



# Tropical Infections in the ICU

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## Abstract

Certain arthropod-borne infections are common in tropical regions because of favorable climatic conditions. Water-borne infections like leptospirosis are common due to contamination of water especially during the monsoon floods. Infections like malaria, leptospirosis, dengue fever and typhus sometimes cause life threatening organ dysfunction and have several overlapping features. Most patients present with classical clinical syndromes: fever and thrombocytopenia are common in dengue, malaria and leptospirosis; coagulopathy is frequent in leptospirosis and viral hepatitis. Hepatorenal syndrome is seen in leptospirosis, falciparum malaria and scrub typhus. The pulmonary renal syndrome is caused by falciparum malaria, leptospirosis, Hantavirus infection and scrub typhus. Fever with altered mental status is produced by bacterial meningitis, Japanese B encephalitis, cerebral malarial, typhoid encephalopathy and fulminant hepatic failure due to viral hepatitis. Subtle differences in features of the organ failure exist among these infections. The diagnosis in some of these diseases is made by demonstration of antibodies in serum, and these may be negative in the first week of the illness. Hence empiric therapy for more than one disorder may be justified in a small proportion of cases. In addition to specific anti-infective therapy, management of organ dysfunction includes use of mechanical ventilation, vasopressor drugs, continuous renal replacement therapy and blood products. Timely transfer of these patients to well-equipped ICUs with experience in managing these cases can considerably decrease mortality and morbidity. ©

## INTRODUCTION

Certain infections are commoner in the tropics due to climatic conditions that favor arthropod vectors like mosquitoes, or to exposure to contaminated water.

Patients present with certain well defined syndromes like fever with thrombocytopenia, fever with hepatorenal dysfunction or fever with pulmonary-renal dysfunction.

### FEVER AND THROMBOCYTOPENIA

Diseases that commonly present with fever and thrombocytopenia are malaria (usually falciparum but also vivax), dengue fever, leptospirosis, rickettsial infections and viral fevers

Thrombocytopenia occurs due to immune destruction, bone marrow suppression, DIC and sometimes hypersplenism. Drugs like quinine can cause thrombocytopenia by immune mechanisms. The platelet counts can fall to as low as  $5000/\text{mm}^3$  predisposing the patient to life threatening bleeding in the central nervous system or from the gastrointestinal and genitourinary tracts. Regular platelet transfusions to maintain a count of at least  $20000/\text{mm}^3$  should be given until the

thrombocytopenia resolves.

Both malaria and leptospirosis usually have an associated derangement of the PT and APTT whereas dengue usually presents with thrombocytopenia. In a Mumbai study of patients with severe falciparum malaria<sup>7</sup> 38% had thrombocytopenia of which 6% required platelet transfusions. The same study showed that 7% had a DIC requiring blood component therapy.

### FEVER WITH HEPATORENAL DYSFUNCTION

Diseases that predominantly present with hepatorenal dysfunction are falciparum malaria, leptospirosis, scrub typhus and hepatitis E or A with fulminant hepatic failure and the hepatorenal syndrome. In pregnant patients hepatitis E commonly produces FHF. Patients are at increased risk of bleeding due to decreased clotting factor production by the liver, DIC due to liver failure and infection, and uremia-induced platelet dysfunction. Continuous renal replacement therapy helps not only to clear the blood of uremic toxins but also helps remove excess bilirubin and other substances normally detoxified by the liver.

Renal failure in patients with severe malaria presents with oliguria whereas patients with leptospirosis usually have a non-oliguric renal failure with hypokalemia due to tubular dysfunction. Patients who

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present with hepatorenal dysfunction are often treated for both malaria and leptospirosis until either 3 smears for malarial parasites are negative or leptospira antibody tests come positive. In a study published from Mumbai<sup>7</sup> the incidence of renal failure in patients with severe falciparum malaria was 30% with a mortality of 50%. 30% of these patients required dialytic therapy. In the same study hepatic failure occurred in 26% of patients with a 49% mortality. A study again from Mumbai showed that 70% of patients with severe leptospirosis had renal failure and 80% of those who died had intra-alveolar hemorrhages.<sup>11</sup>

## FEVER WITH PULMONARY RENAL SYNDROME

Diseases that present with pulmonary-renal dysfunction are falciparum malaria, leptospirosis, hantavirus infection, scrub typhus and severe pneumonias due to Legionella and the pneumococcus. Malaria causes an ARDS type of syndrome whilst leptospirosis can cause ARDS or alveolar hemorrhage which is due to a combination of alveolo-capillary injury and thrombocytopenia. The X-ray in patients with leptospirosis often shows dense pulmonary infiltrates due to the hemorrhage. A useful distinguishing feature between malaria and leptospirosis is the presence of significant conjunctival hemorrhages in the latter. In the Mumbai study quoted above respiratory failure occurred in 26% of patients with severe falciparum malaria and 90% of these patients died.

## FEVER WITH ALTERED SENSORIUM

Important diseases to consider are cerebral malaria, encephalitis, meningitis and typhoid fever besides diseases like brain abscess and septic encephalopathy. Elderly patients with UTI or pneumonia often present with altered sensorium and few other clinical signs.

**Other Important Infections** are tropical pyomyositis and enteric fever. Enteric fever can present with multiorgan dysfunction and septic shock.

## SPECIFIC INFECTIONS

### FALCIPARUM MALARIA

#### Pathophysiology

*P. falciparum* infects RBCs of all ages. The parasite avoids splenic sequestration and destruction of infected RBC's. This occurs by the formation of knobs on the RBC membrane.<sup>1,2</sup> These knobs appear about 16 hours into the asexual cycle and attach to specific receptors like ICAM-1 on the endothelium of capillaries in the brain, chondroitin sulfate in the placenta and CD36 in other organs.<sup>3,4</sup> The infected RBCs also attach to uninfected RBCs by a process called as rosetting. The attachment to the endothelium of the capillaries and the rosetting

causes the blockage of capillaries and venules and leads to end-organ dysfunction. The infected cells eventually rupture and the contents cause macrophages to release cytokines like TNF-alpha, which cause a febrile response. T Helper cells appear to play an important role in the immune response. Temperatures >40° C damage parasites and cause synchronization of the parasitic cycle leading to a tertian fever pattern.

Infected individuals that survive develop a species and strain specific immunity that is both cellular and humoral in nature. A study in South Africa revealed that HIV positive patients with CD4 counts <200 had more severe infections compared to HIV negative controls.<sup>6</sup>

#### Clinical features of severe falciparum malaria:<sup>5,8</sup>

Prognosis is related to the number of organ systems involved with a study showing 6-7% mortality with single organ failure and 40-50% with involvement of two or more organs.<sup>7</sup> This study also showed secondary bacterial sepsis is the major cause of death after day 7 in patients with severe malaria

**Cerebral malaria** : Usually manifests as a diffuse symmetric encephalopathy without focal signs. Patients often have extensor posturing and upgoing plantars. Seizures may occur especially in children and cerebral venous thrombosis or cerebral infarcts may be found. Cerebral malaria has a mortality of 30% in a series from a major public hospital.<sup>7</sup>

**Acute renal failure** : The etiology involves microcirculatory abnormalities in the kidneys and patients develop acute tubular necrosis that initially is oliguric in nature. Massive intravascular hemolysis can cause hemoglobinuria which also damages the tubules. These patients often require hemodialysis or CRRT to deal with the metabolic derangements of a hypercatabolic state.

**Acute respiratory failure** : A noncardiogenic pulmonary edema often develops about 4 days after therapy has been started.<sup>7</sup> The pathogenesis involves release of cytokines that increase capillary permeability. In this setting fluid administration should be guided by either CVP or PCWP monitoring in order to prevent worsening of the oxygenation status.

**Hepatic dysfunction** : Jaundice results from a combination of hemolysis, cholestasis and hepatocyte dysfunction. Rarely hepatocyte dysfunction may be severe enough to cause hypoglycemia, coagulopathy, encephalopathy and lactic acidosis.

**Hypoglycemia** : This occurs due to reduced gluconeogenesis (and in the case of the liver reduced glycogenolysis), increased utilization of glucose by both the host and the parasite and the use of insulin secretagogues like quinine. Hypoglycemia may contribute to CNS injury.

**Acidosis** : Lactic acidosis is secondary to increased anaerobic glycolysis in tissues with sequestered parasites, increased lactate production by parasites, decreased lactate clearance by the liver and kidneys and hypotension.

**Hematologic derangements** : Severe parasitemia can lead to a rapid fall in the hematocrit which if severe enough can give the urine a cola colour due to the presence of free hemoglobin. Besides anemia, severe thrombocytopenia with platelet counts  $<20,000/\text{mm}^3$  may contribute to bleeding from the GI and GU tracts. DIC is common in severe malaria.

**Poor prognostic indicators** : Deep coma, convulsions, shock, anuria, hypoglycemia  $<45\text{-}50\text{ mg/dl}$ , Lactate  $>5\text{ mmol/L}$ , creatinine  $>3.0\text{ mg/dl}$ , platelets  $<50,000/\text{mm}^3$ , PCV  $<15\%$  bilirubin  $>3.0\text{ mg/dl}$ , AST and ALT  $>3\text{X}$  normal, parasitemia  $>100,000/\text{microlitre}$  in non-immune individuals

**Diagnosis** : Thick and thin peripheral smears for degree of parasitemia and speciation.

Tests for detecting *P. falciparum* antigens. e.g. pfHRP-2 or LDH in blood from a finger prick. These tests use monoclonal antibodies to capture the parasite antigens and are read out as coloured bands. Immunofluorescent microscopy and PCR are newer techniques for detection of malaria

**Treatment** : IV quinine, IV artesunate or I.M artemether. Doxycycline may be added as an adjunct if malarial resistance to quinine or artemether derivatives is suspected. Treat hypoglycemia, blood and platelet transfusions, ventilatory therapy for ARDS and renal replacement therapy for oliguric renal failure. In a randomized study from Vietnam, Phu et al found that patients with severe malaria treated by continuous renal replacement therapy (CRRT) had a faster clearance of acidosis and azotemia when compared to patients on peritoneal dialysis. The patients on CRRT had a lower mortality and CRRT was more cost effective when compared to peritoneal dialysis.

## LEPTOSPIROSIS

This is a spirochetal disease caused by *Leptospira interrogans*. The spirochetes also infect rats, dogs, cattle, sheep and swine. Infection occurs due to exposure to contaminated water. The disease has an incubation period of 2-26 days with an average of 10 days.

### Pathobiology relevant to the ICU

Most patients have a nonspecific febrile illness, but in a few the disease manifests with a severe illness characterized by hepatorenal dysfunction often with pulmonary hemorrhage, called as Weil's syndrome.<sup>9,10</sup> This usually develops 4-9 days into the illness. The leptospire directly or through immune mechanisms

damage blood vessels, cause centrilobular necrosis of the liver and renal tubular dysfunction by causing an interstitial nephritis and acute tubular necrosis. Renal function recovers completely by 6 months in most individuals.

**Clinical features** : Patients characteristically have conjunctival suffusion or hemorrhages and uveitis, severe muscle tenderness and non-oliguric renal failure with hypokalemia.

Besides severe hepatorenal dysfunction, patients can present with ARDS, myocarditis, rhabdomyolysis, thrombocytopenia, DIC, hemorrhage into the skin and internal organs, uveitis, and digital gangrene.

An outbreak in Mumbai in 2000 revealed that 35% of patients had pulmonary manifestations. 80% of patients who died had pulmonary hemorrhages and 70% had renal failure. Patients with conjunctival suffusion and pulmonary renal failure were more likely to be MAT positive.<sup>11</sup>

**Laboratory findings** : The white cell count is often  $<10,000$  ranging from 3-26000. Urinalysis shows proteinuria, pyuria, granular casts and microscopic hematuria. The CPK is often elevated, CSF may show an aseptic meningitis like picture and the chest x-ray often shows dense confluent shadows suggestive of pulmonary hemorrhage.

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. Other serologic tests being the ELISA and a commercially available dot test which detects IgM antibody by an enzyme based dot immunoassay with a sensitivity of 30% at 3 days and of 100% at 10 days into the illness.<sup>12,13</sup>

The organism can be grown from the blood and the CSF in the first two weeks of the illness and from the urine in the third week onwards for upto a month.

Since the antibodies may not be demonstrable in serum during the first week of illness, initial treatment is often empirical. In some patients it is virtually impossible to differentiate between severe malaria and leptospirosis; this dilemma is compounded by the fact that the seasonal variation in the incidence of these two disorders is identical (Fig. 1). These patients may receive treatment for both disorders on admission. We usually discontinue antimalarial treatment if several blood smears for malarial parasites over the next 48 hours are negative.

Treatment involves the use of crystalline penicillin at a dose of 6 million units daily or ceftriaxone 1 gram every 12 hourly.<sup>14,15</sup> In penicillin allergic patients intravenous doxycycline 100 mg every 12 hourly can be used. Since rickettsial diseases can mimic leptospirosis ceftriaxone or doxycycline should be used when the

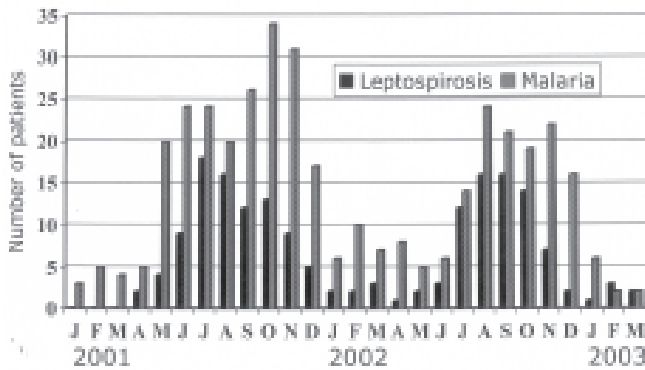


Fig. 1 : Seasonal variation in admissions due to leptospirosis and malaria in the medical ICU of King Edward Memorial Hospital, Mumbai between January 2001 and March 2003. Note the marked increase in admissions between June and November. Also note that cases of both disorders peak and decline at more or less the same time of the year.

diagnosis is in doubt.<sup>16</sup>

Other therapy involves supportive measures like dialysis, ventilation and the use of blood products.

## DENGUE FEVER

An arbovirus disease transmitted by the bite of the Aedes mosquito. The virus initially replicates in the skin and lymph nodes before dissemination in the blood stream.<sup>17,18</sup>

**Pathophysiology** : The virus has an incubation period of 4-7 days though can range from 3-14 days.

Usually it is a nonspecific febrile illness but certain factors can predispose to severe manifestations like dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS).

These factors are :

- Infection with dengue virus serotype 2<sup>19</sup>
- Age less than 11 years<sup>20</sup>
- Good nutritional status (since severe manifestations are related to the host immune response, malnourished individuals are less prone to a vigorous immune reaction to the virus)<sup>21</sup>
- Subsequent infection with a different viral serotype due to antibody dependant enhancement (ADE) of viral entry into monocytes and macrophages, increased antigen-antibody complexes with subsequent vascular injury and increased T cell responses with immune activation.<sup>17,22</sup>

ADE occurs due to persistence of cross reacting antibodies from the previous infection. These antibodies are unable to neutralize viruses from different serotypes but after binding to the viruses enhance uptake via the Fc receptors on monocytes and macrophages with subsequent T cell activation.

The cascade of cytokines then causes endothelial injury, platelet and clotting factor consumption and increased vascular permeability.

A study from Mumbai showed that predictors of DSS in children were younger age, altered sensorium, paralytic ileus and significantly deranged PT. This same study showed a case fatality of 17% in DSS.<sup>23</sup>

There are 3 main clinical subsets of dengue infection<sup>18</sup>

### Nonspecific febrile illness, classic dengue and dengue hemorrhagic fever/dengue shock syndrome

Classic dengue presents with fever and severe headache and myalgias. Giving it the name of 'breakbone fever'.<sup>24</sup> There may be associated lymphadenopathy, pharyngeal and ocular congestion and respiratory or GI symptoms. The fever lasts for 4-5 days and around the time of defervescence about half of patients develop a maculopapular rash that lasts 2-3 days and may be pruritic. Rarely there may be myocarditis, hepatitis, pneumonitis and bleeding into internal organs.

Dengue hemorrhagic fever and dengue shock syndrome occur due to increased capillary permeability and vasodilatation 3-7 days after start of illness, caused by mediators like TNF alpha and IL-1 released from infected monocytes and macrophages. The capillary leak explains the rise in the hematocrit, periorbital edema pleural effusions and ascites.

Capillary leak and thrombocytopenia may give a positive capillary test which is more than 20 petechiae in an area of 1 inch<sup>2</sup> when the blood pressure cuff is inflated midway between systolic and diastolic blood pressure for 5 minutes.<sup>25</sup> Shock often occurs 24 hours before or after defervescence supporting a role for immune mediated injury. The shock lasts for a day or two and patients either die or get better. Encephalopathy, GBS and Acute transverse myelitis have also been associated with dengue virus infection.<sup>26,27</sup>

Leukopenia occurs due to a direct suppressant effect on the bone marrow. Thrombocytopenia occurs mainly due to increased platelet destruction by adsorption of virus or antigen-antibody complexes on the platelet surface with subsequent immune destruction.<sup>24</sup>

A coagulopathy may occur due to consumption of coagulation factors due to DIC, liver dysfunction and molecular mimicry between the viral proteins and coagulation factors.

Liver injury may occur due to direct invasion by the virus or due to immune mediated injury.

**Prognostic factors**: BP < 90/60, hematocrit > 50 %, platelet count < 50,000 bleeding other than petechiae e.g. ecchymoses, hematemesis or epistaxis

## Diagnosis<sup>18</sup>

- a. The gold standard is the detection of antibodies by hemagglutination inhibition assay showing at least a four fold rise in titre of neutralizing antibody in paired samples.
- b. ELISA test for IgM antibodies which appear around the 6<sup>th</sup> day of illness and last from 1-3 months. IgG antibodies appear after 7-10 days and last for months to years, they too can be detected by ELISA. In secondary dengue IgG antibodies are present in high titre early in illness
- c. Virus isolation techniques, which are not easily available
- d. RT-PCR :Detection of the virus within 1-2 days of manifestations with test being negative later in the illness

**Treatment** : Shock is treated with crystalloids like Dextrose normal saline/Normal saline or Ringer's Lactate given 10-20 ml/kg over 30 minutes then every hour until pulse, BP, CVP and urine output normalize. Then the infusion rate is reduced. In profound shock initially colloids like hetastarch or hemaccel may be used. In a study in children with dengue shock syndrome, although a marginally longer time to initial recovery was seen with Ringer's Lactate, it was as effective as dextran 70 and hetastarch in fluid resuscitation and significantly more adverse events were encountered with the dextran solution.<sup>28</sup>

Platelet transfusions need to be given for symptomatic thrombocytopenia.

## HANTAVIRUS INFECTION

This bunyavirus infects vascular endothelium and causes two major syndromes: Hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS). The virus is acquired by exposure to aerosols of rodent urine and saliva and also feces. The disease is found in the US, South America, Europe, Russia and China. A study from Vellore revealed a prevalence of 15% amongst patients who had presented with a febrile illness.<sup>29</sup> Its manifestations can closely mimic either dengue or leptospirosis and hence deserves mention.<sup>30</sup>

### Pathophysiology

Virus infection of the endothelium does not result in significant injury. Like dengue it is the immune response against viral antigens expressed on the endothelial cells in the heart, lungs, kidneys and lymphoid organs that causes most of the damage. This immune response is mediated by T cells and macrophages which release cytokines like TNF-alpha and IL-1 beta which increase capillary permeability and cause leakage of protein rich fluid into the interstitium. Nitric oxide release by TNF plays an important role in the vasodilation underlying

the shock state. The virus may however damage renal tubules.<sup>31,32</sup>

### Cardiopulmonary syndrome

The incubation period is about 3 weeks, the illness begins with non specific constitutional symptoms that last about 3-7 days, and this is then followed by a capillary leak syndrome that lasts 2-8 days causing hypotension and shock. Leak into the pulmonary bed causes a noncardiogenic pulmonary edema that can lead to rapid hypoxia, arrhythmias and arrest. There may be a separate oliguric phase lasting 3-8 days which precedes a polyuric phase lasting for a variable period of time.<sup>33</sup>

Thrombocytopenia, leucocytosis (upto 90,000/mm<sup>3</sup>) with a left shift and increased immunoblasts (upto 10% of circulating lymphocytes) with an increased LDH is characteristic<sup>34</sup> and should prompt diagnosis with more specific tests like the ELISA for IgM and IgG antibodies.<sup>35</sup>

Treatment is mainly supportive with the use of IV fluids, inotropes, mechanical ventilation, extra-corporeal membrane oxygenation and blood products.<sup>36</sup> The use of the nucleoside analogue ribavirin has not been shown to have significant benefit in HCPS.<sup>37</sup>

### Hemorrhagic Fever with Renal Syndrome-HFRS

The manifestations of HFRS also have a similar pathophysiological basis as HCPS.<sup>38</sup>

The renal manifestations are more prominent than the pulmonary, and renal injury occurs due to a combination of shock, immune injury and possible direct invasion by the virus, hemorrhagic manifestations may be severe. Non specific constitutional symptoms are followed by shock, oliguria, DIC and hemorrhagic manifestations. Survivors enter a diuretic phase by day 10-14.

Diagnosis involves similar parameters as HCPS, and treatment includes both supportive treatment (including dialytic modalities) and the use of ribavirin.<sup>39</sup>

## SCRUB TYPHUS

This is a rickettsial disease caused by *Orientia tsutsugamushi*.

**Pathophysiology** : The organism is a Gram-negative coccobacillus that infects vascular endothelium with subsequent vascular injury in organs like the skin, liver, kidneys, meninges and brain. The vascular injury causes a DIC with platelet consumption, vascular leak, pulmonary edema, shock, hepatic and renal failure.<sup>40</sup> The organism is inoculated into the skin by the bite of larval forms of trombiculid mites, these larvae are called as chiggers. The disease occurs 7-10 days after the bite and patients present with fever, relative bradycardia,<sup>41</sup> severe myalgias, a nonpruritic maculopapular rash sometimes with an accompanying eschar and

lymphadenopathy. The disease lasts for 2-3 weeks if untreated and complications due to vasculitis in different organs occur usually in the 2<sup>nd</sup> week of illness.

The diagnosis is made by history of exposure, appropriate physical findings, thrombocytopenia, deranged LFTs, elevated creatinine and serology utilizing tests like IFA and ELISA. The Weil Felix reaction is now no longer used as a diagnostic tool.

Treatment is with either chloramphenicol or doxycycline with often a rapid response to therapy. Doxycycline resistant strains may be treated with either chloramphenicol, azithromycin<sup>42</sup> or the addition of rifampicin.

## JAPANESE B ENCEPHALITIS

This is an arbovirus encephalitis caused by a flavivirus that is transmitted to humans by the bite of the culex mosquito. Birds and pigs are the natural hosts of the virus and humans are dead end hosts. The incubation period lasts from 5-14 days.

**Pathophysiology** : Most infections are asymptomatic with about 1 in 25 non immune adults having symptoms. The virus can infect brain parenchyma (especially the thalamus and basal ganglia) of the cerebral hemispheres, the brainstem and the anterior horn cells of the spinal cord.<sup>43</sup> The spectrum of disease can present as a mild flu like illness, aseptic meningitis or severe encephalomyelitis. 60-75% of symptomatic patients present with encephalitis and 5-10% present with meningitis. The case fatality rate is 20-30% and 50-60% of encephalitis survivors have neuropsychiatric sequelae at discharge with a higher incidence of damage in children compared to adults.<sup>44</sup>

After inoculation into the skin the virus replicates in the subcutaneous tissues, the lymphnodes and blood stream before entering the brain. Previous infection due to other flaviviruses like dengue may protect against severe disease due to the presence of protective cross-reacting antibodies.

Factors which govern severe illness include<sup>43</sup>

- Failure to produce neutralizing antibodies
- Genetic susceptibility to infection by flaviviruses
- Advanced age-possibly due to a breakdown in the blood-brain barrier due to cerebrovascular disease
- Neurocysticercosis : due to a breakdown in the blood-brain barrier due to inflammation
- Virulent genotypes of the virus

**Clinical manifestations** : Patients with encephalitis present with altered sensorium, seizures and abnormal posturing. Severe brainstem injury can cause a 'locked-in' state. Involvement of the basal ganglia can present with a parkinsonian syndrome, opisthotonus, choreoathetosis, myoclonic jerks and opsoclonus myoclonus.<sup>43,45</sup>

Flaccid weakness with absent reflexes may occur in 20-60% of patients with encephalitis. This may involve the respiratory and bulbar musculature and occurs due to direct invasion of the anterior horn cells, acute painful retention of urine may be present.

**Investigations** : Nerve conduction studies show reduced or absent compound muscle action potentials with preserved sensory action potentials and normal conduction velocities. EMG is consistent with denervation. Sometimes demyelination may also occur.

Table 1

Disease	Clinical Features	Commonly Used Diagnostic Tests	Treatment
Malaria	Incubation 10-14 days. Regular fever spikes Splenomegaly. Hepatorenal dysfunction or ARDS, thrombocytopenia	Thick and thin smears. Monoclonal antibody dipstick tests for <i>P. falciparum</i> antigens	IV quinine 10mg/kg q8h or IV artesunate 2.4mg/kg IV stat then 1.2 mg/kg at 12 & 24 h. Then 1.2 mg/kg daily for 7days
Leptospirosis	Incubation 8-14 days. Fever, myalgias, conjunctival hemorrhages, hepatorenal dysfunction, pulmonary hemorrhages, thrombocytopenia	Dridot test for IgM antibody. Serum IgM and IgG antibodies proteinuria, hematuria, pyuria	Crystalline penicillin 1.5 mu q6h. Ceftriaxone 1 g IV q 12 h. Doxycycline 100 mg PO/IV q12h
Dengue	Incubation 4-7 days. Fever, severe myalgias, headache, rash, periorbital edema, pleural and peritoneal effusions, shock hemoconcentration, thrombocytopenia, leucopenia	ELISA for IgM and IgG antibodies	No specific therapy
Scrub typhus	Incubation period 7-10 days. Fever with myalgias, rash, eschar, lymphadenopathy, thrombocytopenia, hepatorenal dysfunction, vasculitic manifestations	ELISA for IgM and IgG antibodies	IV Doxycycline IV Azithromycin IV Chloramphenicol
Hanta virus infection	Incubation 3 weeks. Fever with pulmonary edema, hemorrhagic manifestations, acute renal failure, shock, thrombocytopenia, leucocytosis	ELISA for IgM and IgG antibodies	No specific therapy Possibly ribavirin in HFRS.

Initial leucocytosis may be followed by leukopenia. CSF may show a pleocytosis. MRI is more sensitive than CT for showing characteristic lesions involving the thalamus and basal ganglia.<sup>43,44</sup> EEG may show a generalized slowing.

Diagnosis is with an IgM capture ELISA or reverse transcriptase PCR of blood or CSF.<sup>42</sup>

There is no specific treatment available. Trials have shown that interferon alfa or ribavirin are not useful. Seizures and raised ICP should be treated according to standard protocols.<sup>43</sup>

## TROPICAL PYOMYOSITIS

This is a bacterial invasion of skeletal muscle usually due to *Staphylococcus aureus*.

Other bacteria like *Strep pyogenes*, *Strep pneumoniae*, *H. influenzae*, Gram-negative bacteria and anaerobes can also invade muscle, especially in immunocompromised patients.<sup>46</sup>

The pathogenesis involves the seeding of sites of muscle injury following transient bacteremia. PMNs and opsonins play an important role in defending against staphylococcal infections and quantitative or qualitative defects predispose to pyomyositis.<sup>46</sup>

Large skeletal muscles like the thigh, calf, gluteal and shoulder regions are typically involved.

The disease may have 3 stages with the first stage having muscle pain, swelling and low grade fever, the second stage occurs 1-2 weeks later with progressive supuration of the muscle which then may be followed by the third stage where there is bacteremia with possible complications like septic shock, endocarditis, pneumonia, pericarditis, septic arthritis, brain abscess and rhabdomyolysis.<sup>47</sup>

Leucocytosis is often found, blood cultures may be positive for staph and the serum CPK may be raised at times to levels of 4000 U/L

Imaging with MRI or CT will often show abscess formation.<sup>46</sup> These abscesses should be drained and the pus sent for SCABS.

Treatment involves use of antibiotics like cloxacillin 1-2 g IV q 6h or cefazolin 2g IV q 8 h, addition of clindamycin 600-900 mg IV q6-8h in mixed infection and vancomycin in penicillin allergic patients.

Abscess drainage and debridement is essential in the suppurative stage of the disease.

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