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A 32-year-old male patient was admitted with high-grade fever for 7 days, fatigue and tiredness for around 6 days, jaundice for 2 days, and confusion for 1 day. He had history of travel to a seaside resort 10 days ago. He was drowsy, confused, disoriented, and icteric; hepatomegaly was present. There was an erythematous rash on both the shins.

Severe infection with multiorgan involvement is one of the most common cause of ICU admission in tropical countries. Close monitoring and supportive therapy is the mainstay of treatment in most of these infections, but some of them have specific therapies. Rapid identification of treatable infection is imperative for a better outcome.

Step 1: Initial assessment and resuscitation

- Fluid resuscitation is the mainstay of initial management in most of the tropical infections as they present late, have predominant diarrheal component, and are usually dehydrated.
- Close monitoring for volume overload and pulmonary edema should be done.
- Recent trial conducted in Africa on a pediatric population with severe sepsis have shown fluid loading may be detrimental in this population.
- Patients presenting with encephalopathic syndromes need airway assessment and assisted ventilation.
- While resuscitation is going on, send investigations:
 - Complete blood count—neutropenia is a common feature in many tropical infections. Leptospirosis typically has leukocytosis.

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Table 51.1 Tropical infections presenting as fever

Malaria
Typhoid
Dengue fever
Leptospirosis
Chikungunya
Viral hepatitis A and E
Typhus
Tuberculosis
Brucellosis
Hepatic amebiasis
Visceral leishmaniasis
Parasitic hyperinfection (<i>Strongyloides</i>)
Relapsing fever
Viral hemorrhagic fever
Yersiniosis
Plague
Tularemia
Trypanosomiasis

- C-reactive protein (CRP).
- Malarial parasite (MP), dual malarial antigen.
- Dengue antigen and serology (IgM).
- Blood, urine, and sputum cultures as appropriate.
- Leptospira antibody (IgM).
- Widal test, blood culture.
- Liver and renal profile.
- Depending on local epidemiology, further specific investigations for appropriate organisms should be done.

Step 2: Take focused history

- Tropical infections can have a variety of nonspecific presentations and generalized constitutional symptoms.
- Specific symptoms characteristic of some organisms should be carefully looked for.
- Fever:
 - Many tropical infections have febrile episodes, which are nonspecific (Table 51.1). Rarely, fever pattern can be diagnostic, such as alternate-day fever in tertian malaria (vivax or falciparum) and saddle back biphasic fever (dengue). Biphasic fever with the first phase lasting 5–7 days is followed by a second febrile phase for 1–2 days.
- Anorexia and weight loss:
 - History of severe weight loss is present in some tropical infections such as tuberculosis, visceral leishmaniasis, brucellosis, giardiasis, and schistosomiasis.

- Diarrhea and vomiting:
 - Acute watery diarrhea is a presenting feature of cholera, *Giardia*, rotavirus, *Cryptosporidium*, *Isospora*, and *Bacillus cereus* (toxin).
 - Bloody diarrhea occurs in amebic dysentery, enteroinvasive and enterohemorrhagic *Escherichia coli*, *Shigella*, *Salmonella*, *Yersinia*, *Clostridium perfringens*, and *Campylobacter*.
 - Chronic diarrhea (>2 weeks) is characteristic of giardiasis, amebiasis, ileocecal tuberculosis, strongyloidiasis, schistosomiasis, and *Trichuris* infestation.
- Abdominal pain:
 - Acute abdomen with features of peritonitis may be present in typhoid perforation and ruptured amebic liver abscess.
 - Other tropical infections presenting as acute abdomen are amebic liver abscess, splenic rupture (malaria, typhoid), biliary colic (*Ascaris*), intestinal obstruction or volvulus (*Ascaris*), acute salpingitis (*Chlamydia*), and severe gastroenteritis.
- Jaundice:
 - Jaundice with fever may be a presenting feature of certain tropical infections such as viral hepatitis, leptospirosis, typhus, typhoid, yellow fever, brucellosis, amebic liver abscess, miliary tuberculosis, malaria (hemolysis—G6PD deficiency), ascending cholangitis (*Ascaris*), and hemolytic uremic syndrome (*Shigella*, *E. coli*).
- Cough and dyspnea:
 - These may be prominent in infections such as extensive pulmonary tuberculosis, amebic lung abscess, acute respiratory distress syndrome (leptospirosis, malaria), diffuse intra-alveolar hemorrhage (dengue, leptospirosis, hemorrhagic fever), pulmonary hydatid disease, paragonimiasis, and pneumonic plague.
- Headache:
 - Most febrile illnesses—especially malaria, typhoid, and dengue fever—are accompanied by headache.
- Sore throat:
 - Severe sore throat with painful swallowing is characteristic of *Corynebacterium diphtheriae* infection, though rare due to vaccination programs.
- Hematuria, dysuria, and renal colic:
 - Some tropical infections such as schistosomiasis, renal tuberculosis, and chlamydial urethritis can present with hematuria.
- History of skin rash (*see Step 3*).
- Travel history: A list of places visited in recent past in chronological order should be elicited. Endemic infections in different geographical areas should be considered in differential diagnosis.
- Occupational history: Exposure to contaminated water source may be a clue to leptospirosis.
- Seasonal variation: Many tropical infections have propensity to occur during the monsoon season.
- Rash: Presence and distribution of rash can point toward different infections.
- Animal exposure: pet dogs (ticks—ricketsial infection).

Step 3: Perform focused physical examination

- General examination: Examine for anemia, lymphadenopathy, jaundice, and edema.
- Skin: Many tropical infections present with skin manifestations, and these should be searched meticulously:
 - Maculopapular rash—dengue, typhus, measles, and rubella
 - Urticaria—strongyloidiasis and schistosomiasis
 - Petechial rash—typhus, meningococemia, and viral hemorrhagic fever
 - Vesicles—chicken pox, herpes simplex, and herpes zoster
 - Eschar—typhus
- Abdomen: Examine for hepatosplenomegaly and abdominal distension:
 - Predominant hepatomegaly—viral hepatitis, amebic liver abscess, leptospirosis, yellow fever, and brucellosis.
 - Predominant splenomegaly—malaria, typhoid, typhus, visceral leishmaniasis, and hydatid disease.
 - Abdominal distension could be due to ascites (tuberculosis) or dilated bowel loops (*Shigella* dysentery).
- Cardiorespiratory system:
 - Relative bradycardia is a feature of typhoid and typhus fever.
 - Pleural effusion (tuberculosis).
 - Appearance of new murmurs—especially regurgitant—and infective endocarditis.
- Central nervous system:
 - Confusion and decreased conscious level: cerebral malaria, typhoid, dengue fever, leptospirosis, typhus, rabies, and viral hemorrhagic fever
 - Predominant encephalitic features: arbovirus, herpes simplex, measles, chickenpox, yellow fever, and rabies
 - Predominant meningitic feature: enterovirus, tuberculosis, amebiasis, and strongyloidiasis, bacterial
 - Seizures: cerebral malaria, schistosomiasis, neurocysticercosis, tuberculoma, and cerebral hydatid
- Eyes: conjunctival infection, petechiae (leptospirosis and typhus), viral infection.

Step 4: Send investigations

These should be sent on the basis of initial presentation and suspected infection.

- Presenting syndrome
 - *Fever with a rash*: dengue serology, platelet count, chikungunya serology, meningococcal serology, rickettsial serology, Widal test (typhoid), Epstein–Barr virus serology
 - *Fever with hepatorenal dysfunction*: malaria parasite thick and thin blood film and antigen, *Leptospira* antibody, hepatitis E and A (hepatitis serology), sputum for acid-fast bacilli (disseminated tuberculosis), Widal test, blood cultures
 - *Fever with severe sepsis and multiorgan failure*: malaria antigen, MP smears, *Leptospira* serology, dengue serology, *Legionella* serology, varicella and influenza serology

- *Fever with decreased level of consciousness—specific investigation:* MP smear and antigen; lumbar puncture; CT scan for tubercular meningitis, pyogenic meningitis, and viral encephalitis; herpesvirus serology and PCR

- Specific tests

- *Dengue*

- ELISA test for IgM antibodies (positive day 6)—IgG antibodies appear after 7–10 days and last for months to years. In the secondary dengue, IgG antibodies are present in high titer early in illness.
- The gold standard test is the detection of antibodies by hemagglutination inhibition assay showing at least fourfold rise in titer of neutralizing antibodies in paired samples.
- Dengue NS 1 antigen which becomes positive in 4–5 days.

- *Leptospirosis*

- Serology with the microscopic agglutination test is the gold standard with either a fourfold rise in titers between acute and convalescent serum or a single titer of more than 1:800 being diagnostic.
- Other serological tests are 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.
- Polymerase chain reaction (PCR) test for *Leptospira* antigen shows considerable promise.

- *Malaria*

- Three thick and thin smears 12–24 h apart should be obtained. The highest yield of peripheral parasites occurs during or soon after a fever spike; however, smears should not be delayed while awaiting fever spikes.
- Thick smears are 20 times more sensitive than thin smears, but speciation may be more difficult. The parasitemia can be calculated based on the number of infected RBCs.
- Thin smears are less sensitive than thick smears but facilitate speciation. This should be considered a qualitative test.
- The quantitative buffy coat is a technique that is as sensitive as thick smears.
- Malarial antigen—immunochromatographic tests based on antibodies to malarial antigen like histidine-rich protein-2 (PfHRP2), parasite LDH (pLDH), or plasmodium aldolase appear to be very sensitive and specific.

- Rickettsial infection

- Look for eschar
- Serology for typhus fever

- Special investigations

- Procalcitonin, ESR, CRP.
- Aspirates, scrapings, and pustular fluid may be obtained for Gram staining and culture. When a herpes simplex virus infection is suspected, a Tzanck test may be performed by unroofing a lesion and taking a scraping of the lesion base.

- Biopsy samples from nonhealing or persistent purpuric lesions: Biopsy of inflammatory dermal nodules, ulcers, and muscles (tropical pyomyositis) should be done.
- HIV serology.
- Imaging: chest x-ray, echo, ultrasound of abdomen, and CT scan (when indicated).

Step 5: Start general supportive care and specific organ support (see Chap. 79)

- Many tropical infections are self-limiting. Close monitoring and general organ support in the initial days or weeks of viremia or parasitemia will salvage many patients.

Step 6: Initiate empirical therapy based on initial presentation

- Specific therapy is available only for a few tropical infections.
- Depending on the clinical presentation and endemicity of a particular infection in the geographical region, an educated guess for initial therapy has to be decided till definitive investigations are available.
- Usually, intravenous ceftriaxone, 2 g IV twice daily, to cover typhoid fever and leptospirosis is started if MP and dual antigen is negative.
- In patients with shock and MODS, broad-spectrum antibiotics should be started immediately. De-escalate antibiotics once specific infection is identified.

Step 7: Start specific treatment once the diagnosis is confirmed

- Dengue
 - A protocol for intravenous fluid therapy has been developed by the World Health Organization (WHO).
 - An initial bolus of 5% dextrose in normal saline or Ringer lactate (20 mL/kg of body weight) is infused over 15 min, followed by continuous infusion (10–20 mL/kg/h, depending on the clinical response) until vital signs and urine output normalize.
 - Crystalloids are equally effective as colloids in fluid resuscitation.
 - Normalization of the hematocrit is an important goal of early fluid repletion.
 - However, a normal or low hematocrit may be misleading in patients with overt bleeding and severe hypovolemia.
 - Close clinical observation is essential, even after normal blood volume is restored, because patients can develop shock for 1–2 days after initial fluid resuscitation, which represents the period of increased vascular permeability in dengue hemorrhagic fever.
 - Management of fever:
 - Control fever with paracetamol, cold sponging, and cold IV fluids.
 - Avoid aspirin and nonsteroidal anti-inflammatory drugs due to bleeding risk and risk of developing Reye syndrome (encephalopathy).
 - Manage shock and multiorgan failure.
 - Manage secondary infections.

- Manage complications.
- Platelet transfusions need to be given for symptomatic thrombocytopenia.
- Platelet transfusions have not been shown to be effective in preventing or controlling hemorrhage but may be warranted in patients with severe thrombocytopenia ($<10,000/\text{mm}^3$) and active bleeding. Prophylactic platelet transfusions in patients with severe thrombocytopenia but without active bleeding are generally not recommended.
- Manage complications of fluid therapy in dengue fever.
- A decrease in hematocrit together with stable hemodynamic status and adequate urine output indicates hemodilution and/or reabsorption of extravasated fluids.
- Judicious use of intravenous fluids with proper monitoring is recommended.
- Fluid therapy may have to be discontinued if required, immediately, to avoid pulmonary edema, electrolyte imbalance, hypo- or hypernatremia, and hyperchloremic metabolic acidosis.
- Leptospirosis
 - Treatment involves the use of crystalline penicillin at a dose of six million units daily or ceftriaxone 1 g every 12 h.
 - In penicillin-allergic patients, intravenous or oral doxycycline, 100 mg every 12 h, can be used.
 - Manage shock, disseminated intravascular coagulation, and multiorgan failure.
- Falciparum malaria
 - For *Plasmodium falciparum* infections acquired in areas without chloroquine-resistant strains, patients should be treated with oral chloroquine. A chloroquine dose of 600 mg base (=1,000 mg salt) should be given initially, followed by 300 mg base (=500 mg salt) at 6, 24, and 48 h after the initial dose for a total chloroquine dose of 1,500 mg base (=2,500 mg salt).
 - For chloroquine-resistant strains, treatment options are as follows:
 - Quinine sulfate: Quinine has a rapid onset of action and, in combination with tetracycline, doxycycline, or clindamycin, it has been shown to be a very efficacious treatment option for *P. falciparum* infections acquired in regions with chloroquine-resistant strains.
 - Artemisinin derivatives clear parasites very rapidly, are now a key component of malaria treatment worldwide, and have been shown to reduce mortality in severe malaria compared with parenteral quinine. Artemisinin-based combination therapies, including artesunate–mefloquine, artemether–lumefantrine, artesunate–amodiaquine, and dihydroartemisinin–piperaquine, are highly efficacious.
 - Under the CDC protocol, intravenous artesunate is administered in four equal doses of 2.4 mg/kg of body weight over a period of 3 days. The dosing schedule recommended by the WHO entails doses every 12 h on day 1 and then once daily.
 - Up to 7 days of therapy may occasionally be indicated in very ill patients.

Suggested Reading

1. Maitland K, Kiguli S. Mortality after fluid bolus in African children with severe infection. *N Engl J Med.* 2011;364(26):2483–95.
Fluid boluses significantly increased 48-h mortality in critically ill children with impaired perfusion in the resource-limited settings in Africa.
2. Hess KM, Goad JA. Intravenous artesunate for the treatment of severe malaria. *Ann Pharmacother.* 2010;44(7–8):1250–8.
Three major studies regarding the use of intravenous artesunate are reviewed. Several international studies comparing intravenous quinine and artesunate conclude that artesunate has the highest treatment success, with lower incidence of adverse events.
3. World Health Organization. Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. 3rd ed. Geneva: World Health Organization; 2008.
4. World Health Organization. Guidelines for prevention and control of leptospirosis. Geneva: World Health Organization; 2006.
5. World Health Organization. Guidelines for malaria Geneva: World Health Organization; 2010.
6. Chawla V, Trivedi TH, Yeolekar ME. Epidemic of leptospirosis: an ICU experience. *J Assoc Physicians India.* 2004;52:619–22.
Leptospirosis is an important infection with high mortality when associated with organ dysfunction. The poor prognostic factors are preponderance of male sex, alcohol dependence, age group more than 50 years, MODS, acute respiratory distress syndrome (ARDS), presence of acidosis, and need for mechanical ventilation.

Websites

1. www.thehtd.org
The Hospital for Tropical Diseases is dedicated to the prevention, diagnosis, and treatment of tropical diseases and travel-related infections.
2. www.who.int/topics/tropical_diseases
An extensive repository on guidelines for many tropical infections