critically ill patient. (67) In patients with amoebic liver abscesses, presence of jaundice with serum bilirubin above 3.5 mg/dl and presence of encephalopathy are poor prognosis factors. (68)

Brucellosis

Brucellosis is a systemic febrile illness caused by Brucella species. The four species responsible for disease in humans include B. melitensis (sheep, goat), B. abortus (cows), B. canis (dogs), and B. suis (pigs, boar). The majority of human infections are caused by B. melitensis. Exposure to domestic animals is the usual mode of transmission. The incubation period is usually variable Apart from fevers and constitutional symptoms, clinical manifestations are varyable. Hepatomegaly is common (20–40% of patients) (69) along with osteoarticular involvement (23% of cases). Elevations in aminotransferase levels occur in around 25% of cases but clinical jaundice is a rare. (69) Hepatitis associated with brucella appears to be mild, with no reports of acute liver failure. In its more severe form there can be hepatic abscesses (B. suis). Histopathology varies, with the most common finding being hepatic granulomas, inflammatory cell infiltrates and mild, localized parenchymal necrosis. (69)

Diagnosing brucellosis is challenging, Serological assays are the most common diagnostic test used. Serum agglutination titer >1:160 in the presence of a compatible illness is considered diagnostic. Blood cultures have a sensitivity of 15 to 70%. Bone marrow cultures have a higher yield of organisms.

Doxycycline 200mg daily for 6 weeks combined with either rifampin 600–900 mg daily for 6 weeks or IM streptomycin 1 gm daily for 2 weeks is the treatment of choice.(70)

Hemophagocytic lymphohistiocytosis (HLH)

HLH is a potentially fatal syndrome characterized by fever, splenomegaly, jaundice, and the pathologic finding of hemophagocytosis in bone marrow and other tissues.(71) It may be primary (genetic), or secondary (acquired) to viral infections, autoimmune diseases or

malignancy such as lymphoma. It is caused by excessive inflammation and tissue destruction due to abnormal immune activation and excessive inflammation caused by a lack of normal downregulation of activated macrophages and lymphocytes.(72) There is significant tissue damage which ultimately leads to multiorgan failure associated with very high mortality.

The initiating trigger for an acute episode is often an infection or an alteration in immune homeostasis. HLH varies from other syndromes of immune activation, immunodeficiencies, and inflammatory states due to the coexistence of immune dysregulation with unchecked inflammation.(73)

Clinically patients will present with fever, hepatosplenomegaly, lymphadenopathy, jaundice and maculopapular rash. Nearly half the cases have encephalopathy, meningismus, and seizures.(74) The most prominent laboratory abnormalitie is cytopenias. There is also biochemical evidence of hemolysis, hypertriglyceridemia , marked elevation of ferritin and lactate dehydrogenase. Serum fibrinogen is typically low. Typical hemophagocytosis is seen in bone marrow, spleen, and lymph nodes, liver and occasionally in central nervous system, skin.(75)

Diagnosis can be made if five of following eight findings are present (a) Fever ≥38.5 °C (b) Splenomegaly (c) Peripheral blood cytopenia, with at least two of the following: hemoglobin <9 g/dL (for infants <4 weeks, hemoglobin <10 g/dL); platelets <100,000/microL; absolute neutrophil count <1000/microL (d) Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL) (e) Hemophagocytosis in bone marrow, spleen, lymph node, or liver (f) Low or absent NK cell activity (g) Ferritin >500 ng/mL (often >3000 ng/mL) and (g) Elevated soluble CD25 (soluble IL-2 receptor alpha).

Treatment is mainly supportive but high dose steroids and cyclosporine have been tried too.

Table 2: Details of various tropical infections presenting with jaundice

Aetiological agent	Mode of transmission	Clinical features	Lab diagnosis	Treatment
Malarial hepatopathy Plasmodium species	Bite of anopheles mosquito	Fever, chills and sweats Hepatosplenomegaly Severe malaria: altered sensorium, coma, severe anemia, hypoglycemia, metabolic acidosis, acute kidney injury, ARDS, DIC, shock	Microscopy: (gold std) Both thick and thin smears Rapid diagnostic tests (RDTs) HRP (histidine rich protein)/ LDH (lactate dehydrogenase based)	Artesunate 2.4 mg/kg i.v. bolus at admission, 12 h and 24 h; followed by once a day for 7 days + Doxycycline 100 mg p.o. 12 hourly/ Clindamycin 600mg bd Alternative: quinine 20 mg/ kg loading dose, followed by 10 mg/kg i.v. infusion 8 hourly + Doxycycline 100 mg p.o. 12 hourly/ Clindamycin 600 mg bd Exchange transfusion if parasitemia >10%

| Dengue / DHF

Dengue virus serotypes 1–4 | Bite of Aedes mosquitoes | Dengue fever: headache, retro-orbital pain, myalgia, rash

Dengue fever with warning signs:Pain abdomen

DHF: thrombocytopenia, skin, mucosal and gastrointestinal bleeds, rise in hematocrit. Hepatomegaly is common

Dengue shock syndrome. Weak pulse, cold clammy extremities, pulse pressure <20 mmHg, hypotension | Nonstructural protein 1 antigen detection (< 5 days)

IgM, serology: (> 5 days)

Single IgG titer > 1:1280 (90% sensitive and 98% specific) | Isotonic fluid to maintain effective circulation; guided by serial hematocrit determinations

Blood / platelet transfusion: overt bleeding/ rapid fall in hematocrit

Supportive therapy |
| Enteric fever

Salmonella typhi, serovar paratyphi A, B or C | Oral, through contaminated food and water | Week 1: fever, headache, relative bradycardia

Week 2: abdominal pain, diarrhea, constipation, hepatosplenomegaly, jaundice and encephalopathy. Week 3: GI bleeding, perforation, MODS | Blood culture (1st week)

Typhidot: (2nd week onwards) Bone marrow cultures— during / after t/t | Ceftriaxone i.v. 50–75 mg/kg/ day for 10–14 days Alternative: Azithromycin and ciprofloxacin |

Leptospi-rosis Leptospira interrogans	Direct contact of skin or mucosa with water contaminated with urine or body fluid of an infected animal.	Biphasic illness, (a) Anicteric lep-tospirosis: abrupt onset of fever, chills, head-ache, myalgia, abdominal pain, conjunctival suffusion, skin rash. (b) Weil's disease: (5–15%) Jaundice, proteinuria, he-maturia, oliguria and/or anuria, pulmonary hem-orrhages, ARDS, myocarditis. Hepatomegaly	Culture (blood, cerebrospinal fluid, urine) Serology IgM ELISA (> 7 days) Microscopic agglutination test (gold std)	Penicillin G 1.5 MU 6 hourly for 7 days Alternative: Third genera-tion cephalo-sporin. Oral Doxycy-cline (100 mg bd X 7 d)
Scrub typhus Orientia tsut-sugamushi	Bite of chig-gers (larva of trombiculid mite)	Fever, head-ache, myalgia, ARDS, deliri-um, vomiting, cough, jaundice. Hepatomegaly Eschar (30-50%)	ELISA IgM (>7days) Widal : false positive PCR: confirma-tory	Doxycycline 100 mg BD for 7 d Azithromycin or Rifampicin Chloramphen-icol (safe in severe liver dysfunction)
He-mophago-cytic lymphohis-tiocytosis (post viral EBV, HSV, dengue) Pots parasit-ic infections	Genetic pre-disposition	Fever, hepato-splenomegaly, lymphadenopa-thy, neurological manifestations	Cytopenias, elevated LDH, triglycerides and FDPs. Serum ferritin, (>1000, highly suggestive) Bone marrow: hemophagocy-tosis	High-dose dexamethasone, etoposide, and cyclosporine A

Amoebiasis Entameba histolytica	Feco–oral transmission	Pain right upper abdomen, right lower chest, fever, tender hepatomegaly Encephalopathy and jaundice (rarely)	ELISA or IHA: 90% sensitive USG: amoebic liver abscess	Metronidazole 500 mg IV tid X 14d or 800mg tid PO X 14d Alternatively, Chloroquine phosphate 600 mg stat , 300mg POX 2–3 weeks
Sepsis syndrome Gram negative or gram positive organisms, fungi	Community acquired or hospital acquired	Fever, localizing symptoms of infection such as cough, dysuria etc. Later MODS	SIRS with positive Blood culture	Fluids and appropriate antimicrobials

Management strategy:

The management strategy in patients having tropical jaundice is aimed at treating the underling cause and supporting the liver till recovery occurs. (76)

Since the febrile patient may be vomiting and not having adequate fluid the management stars by accessing the hydration status and hydrate using isotonic fluids. Fever is the most disturbing symptom and needs to be brought down. One can safely use antipyretics for control of fever and paracetamol is the preferred agent but one has to be careful as frequent, high dose may lead to potential hepatotoxicity. Liberal use of cold sponging may be beneficial. Although malarial infection is the most common cause of tropical hepatopathy empiric use antimalarials is not indicated. (76) rapid diagnostic tests to rule out malaria have a very high negative predictive value for ruling out malarial infection at the bedside, however, when in doubt, a thick and a thin smear should be performed to rule out malaria. (76) Artesunate based combination therapy is the drug of choice for complicated malaria. Alternatively quinine can also be used. For uncomplicated vivax malaria, chloroquine followed by primaquine is the treatment of choice.

Antibiotics should routinely be given in a patient with fever and jaundice to cover for Enteric fever, Leptospirosis, Scrub typhus, the commonest of the tropical infections. Third generation cephalosporins (Injection ceftriaxone 2 g IV BD) for 7 to 10 days are required . Doxycycline 100 mg BD or Azithromycin 500mg OD can also be used. In patients with severe hepatic dysfunction chloramphenicol IV is a safe and effective drug and covers most of the pathogens. (76)

In patients having encephalopathy indistinguishable from FHF, oral/IV N Acetyl cystine (NAC) at a dose of 140 mg/kg, followed by 70 mg/kg Q4 h for upto 16 doses can be safely given. Although there is no study to support its use in tropical jaundice but I has shown to be beneficial in patients with ALF/FHF. (9, 77)

Supportive therapy is the cornerstone for treatment for very sick patients. Patients should be watch for development of multiorgan dysfunction, with careful watch on urine output, blood pressure, seizures, encephalopathy and bleeding. Blood and blood products should be liberally transfused if there is high risk of bleeding. One must use local guidelines for transfusing platelets in thrombocytopenic patients at high risk of bleeding . (76) Prophylactic platelet transfusion in dengue is not indicated even if the platelet count is less than 10,000. (76)

Table 3: Management strategy in patients presenting with Fever with jaundice

- Access hydration status
    - hydrate using isotonic fluids
- Antipyretics for control of fever.
    - Paracetamol is preferred but high dose may be avoided in view of potential hepatotoxicity
- Antimalarials
    - Empiric use is not indicated
    - Artesunate/ quinine 9for Pf if RDT or peripheral smear is positive
    - Chloroquine for uncomplicated Pv
- Antibiotics: (to cover for Enteric fever/Leptospirosis/Scrub typhus/ Brucellosis)
    - Injection ceftriaxone 2 g IV BD
    - Tablet doxycycline 100 mg BD
    - Inj / tab Azithromycin 500mg OD
    - Alternative : chloramphenicol is safe if severe dysfunction
    - Watch for urine output, seizures, encephalopathy, bleeding
- Blood and blood products
    - FFP/cryoprecipitate for bleeding (Level III)
- For encephalopathy:
    - Oral/IV NAC at a dose of 140 mg/kg, followed by 70 mg/kg Q4 h X 16
    - Supportive T/T

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