Guidelines

Tropical fevers: Management guidelines

From: The Indian Society of Critical Care Medicine Tropical fever Group
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Abstract

Tropical fevers were defined as infections that are prevalent in, or are unique to tropical and subtropical regions. Some of these occur throughout the year and some especially in rainy and post-rainy season. Concerned about high prevalence and morbidity and mortality caused by these infections, and overlapping clinical presentations, difficulties in arriving at specific diagnoses and need for early empiric treatment, Indian Society of Critical Care Medicine (ISCCM) constituted an expert committee to develop a consensus statement and guidelines for management of these diseases in the emergency and critical care. The committee decided to focus on most common infections on the basis of available epidemiologic data from India and overall experience of the group. These included dengue hemorrhagic fever, rickettsial infections/scrub typhus, malaria (usually falciparum), typhoid, and leptospira bacterial sepsis and common viral infections like influenza. The committee recommends a 'syndromic approach' to diagnosis and treatment of critical tropical infections and has identified five major clinical syndromes: undifferentiated fever, fever with rash / thrombocytopenia, fever with acute respiratory distress syndrome (ARDS), fever with encephalopathy and fever with multi organ dysfunction syndrome. Evidence based algorithms are presented to guide critical care specialists to choose reliable rapid diagnostic modalities and early empiric therapy based on clinical syndromes.

Keywords: Tropical fever, Dengue, Malaria, Typhoid, Leptospirosis, Scrub typhus, Sepsis, Influenza, Guidelines

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Introduction

Every year different parts of India are hit by seasonal fevers in the post monsoon period. These fevers include Dengue, Malaria, Scrub Typhus, Leptospirosis, Typhoid fever and some other fevers leading to very high morbidity and mortality. A large number of these patients require intensive care unit (ICU) care like mechanical ventilation, renal replacements therapy, vasopressor support, blood and blood component therapy due to single or multiorgan failure. The clinical picture of these diseases is so overlapping that it is almost impossible to achieve differential diagnosis of these diseases in emergency and ICU settings when the time available for intervention is limited. Indian Society of Critical Care Medicine (ISCCM) was seized of the matter for several years. Given this background, ISCCM decided to develop a consensus statement and guidelines for management of these diseases in ICU.

Methods

An expert committee consisting of scientists, teachers and researchers from India was constituted to discuss this topic, track the literature, share the experience and brainstorm to develop guidelines. The committee included experts from Critical care, Emergency Medicine, Infectious diseases, Internal Medicine, Pediatrics, Microbiology [Appendix 1].

The group of experts after exchanging notes on E-mails

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Table 1: Hierarchy of evidence

Level of evidence	Type of evidence
IA	Evidence from systematic reviews or meta-analysis of randomized controlled trials
IB	Evidence from at least one randomized controlled trial
IIA	Evidence from at least one controlled study without randomization
IIB	Evidence from at least one other type of quasi experimental study
III	Evidence from non-experimental descriptive studies such as comparative studies, correlation studies and case-control studies
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

established a literature bank, which was shared by all the members. Each one shared his inputs on E-mail with all. Thus, a thorough review of literature was done using available resources including PubMed. The scope of review covered both, adults and children, presenting in ICU. This resulted in background resource. Then each expert was allotted a specific topic for discussion from the reviewed literature and preparing a PowerPoint presentation on the same. All experts got together for 2 days for a face to face meeting and had extensive brainstorming, discussion based on literature and PowerPoint presentations prepared by each expert. Inferences were drawn based on the available evidence and expert opinion. Then each expert was further requested to compile recommendations on the topic allotted to him based on the discussions. The recommendations were again shared and discussed on e-meetings. Finally after full 1 year's search, work, brainstorming and coordination, a consensus statement has been arrived which is strongly evidence based.

The levels of evidence used in this guideline are given in Table 1. It is to be noted that the hierarchy of evidence relate to the strength of literature and not to clinical importance.

Tropical diseases were defined as diseases that are prevalent in, or unique to tropical and subtropical regions. The diseases are less prevalent in temperate climates, due in part to the occurrence of a cold season, which controls the insect population by forcing hibernation.[1] Most often disease is transmitted by an insect "bite", which causes transmission of the infectious agent. The Indian subcontinent by its very location represents one of the largest tropical and subtropical regions with many of these infections being prevalent. Some of these occur throughout the year and some are greatly influenced by the seasons (especially rainy season) and geography.[2] On the basis of limited epidemiologic data from the north (Rohtak) and South (Vellore) and overall experience of the group, it was decided to focus on seven most common infections, with reference to other infections wherever appropriate.[3-5] These are dengue, rickettsial infections especially scrub typhus, malaria (usually due to *Plasmodium falciparum*), typhoid and leptospirosis; bacterial sepsis and common viral infections like influenza. It was recognized that occasionally the patients may have concomitant infections and can present with atypical manifestations.[6-8]

The group accepted that management of sick patients with tropical infections must begin as soon as the patient reports to the emergency department/ICU in a hospital. These infections must be suspected in all febrile patients as delay in the institution of specific therapy may lead to increased morbidity and mortality. Since the symptoms of many infections may overlap with one another and with severe bacterial sepsis, it may be very difficult to identify these infections at the time of presentation. Yet, most of the time, empiric therapy needs to be initiated at the outset. There can be no uniform guideline for empiric therapy but trends of tropical infections should guide the treating physician. In a sick patient, the idea is to hit wide and hit early with the intention to deescalate once the definitive diagnosis is established.[9]

Results and Recommendations

The group agreed that a "syndromic approach" to tropical infections can guide the intensivists regarding the commonest etiologies, investigative modalities and help them to choose early empiric therapy. For ease of diagnosis these infections were divided into five major syndromes: undifferentiated fever, fever with rash/thrombocytopenia, fever with acute respiratory distress syndrome (ARDS), fever with encephalopathy and fever with multi organ dysfunction syndrome.[10] Common infections that are likely to cause these syndromes are as follows [Table 2]:

Undifferentiated fever

Malaria (*P. falciparum*), scrub typhus, leptospirosis, typhoid, dengue and other common viral illness.

Fever with rash/thrombocytopenia

Dengue, rickettsial infections, meningococcal infection, malaria (usually *falciparum*), leptospirosis, measles, rubella and other viral exantem.

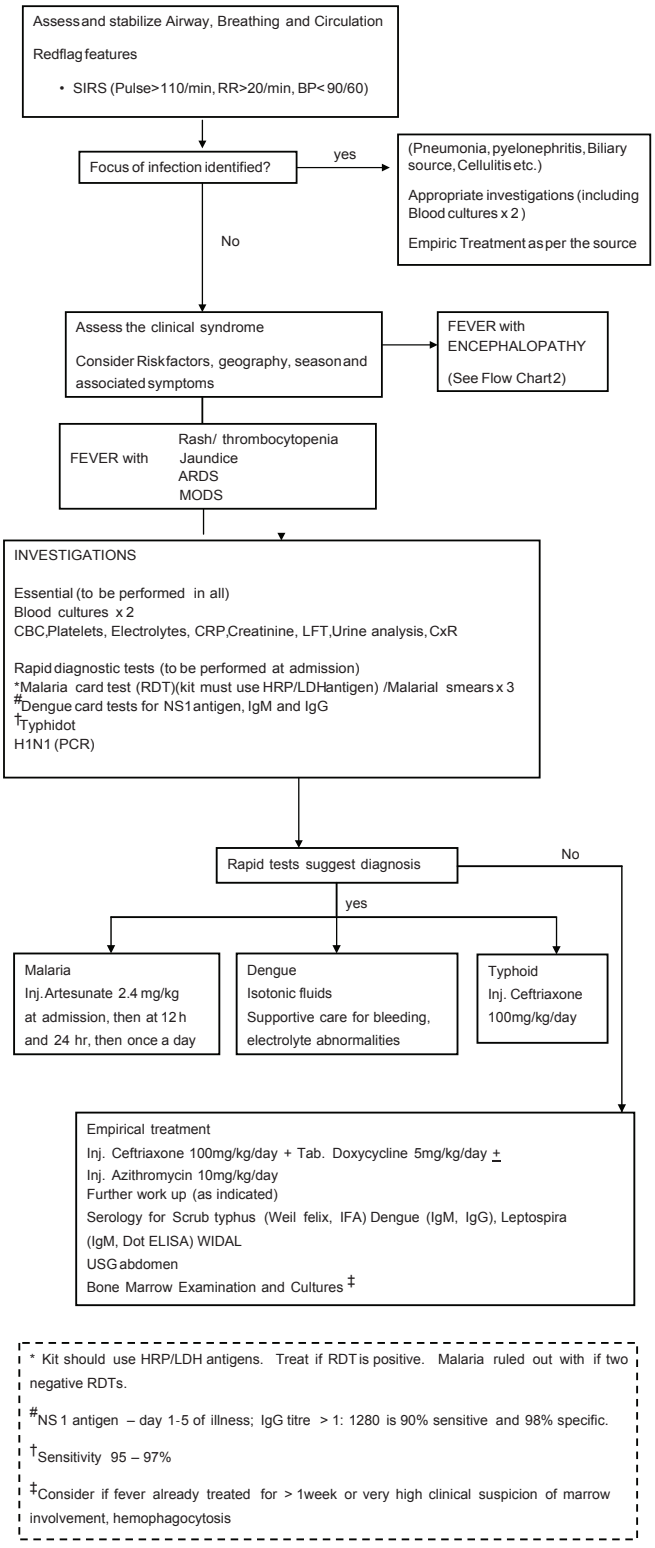
Fever with ARDS

Scrub typhus, *falciparum* malaria, influenza including H1N1, leptospirosis, hantavirus infection, meliodosis,

Table 2: Syndrome based Treatment guidelines for critical tropical infections

Fever with thrombocytopenia	Antipyretics for control of fever IV fluids Avoid aspirin/anticoagulants (Level IV) Watch for bleeding, dyspnea, shock Platelet transfusion if the platelet count<20,000 or clinical bleeding (Level IV) No role of steroids (Level IB) Specific therapy once the diagnosis is established
Fever with jaundice	Antipyretics for control of fever Injection ceftriaxone 2 g IV BD Tablet doxycycline 100 mg BD□ IV fluids Watch for urine output, seizures, encephalopathy, bleeding FFP/cryoprecipitate for bleeding (Level III) Specific therapy once the diagnosis is established
Fever with renal failure	Antipyretics for control of fever Injection ceftriaxone 2 g IV BD* Tablet doxycycline 100 mg BD* IV fluids according to CVP Watch for encephalopathy, bleeding, seizures, ARDS Renal replacement therapy (intermittent HD/CRRT) Specific therapy once the diagnosis is established
Fever with encephalopathy	Antipyretics for control of fever Injection ceftriaxone 2 g IV BD*□ IV acyclovir 10 mg/kg in adults (up to 20 mg/kg in children) intravenously every 8 h IV fluids IV mannitol for raised ICP Watch for seizures Specific therapy once the diagnosis is established
Fever with respiratory distress	Antipyretics for control of fever IV fluids Oxygen by Venturi mask (level IV) Injection ceftriaxone 2 g IV BD* Injection azithromycin 500 mg IV OD* Tablet oseltamivir 150 mg BD, if H1N1 is a possibility (Level IA) Watch for impending respiratory failure, shock, renal failure, alveolar hemorrhage Specific therapy on ce diagnosis is established

□Doxycycline is to be taken empty stomach/1 h before or after a meal. It is contraindicated in pregnant women and young children. *For possible typhoid, leptospirosis and scrub typhus. □For possible bacterial meningitis, typhoid and leptospirosis. FFP: Fresh frozen plasma; CVP: Central venous pressure, ARDS: Acute respiratory distress syndrome, HD: Hemodialysis, CRRT: Continuous renal replacement therapy, ICP: Intracranial pressure



Flow chart 1: An algorithmic approach for the diagnosis and management of critical tropical infections

severe community acquired pneumonias due to *Legionella* spp. and *Streptococcus pneumoniae* and diffuse alveolar hemorrhage due to collagen vascular diseases.

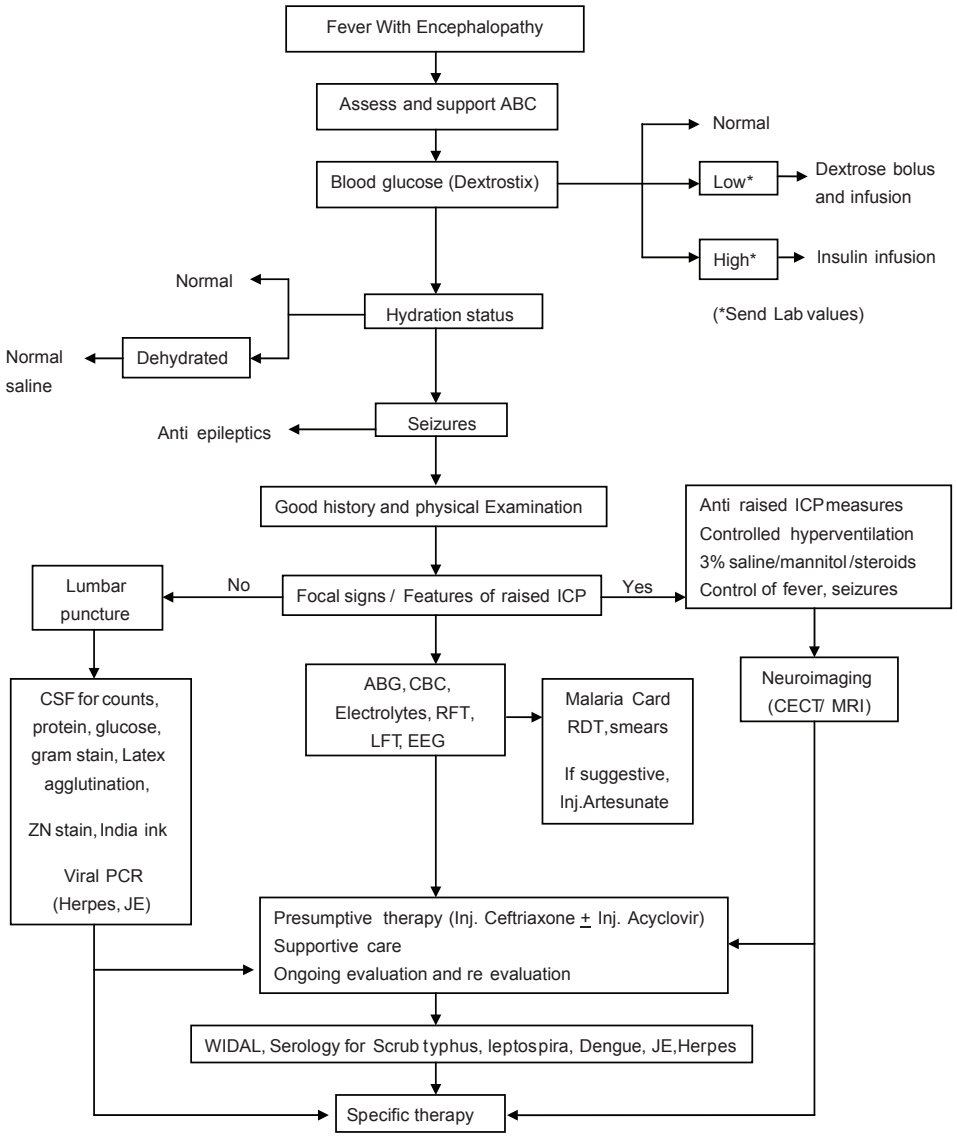
Febrile encephalopathy

Encephalitis (Herpes simplex virus encephalitis, Japanese B and other viral encephalitis), meningitis (*S. pneumoniae, Neisseria meningitidis, Haemophilus influenzae,* enteroviruses), scrub typhus, cerebral malaria and typhoid encephalopathy.

Fever with multiorgan dysfunction

Bacterial sepsis, *falciparum* malaria, leptospirosis, scrub typhus, dengue, hepatitis A or E with fulminant hepatic failure and hepato-renal syndrome, Hanta virus infection, hemophagocytosis and macrophage activation syndrome.

An algorithmic approach for the diagnosis and management of critical tropical infections is given



Flow Chart 2: Algorithmic approach to fever with encephalopathy

in Flow Chart 1 and 2.

Following are the syndrome-based management principles for critical tropical infections.

Specific infections

Salient features of common tropical infections are given below.

Scrub typhus

- Causative organism: *Orientia tsutsugamushi*
- Vector: chiggers (larva of Trombiculid mite).

Outbreaks are reported from all over India starting from the sub-Himalayan belt to more eastern and southern Indian regions.[11-13]

Pathophysiology: The organism infects vascular endothelium with subsequent vascular injury in organs like the skin, liver, kidneys, meninges and brain resulting in multi organ manifestations.

Clinical Features: Incubation period: 1-3 weeks:

- Fever, headache and myalgia, breathing difficulty, delirium, vomiting, cough, jaundice
- Eschar.

Complications: Overwhelming pneumonia with ARDS – like presentation, hepatitis, aseptic meningitis, myocarditis and disseminated intravascular coagulation (DIC).

Lab Diagnosis (Serology):[14]

- Weil-Felix: poor sensitivity and specificity
- Indirect fluorescent antibody: "Gold standard" (Level IIA)
- Enzyme-linked immunosorbent assay (ELISA) for immunoglobulin G (IgG) and IgM antibodies: sensitivity and specificity > 90%.

Treatment:[15,16]

- First line: Doxycycline 100 mg BD for 7 days (Level IA)
- Azithromycin or Rifampicin or chloramphenicol as alternatives in children and pregnant women. (Level IIB).

Leptospirosis

- Causative organism: *Leptospira interrogans*
- Source of infection: Direct contact of skin or mucosa with water contaminated with urine or body fluid of an infected animal.

Peak incidence during the rainy season. Rampant in southern, western and eastern India. Increasing incidence in "non-endemic" northern India.[17,18]

Pathophysiology: Leptospires multiply in the small blood vessel endothelium, resulting in damage and vasculitis and clinical manifestations.

Clinical features: Incubation period: usually 5-14 days but can be 72 h to a month or more.

Biphasic clinical presentation:

- Anicteric leptospirosis
  Abrupt onset of fever, chills, headache, myalgia, abdominal pain, conjunctival suffusion, transient skin rash.
- Icteric leptospirosis (Weil's disease) occurs in 5-15% – Jaundice, proteinuria, hematuria, oliguria and/or anuria, pulmonary hemorrhages, ARDS, myocarditis.

Diagnosis:[19,20]

- Raised creatine phosphokinase levels, Culture (blood, cerebrospinal fluid (CSF), urine)
- Positive serology
- Microscopic agglutination test (Sensitivity 30-63%, specificity > 97%)
- IgM ELISA (Sensitivity 52-89%, specificity > 94%).

Treatment:[21,22]

- First line: Penicillin G 1.5 MU 6 hourly for 7 days (Level IA)

Alternative: Third generation cephalosporins. Oral Doxycycline in uncomplicated infections.

Plasma exchange, corticosteroids and intravenous (i.v.) Ig in selected patients (Level III) in whom conventional therapy does not elicit a response.

Dengue

Causative organism: Dengue virus (Flavivirus) serotypes 1-4.

Vector: *Aedes* mosquitoes:

Dengue is endemic throughout India with a recent resurgence of epidemics over the past two decades.[23]

Pathogenesis:

- Cross-reactive (but non-neutralizing) anti-dengue antibodies from previous infection enhance newly infecting strain with viral uptake of monocytes and macrophages
- Amplified cascade of cytokines and complement activation
- Endothelial dysfunction, platelet destruction and consumption of coagulation factors, Plasma leakage and hemorrhagic manifestations.

Clinical features: Incubation period 4-10 days:[24]

- Dengue fever

Headache, retro-orbital pain, myalgia, arthralgia, rash

- Dengue Hemorrhagic fever
  Thrombocytopenia (<100,000), skin, mucosal and gastrointestinal bleeds, third spacing, rise in hematocrit
- Dengue shock syndrome
  Weak pulse, cold clammy extremities, pulse pressure < 20 mmHg, hypotension
- Expanded dengue syndrome

Encephalitis, myocarditis, hepatitis, renal failure, ARDS, hemophagocytosis.

Diagnosis:

- Nonstructural protein 1 antigen detection (Rapid card test) – Sensitivity 76-93%, Specificity >98%.[25]
- IgM, IgG serology (IgG titer > 1:1280 is 90% sensitive and 98% specific).

Treatment:[26]

- Isotonic fluid infusion just sufficient to maintain

effective circulation during the period of plasma leakage; guided by serial hematocrit determinations. (Level IA)
- Blood transfusion is done only with overt bleeding/ rapid fall in hematocrit.

Malaria

Causative organism: *Plasmodium protozoa* (*P. falciparum, Plasmodium vivax, Plasmodium malariae* [Odisha]).

Vector: *Anopheles* mosquito.

Plasmodium species are unevenly distributed across India. Orissa, Chhattisgarh, West Bengal, Jharkhand and Karnataka contribute the most to the endemicity.[27]

Pathophysiology:
- Mechanical microcirculatory obstruction caused by cytoadherence to the vascular endothelium of parasitized RBC and sequestration
- Intra-vascular hemolysis.

Clinical features:

Paroxysm of fever, shaking chills and sweats occur every 48 or 72 h, depending on species. Hepatosplenomegaly may be present.

Manifestations of severe malaria:[28]
- Cerebral malaria (sometimes with coma)
- Severe anemia
- Hypoglycemia
- Metabolic acidosis
- Acute renal failure (serum creatinine > 3 mg/dl)
- ARDS
- Shock ("algid malaria")
- DIC
- Hemoglobinuria
- 10. Hyperparasitemia (>5%).

Diagnosis:
- Microscopy: Thick smears – parasite detection; Thin smears– species identification
- Quantitative buffy coat test
- Rapid diagnostic tests (RDTs) – histidine rich protein, lactate dehydrogenase antigen based immune-chromatography (Level IA)
  Sensitivity and specificity > 95%
  Malaria ruled out if two negative RDTs.[29]

Treatment:[28]
- Drug of choice: Artesunate (Level IA)
- Dose: 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.

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 is recommended in place of doxycycline in pregnant women and children.(Level IA) Exchange transfusion is a treatment option for parasitemia > 10%.(it is not recommended with Artesunate, Level IIA).

Enteric fever
- Causative organism: *Salmonella typhi,* serovar paratyphi A, B or C
- Transmission: focally contaminated food and water
- Most prevalent in urban areas, with high incidence in children 15 years of age and younger.[30]

Pathophysiology: Bacteria spread throughout the reticulo-endothelial system and in areas of greatest macrophage concentration such as the Peyer's patches.

Clinical features: Incubation period 1-14 days.

Manifestations:
- 1st week - fever, headache, relative bradycardia
- 2nd week - Abdominal pain, diarrhea, constipation, hepatoslenomegaly, encephalopathy
- 3rd week - Intestinal bleeding, perforation, MODS.

Diagnosis:[31]
- Typhidot (RDT) – Sensitivity 95-97%, Specificity > 89%, Level III
- Widal test-non-specific
- Blood culture – Gold standard, positive in 40-80% of patients
- Bone marrow cultures – sensitivity 80-95%; may remain positive even after 5 days of pre-treatment.

Treatment:[32]
- First line: Ceftriaxone i.v. 50-75 mg/kg/day for 10-14 days (Level IA) to cover MDR S. typhi.
- Azithromycin and Ciprofloxacin are alternatives

Consider dexamethasone 3 mg/kg followed by 1 mg/kg 6 hourly for 48 h in selected cases with encephalopathy, hypotension or DIC (Level IB).

Japanese encephalitis

Causative organism: Japanese encephalitis virus,

Vector: *Culex tritaeniorhynchus.*

Prevalent in Southern, central and North-Eastern Indian states such as Uttar Pradesh, Haryana, Bihar, Maharastra, Andhra Pradesh and Tamil Nadu.[33]

Pathophysiology: Virus reaches the central nervous system through leukocytes and affects various parts of the brain to cause vascular congestion, microglial proliferation, formation of gliomesenchymal nodules, focal or confluent areas of cystic necrosis and cerebral edema.

Clinical features: Incubation period averages 6-8 days, with a range of 4-15 days.

Prodromal period-fever, headache, vomiting and myalgia.

Neurological features[34] - range from mild confusion to agitation to overt coma. Parkinson like extrapyramidal signs are common, including masklike facies, tremor, rigidity and choreoathetoid movements.

Diagnosis:

IgM capture ELISA Serum: sensitivity 85-93%, Specificity 96-98%, CSF: Sensitivity 65-80%, Specificity 89-100%.

Treatment:

Supportive-Airway management, seizure control and management of raised intracranial pressure.

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Appendix 1

ISCCM tropical fever Expert Committee

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