

# **Quarterly Medical Review**

**Vol 59, No. 2, April- June 2008**

## **Fever in General Practice**

Dr Sandhya Kamath

Professor & Head, Department of Medicine

Topiwala National Medical College & B Y L Nair Charitable Hospital, Mumbai

### **INDEX**

Sr No	Topic
1.	General Considerations
2.	Leptospirosis
3.	Dengue Fever
4.	Typhoid Fever
5.	Malaria
6.	Chikungunya
7.	Avian Influenza
8.	Fever with Rash

***“Fever - a symptom of more than 300 diseases, a manifestation of man's protest against the insults and intrusions to his system.”***

Fever also known as pyrexia describes an increase in internal body temperature. Fever is not a disease but a symptom of disease.

Normal human body temperature is  $36.8 \pm 0.7$  °C or  $98.2 \pm 1.3$  °F in the oral cavity.

Fever is most accurately characterized as a temporary elevation in the body's thermoregulatory set-point, usually by about 1–2°C. Fever differs from hyperthermia, which is an increase in body temperature over the body's thermoregulatory set-point (due to excessive heat production or insufficient thermoregulation, or both).

Fever is present if:

- temperature in the anus (rectum/rectal) or in the ear (otic) is at or over 38.0°C (100.4°F)
- temperature in the mouth (oral) is at or over 37.5°C (99.5°F)
- temperature under the arm (axillary) is at or over 37.2°C (99.0°F)

The above values given are for an otherwise healthy, non-fasting adult, dressed comfortably, indoors, in a room that is kept at a normal room temperature, during the morning, but not shortly after arising from sleep. Furthermore, for oral temperatures, the subject must not have eaten, drunk, or smoked anything in at least the previous fifteen minutes.

### **Variations in Normal Body Temperature**

Body temperature normally fluctuates over the day, with the lowest levels at 4 a.m. and the highest at 6 p.m. Therefore, an oral temperature of 37.5°C (99.5°F) would strictly be a fever in the morning, but not in the afternoon. Normal body temperature may differ as much as 0.4°C (0.7°F) between individuals or from day to day. In women, temperature differs at various points in the menstrual cycle, and this can be used for family planning (although it is only one of the variables of temperature). Temperature is increased after meals, and psychological factors (like the first day in the hospital) also influence body temperature.

Children develop higher temperatures with activities like playing, but this is not fever because their set-point is normal. Elderly patients may have a decreased ability to generate body heat during a fever, so even a low-grade fever can have serious underlying causes in geriatrics

### **Mechanism of Fever**

Temperature is regulated in the hypothalamus, in response to PGE<sub>2</sub>. PGE<sub>2</sub> release, in turn, comes from a trigger, which is a pyrogen. The hypothalamus generates a response back to the rest of the body, making it increase the temperature set-point.

**Hyperthermia:** is an increase in temperature above the thermoregulatory set-point.  
**Hypothermia:** is a decrease in temperature below the thermoregulatory set-point.

### **What is a Pyrogen?**

A pyrogen is a substance that induces fever. These can be either internal (endogenous) or external (exogenous). The bacterial substance lipopolysaccharide (LPS) is an example of an exogenous pyrogen.

### **Endogenous Pyrogens**

The cytokines (such as interleukin 1) are a part of the innate immune system, produced by phagocytic cells, and cause the increase in the thermoregulatory set-point in the hypothalamus. Other examples of endogenous pyrogens are interleukin 6 (IL-6), and the tumor necrosis factor-alpha.

These cytokine factors are released into general circulation where they migrate to the circumventricular organs of the brain, where the blood-brain barrier is reduced. The cytokine factors bind with endothelial receptors on vessel walls, or interact with local microglial cells. When these cytokine factors bind, they activate the arachidonic acid pathway.

### **Exogenous Pyrogens**

One model for the mechanism of fever caused by exogenous pyrogens includes LPS, which is a cell wall component of gram-negative bacteria. An immunological protein called lipopolysaccharide-binding protein (LBP) binds to LPS. The LBP-LPS complex then binds to the CD14 receptor of a nearby macrophage. This binding results in the synthesis and release of various endogenous cytokine factors such as interleukin 1 (IL-1), interleukin 6 (IL-6) and the tumor necrosis factor-alpha. In other words, exogenous factors cause release of endogenous factors, which, in turn, activate the arachidonic acid pathway.

### **PGE2 release**

PGE2 release comes from the arachidonic acid pathway. This pathway (as it relates to fever), is mediated by the enzymes phospholipase A2 (PLA2), cyclooxygenase-2 (COX-2), and prostaglandin E2 synthase. These enzymes ultimately mediate the synthesis and release of PGE2.

PGE2 is the ultimate mediator of the febrile response. The set-point temperature of the body will remain elevated until PGE2 is no longer present. PGE2 acts on neurons in the preoptic area (POA) through the EP3 subtype of PGE receptors and the EP3-expressing neurons in the POA innervate the dorsomedial hypothalamus (DMH), the rostral raphe pallidus nucleus in the medulla oblongata (rRPa) and the paraventricular nucleus of the hypothalamus (PVN). Fever signals sent to the DMH and rRPa lead to stimulation of the

sympathetic output system, which evokes non-shivering thermogenesis to produce body heat and skin vasoconstriction to decrease heat loss from the body surface. It is presumed that the innervation from the POA to the PVN mediates the neuroendocrine effects of fever through the pathway involving pituitary gland and various endocrine organs.

### **Hypothalamus response**

The brain ultimately orchestrates **heat effector mechanisms**. These may be

- increased heat production by increased muscle tone, shivering and hormones like epinephrine.
- prevention of heat loss, such as vasoconstriction.

The autonomic nervous system may also activate brown adipose tissue to produce heat (non-exercise-associated thermogenesis, also known as non-shivering thermogenesis), but this seems mostly important for babies. Increased heart rate and vasoconstriction contribute to increased blood pressure in fever.

### **Types of Fever**

According to one common rule of thumb, pyrexia (fever) is generally classified for convenience as:

- low grade: 38–39°C (100.4–102.2°F)
- moderate: 39–40°C (102.2–104.0°F)
- high-grade: 40–42°C (104.0–107.6°F)
- hyperpyrexia: over 42°C (107.6°F)

The last is a medical emergency because it approaches the upper limit compatible with human life.

Generally fever types cannot be used to find the underlying cause. However, there are specific fever patterns that may occasionally hint at the diagnosis:

- **Pel-Ebstein fever:** A specific kind of fever associated with Hodgkin's lymphoma, being high for one week and low for the next week and so on. However, there is some debate as to whether this pattern truly exists.<sup>[1]</sup>
- **Continuous fever:** Temperature remains above normal throughout the day and does not fluctuate more than 1°C in 24 hours, e.g. lobar pneumonia, typhoid, urinary tract infection, brucellosis, or typhus. Typhoid fever may show a specific fever pattern, with a slow stepwise increase and a high plateau.
- **Intermittent fever:** Elevated temperature is present only for some hours of the day and becomes normal for remaining hours, e.g. malaria, kala-azar, pyaemia, or septicemia. In malaria, there may be a fever with a periodicity of 24 hours (*quotidian*), 48 hours (*tertian fever*), or 72 hours (*quartan fever*, indicating *Plasmodium vivax*). These patterns may be less clear in travelers.

- **Remittent fever:** Temperature remains above normal throughout the day and fluctuates more than 1°C in 24 hours, e.g. infective endocarditis.
- **Saddle Back:** Patient has fever for 1-2 days, followed by remission for 2-3 days and then relapse of fever e.g. dengue
- **Double Quotidian:** Patient gets two spikes of fever every day, generally once in the morning and once in the evening. It may be a feature of miliary tuberculosis
- **Inverse fever:** The temperature rises in the early hours of morning rather than in the evening, seen in some cases of miliary tuberculosis.

Febricula is a mild fever of short duration, of indefinite origin, and without any distinctive pathology.

### Causes of Fever

- Infectious diseases, e.g. influenza, common cold, HIV, malaria, infectious mononucleosis, leptospirosis, dengue, enteric fever, urinary tract infections, respiratory tract infections, pneumonia
- Skin inflammations, e.g. boils, pimples, acne, or abscess.
- Immunological diseases, e.g. systemic lupus erythematosus, sarcoidosis, inflammatory bowel diseases.
- Tissue destruction, which can occur in hemolysis, surgery, infarction, crush syndrome, rhabdomyolysis, cerebral hemorrhage, etc.
- Drug fever
  - directly caused by the drug, e.g. lamictal, progesterone, or chemotherapeutics causing tumor necrosis.
  - as an adverse reaction to drugs, e.g. antibiotics or sulfa drugs.
  - after drug discontinuation, e.g. heroin withdrawal.
- Cancers, e.g. Hodgkin disease.
- Metabolic disorders, e.g. gout or porphyria.
- Thrombo-embolic processes, e.g. pulmonary embolism or deep venous thrombosis.

Persistent fever which cannot be explained after repeated routine clinical inquiries, is called fever of unknown origin.

### Fever - History of the illness

Like in any other illness, a detailed history plays a vital role in making a diagnosis. Attention should be paid to the following details:

- Onset - Sudden / insidious / unnoticed. Sudden onset of fever is due to acute infections. Pneumococcal pneumonia is one cause of fever of sudden onset.
- Type - Sustained / intermittent / remittent / relapsing
- Duration

- Associated complaints - head ache, body ache, running nose, rashes, sore throat, cough,
- Chest pain, breathlessness, dysuria, frequency of micturition, diarrhoea, vomiting, abdominal pain,
- Pain / redness of limbs, swellings, joint pains etc.
- Weight loss is common with infections like tuberculosis, malignancies
- Contacts with infections especially tuberculosis is very important in our country.
- Occupation
- Travel - Trekking / endemic areas
- Stay ( hotel, hostel, ashram, hospital)
- Habits
- Past history
- Treatment history - Transfusions, injections, allergies, medications, hospital interventions
- Sexual practice

### **Fever - Examination**

On General Examination of a patient of fever, one should look for the following:

1. Temperature - Oral preferred, record for 3 minutes
2. Pulse - For every 1<sup>o</sup> rise in temperature, pulse increases by 10. Pulse - temperature dissociation is seen in typhoid, brucellosis, leptospirosis, viral myocarditis, diphtheria, rheumatic carditis, bacterial endocarditis.
3. BP - Hypotension signifies septic shock
4. Respiratory Rate – tachypnea - For every 1<sup>o</sup> rise in temp., respiratory rate rises by 4. Higher RR signifies pneumonia, bronchitis, pulmonary oedema or some respiratory cause of fever. Tachypnea is also seen in sepsis.
5. Breathlessness - Bronchitis, pulmonary oedema, ARDS
6. Prostration indicates severe infection
7. Sensorium - Altered sensorium could be due to fever, metabolic disturbances, CNS involvement
8. Nails - Anemia, jaundice, cyanosis, haemorrhages
9. Lymph nodes - Cervical, axillary, inguinal
- 10 Oral cavity - Thrush, palatal haemorrhages, dental sepsis, oral hygiene, tonsils, pharynx, ulcers, pallor, jaundice

11. Skin Rashes - haemorrhagic/ non haemorrhagic, purpura, lymphangitis, cellulitis, pallor, jaundice

12. Eyes - Injection of conjunctivae, jaundice, pallor, papilloedema

### **Fever - Systemic Examination**

Careful and detailed systemic examination is very important in all cases of fever. All systems should be carefully examined since the infection or the cause of fever could be lurking inside any system. What to look for during systemic examination and what could be the inference is given in Table 1.

**Table 1**

#### **Systemic Examination in Fever**

<b>System</b>	<b>What to look for</b>	<b>Possibilities</b>
Upper Respiratory Tract	Oral cavity for tonsils, pharynx, dental sepsis; sinuses for tenderness; ears for swollen membrane, perforation, discharge	Tonsillitis, pharyngitis, sinusitis, ASOM, CSOM etc.
Respiratory System	Tachypnoea, diminished breath sounds, Bronchial breathing, crepitations, rhonchi, rub, dullness	Pneumonia, bronchitis, cavities, pleurisy, effusion, empyema
Abdomen	Tenderness, organomegaly, free fluid, mass	Hepatitis, splenomegaly in various infections, intra abdominal abscesses, peritonitis
Cardio Vascular System	Heart rate, murmurs, pericardial rub	Endo /peri / myo carditis
Central Nervous System	Altered sensorium, neck stiffness, ocular fundii, deficits	Meningitis, encephalitis, Brain abscess
Musculo Skeletal	Muscular tenderness in shoulders, gluteals, calf; joint pain, swelling, tenderness; spine tenderness	Dengue, Leptospirosis; arthritis, myositis etc.
Genitalia	Scrotum, testes, vagina, cervix	Orchitis, pyocele, balanoposthitis, STDs, abscess
Per Rectal	Perianal abscess, prostate & seminal vesicles	Perianal abscess, prostatitis, seminal vesiculitis
Pelvic Examination		PID

**Duration of Fever and Approach:**

The differential diagnosis of fever of less than 7 days duration is given in Table 2 and that of more than 7 days duration is given in Table 3.

**Table 2**

**Fever of less than 7 days duration**

<b>Duration</b>	<b>What is to be done</b>	<b>Possibilities</b>
< 3 Days It is the beginning!	<ul style="list-style-type: none"> <li>- If in a endemic malaria area - Do MP test in ALL cases, and administer presumptive antimalarial treatment to everybody</li> <li>- Suggestive symptoms &amp; signs - Manage accordingly</li> <li>- Only fever, nothing else - Treat symptomatically</li> <li>- Symptoms &amp; signs of severe illness - admit &amp; investigate</li> <li>- Investigations: Blood count; urine analysis, particularly in a female; MP test</li> </ul>	Viral fever Malaria URTI LRTI UTI Any other
3 days to 7 days	<ul style="list-style-type: none"> <li>- Old case - Clinical review</li> <li>- New case - Detailed examination</li> <li>- Typical symptoms &amp; signs - Manage accordingly</li> <li>- No signs - Administer antimalarials, if not already done and investigate</li> <li>- Invetigations: Blood count, urine analysis, MP</li> <li>- repeat, ? Blood culture, ? Chest X Ray</li> </ul>	All above Enteric Fever

**Table 3**

**Fever - 7 days to 15 days**

<b>Symptom</b>	<b>Possibilities</b>
Head ache	Sinusitis, Otitis, dental sepsis, malaria, subacute meningitis

Cough	Tonsillitis, pneumonia, bronchitis, malaria, Tuberculosis.
Chest pain	Pleural effusion / empyema, pericarditis, liver abscess, root pain
Diarrhoea	Enteric fever, colitis, drug induced
Pain abdomen	Hepatitis, liver abscess, appendicitis, PID, other intra abdominal sepsis

**Signs:** Specifically look for lymph nodes, jaundice, anemia, chest signs, abdominal tenderness, organomegaly, free fluid, neck stiffness etc.

**Consider:** Prolonged viral fever (infectious mononucleosis, C.M.V., H.I.V.); malaria; enteric fever; tuberculosis; partially treated or resistant infections

**Investigations:** Blood count, ESR, Urine analysis, MP test, Widal, serological tests for EBV, CMV, Leptospira, amebiasis, rickettsiae; Chest X ray, Ultra sound abdomen

### **Fever - Empirical Therapy**

Empirical therapy should be avoided as far as possible. However, on certain demanding situations, one may have to resort to empirical treatment. Some examples are given below:

**Presumptive therapy for malaria:** For ALL cases of fever in a malarious area or in a visitor to malarious area. Only the first full dose of chloroquine should be used for presumptive treatment and second line drugs should be avoided. In areas with known resistance to chloroquine, pyrimethamine/sulfadoxine can be added.

**Empirical antimicrobial therapy:** Severe sepsis, shock, severe neutrophilic leukocytosis, immunocompromised patients F.U.O. are indications to start empirical broad spectrum antibacterial therapy (to cover Gram positive, Gram negative and anaerobes). Examples include 3rd generation cephalosporins + Aminoglycosides + Metronidazole OR Pseudomonas specific penicillins / cephalosporins + Metronidazole.

**Empirical antitubercular therapy:** This can be used when all investigations are negative and there is reasonable doubt about Tuberculosis, particularly in areas where tuberculosis is common. Only INH and Ethambutol should be used in this therapeutic trial (since other antitubercular drugs like rifampicin and streptomycin are effective against other bacterial infections as well). A fair trial for up to 8 weeks should be given and if the disease is indeed tuberculosis, the patient will show signs of recovery and may become afebrile.

**Empirical steroids:** It can be tried only when all infections are ruled out and reasonable doubt of autoimmune syndromes exists.

### **Viral Fevers**

**Examples:** Influenza, Parainfluenza, Adeno, Rhino, RSV, Corona, Mumps, Measles, Rubella, Rota, Hepatitis, Herpes group; Enteroviruses like Polio, Coxsackie A,B and Echo; Arbo viruses like Encephalitis, Dengue, K.F.D.

**Common symptoms:** Body ache, head ache, back ache, coryza, rashes, diarrhoea, conjunctival injection, pharyngitis, palatal haemorrhages, lymphadenopathy, hepatosplenomegaly etc.

**Diagnosis:** Atypical lymphocytosis, serology, culture

**Treatment and Course:** Most viral infections are self limiting. Only reassurance and supportive treatment are enough. In some infections like the ones with the Herpes group, antiviral agents like acyclovir can be used in early infection. Anticipate complications in patients with haemorrhagic rashes, muscular tenderness, severe prostration etc.

### **Leptospirosis**

It is a zoonosis with a world wide distribution caused by spirochetes of the genus leptospira.

**Etiologic Agent** Leptospire are long, thin motile spirochetes. They may be free-living or associated with animal hosts and survive well in fresh water, soil, and mud in tropical areas. Organisms are antigenically complex, with over 200 known pathogenic serologic variants. They have identified 13 named and 4 unnamed species of pathogenic leptospire.

### **Epidemiology:**

The major vectors to man are rodents. **Transmission** occurs through direct or indirect transmission from a mammalian host. Indirect transmission via contact with *Leptospira* contaminated water or soil, is thought to be responsible for most cases.

Associated positively with –

- Walking barefoot in contaminated soil.
- Gardening in soil
- Wet soil around home
- Refuse around home-chawls, slums
- Rats visible around home
- Activities in forest, farm, paddy sowing, sugarcane crops
- Washing in streams

**Clinical Features** Symptoms include fever, headache, chills, muscle aches, vomiting, jaundice, anemia, and sometimes a rash. The incubation period usually is 7 days, with a range of 2-29 days. The disease has a biphasic course with: 1) Septicemic phase, & 2) Immune phase

**Faine’s Criteria**

<b>Part A</b>	<b>Score</b>
Headache	2
Fever	2
Temp > 39 <sup>0</sup> C	2
Myalgia	5
Muscle pain (esp calf)	4
Bil Conjunctival suffusion	4
Meningism	4
Conj suffusion + Meningism + muscle pain	10
Jaundice	1
Albuminuria	2

<b>Part B</b>	<b>Score</b>
Contact with animals/known contaminated water	10

Score >26 suggests Leptospirosis  
 Even single of these should arouse high clinical suspicion.

**Complications:**

1. Hepatitis – Febrile illness with neutrophilic leucocytosis, mildly raised SGOT, SGPT. Alcoholics are more prone to bleeding.
2. Acute renal failure – oliguric / nonoliguric renal failure may set in. Patient usually has hypokalemia. Dialysis may be required if Creatinine value raises above 4.5
3. ARDS – Characterized by short febrile illness with dyspnoea, haemoptysis, chest pain, rapid worsening and death.
4. Bleeding Manifestations – Epistaxis, gum bleeding, purpura, haematemesis, haemoptysis
5. Cardiac – Myocarditis, pericarditis.
6. Hepatorenal failure.

**Sequelae** Clinical course is highly variable. The serious icteric form (Weil's disease) is not common, but hemorrhage, hepatomegaly, pulmonary hemorrhage, ARDS, renal failure and jaundice are among the severe features. Case fatality rate is 1 to 5%.

**Risk Groups** Wading through flooded rainwater is the commonest reason for infection with leptospirosis in our country. Workers in rice fields, sugar cane plantations, mines, sewer systems, and slaughterhouses; animal caretakers and veterinarians are most likely to get infected with leptospirosis. Travelers to tropical parts of the world involved in recreational activities in fresh water also have a high risk. Recreational exposures can include rafting, kayaking, and swimming, in tropical and temperate climates.

**Trends** In India, leptospirosis is very common during the monsoon and should be suspected as a cause of fever in that season. Leptospirosis continues to re-emerge as a notable source of morbidity and mortality in the Western Hemisphere. The largest recorded outbreak in the continental United States (110 cases in a group of 775 exposed persons who participated in triathlons, which included swimming in a lake) occurred in June and July 1998. Significant increases in incidence were also reported from Peru and Ecuador following heavy rainfall and flooding in the spring of 1998. Thailand has also reported a rapid increase in incidence between 1995 and 2000. **Challenges** The confirmatory microscopic agglutination test (MAT) is labor intensive and not widely available. Rapid serologic assays detecting *Leptospira*-specific IgM have been shown to be sensitive and specific. The challenge is to increase awareness of new diagnostic assays and their advantages. **Opportunities** Community-based trials of weekly doxycycline for prevention of leptospirosis during periods of high risk may be useful in developing an approach to control leptospirosis epidemics. New diagnostic assays should decrease reliance on the more cumbersome MAT.

**Laboratory Diagnosis:**

- Antibody tests / Serology
- Culture from Blood (upto 10<sup>th</sup> day)
  - CSF (7<sup>th</sup> – 14<sup>th</sup> day)
  - Urine (10<sup>th</sup> – 30<sup>th</sup> day)
- Microscopy Blood
  - Urine

Can be tested by dark field microscopy, DFA, IHC.

**Laboratory criteria for diagnosis:**

1. Dipstick, Dridot, Panbio tests used as rapid screening tests for detection of IgM antibodies to *Leptospira*.
2. Rising titre of microscopic agglutination test (MAT) in paired sera.  
(3-5 ml of blood collected in a test tube on admission / clinical suspicion and repeated after 10 – 14 days) considered Gold Standard .
3. Rising titre in paired samples by IgM Elisa.
4. Initial high titre of MAT/IgM Elisa (1:320)

**A NEGATIVE TEST IN THE EARLY PHASE OF THE DISEASE DOES NOT RULE OUT LEPTOSPIROSIS**

**DIAGNOSIS:**

**Probable Case:**

Clinical features with any one of the following

- Initial high titre of MAT/IgM Elisa (> 1:320)
- Positive Dridot test
- Positive dipstick test

**Confirmed Case:**

- Clinical criteria with positive culture  
Or
- Clinical criteria with rising titre of MAT in paired serum sample  
Or
- Clinical criteria with rising titre of IgM Elisa in paired samples.

**Other Investigations:**

1. CBC - Leucocytosis, thrombocytopenia
2. LFT – Raised bilirubin
  - Marginally raised SGOT/PT (2-3 fold)
  - raised CPK
3. RFT – Prolonged PT/PI, increased BUN & Creatinine, reduced potassium
4. XRC – Alveolar infiltrates, pleural effusion
5. Arterial blood gas – hypoxia
6. ECG in myocarditis ST-T changes

**TREATMENT**

**Outpatient Basis**

A) **Antibiotics**

Cap. Doxycycline (100 mg) 1 – 0 – 1 x 7 days

OR

Cap. Ampicillin/Amoxycillin

2 gm/day in divided doses x 7 days

OR

T. Erythromycin 2g/day in divided doses x 7 days

The patient must be asked to follow up in case of non-response to treatment / appearance of complications.

Anicteric leptospirosis may be managed on outpatient basis.

Admission is indicated if patient does not respond to treatment or has complications.

**Inpatient Treatment**

Inj. Crystalline Penicillin 20 lac units IV 6 m hrly after test dose x 10 days

OR

Inj. Ampicillin 2-3 gm / day x 7 – 10 days

OR

Inj. Ceftriaxone 2 g/day

OR

T. Erythromycin 2.3 g/day in divided doses (for Penicillin allergy)

### **Monitoring**

- Vital parameters – TPR & BP
- Watch for tachypnoea, worsening shadows on x-ray, hypoxia on ABG for early ARDS
- Urine output – renal involvement may present with oliguria
- Altered sensorium
- Bleeding manifestations like epistaxis, echymosis, hemoptysis, GI bleed.
- Arrhythmias

### **Dengue Fever**

Dengue (pronounced den' gee) is a disease caused by any one of four closely related viruses (DEN-1, DEN-2, DEN-3, or DEN-4). The viruses are transmitted to humans by the bite of an infected mosquito. The *Aedes aegypti* mosquito is the most important transmitter or vector of dengue viruses, although a 2001 outbreak in Hawaii was transmitted by *Aedes albopictus*. Dengue cannot be spread directly from person to person. It is estimated that there are over 100 million cases of dengue worldwide each year.

**Dengue Fever** is an acute febrile disease with headaches, musculoskeletal pain, and rash, but the severity of illness and clinical manifestations vary with age.

**Dengue hemorrhagic fever (DHF) / Dengue shock syndrome (DSS)** is an Immunopathologic syndrome that occurs in:

- Infants infected for the first time who have acquired maternal **dengue** antibody in utero and
- Children and, less commonly, adults during a second **dengue** virus infection

DHF is a more severe form of dengue. It can be fatal if unrecognized and not properly treated. DHF is caused by infection with the same viruses that cause dengue. With good medical management, mortality due to DHF can be less than 1%.

### **Clinical Features:-**

The incubation period is 4 to 7 days.

In adults the illness is more severe and more acute. The spectrum in dengue ranges from asymptomatic to symptomatic which includes undifferentiated viral syndrome, uncomplicated dengue fever to dengue hemorrhagic fever and dengue shock syndrome.

The infection is asymptomatic in 80% of infants and children. In others it may manifest as fever, malaise or irritability, pharyngeal injection, upper respiratory symptoms, and rash that cannot be readily differentiated from other common childhood infection.

The presenting symptoms are:-

1. Bimodal Fever (saddle back pattern), often with chills typically with a second spike after a brief period of 2-3 days of decrease in fever.
2. Severe frontal headache with Retro-orbital pain
3. Severe musculoskeletal and lumbar back pain with hyperesthesia of skin
4. Anorexia, nausea, vomiting,
5. Breathlessness
6. Rash - Initially, flushed skin, indistinct macular to scarlatiniform rash. This rash typically spares the palms and soles.
7. The rash fades or desquamates with localized clusters of petechiae on the extensor surfaces of the limbs.
8. Minor bleeding is common. There may be epistaxis and bleeding from the gums,
9. Gastrointestinal bleed, hematuria, metrorrhagia in women is uncommon
10. Altered sensorium.

Dengue hemorrhagic fever is characterized by a fever that lasts from 2 to 7 days, with general signs and symptoms that could occur with many other illnesses (e.g., nausea, vomiting, abdominal pain, and headache). This stage is followed by hemorrhagic manifestations, tendency to bruise easily or other types of skin hemorrhages, bleeding nose or gums, and possibly internal bleeding. The smallest blood vessels (capillaries) become excessively permeable (“leaky”), allowing the fluid component to escape from the blood vessels. This may lead to failure of the circulatory system and shock, followed by death, if circulatory failure is not corrected.

#### **Grading Severity of DHF:-**

DHF is classified into 4 grades. Grade III & IV is DSS. The presence of thrombocytopenia with concurrent hemoconcentration differentiates Grade I & II from DF.

**Grade I:-** fever with non-specific constitutional symptoms, the only positive finding being a positive tourniquet test or easy bruising.

**Grade II:-** Spontaneous bleeding in addition to manifestation of Grade I patients, usually in the form of skin or other hemorrhages.

**Grade III:-** Circulatory failure manifested by a weak rapid pulse & narrowing of pulse pressure or hypotension, with the presence of cold, clammy skin and restlessness.

**Grade IV-** Profound shock with undetectable BP or pulse.

#### **DSS:-**

Patho-physiologic presentation of classic DSS is unique & includes.

1. History of recent high grade fever
2. Thrombocytopenia
3. Elevated hematocrit and hypotension or narrow pulse pressure (e.g. BP or 90/70 or 100/80)

## **Management**

There is no specific medication for treatment of a dengue infection. Persons who think they have dengue should use analgesics (pain relievers) with acetaminophen and avoid those containing aspirin. They should also rest, drink plenty of fluids, and consult a physician.

As with dengue, there is no specific medication for DHF. It can however be effectively treated by fluid replacement therapy if an early clinical diagnosis is made. Hospitalization is frequently required in order to adequately manage DHF.

## **Prevention**

Outbreaks of dengue occur primarily in areas where *Aedes aegypti* (sometimes also *Aedes albopictus*) mosquitoes live. This includes most tropical urban areas of the world. Dengue viruses may be introduced into areas by travelers who become infected while visiting other areas of the tropics where dengue commonly exists.

There is no vaccine for preventing dengue. The best preventive measure for residents living in areas infested with *Aedes aegypti* is to eliminate the places where the mosquito lays her eggs, primarily artificial containers that hold water. Items that collect rainwater or are used to store water should be covered or properly discarded. Pet and animal watering containers and vases with fresh flowers should be emptied and scoured at least once a week. This will eliminate the mosquito eggs and larvae and reduce the number of mosquitoes present in these areas.

For travelers to areas with dengue, as well as people living in areas with dengue, the risk of being bitten by mosquitoes indoors is reduced by utilization of air conditioning or windows and doors that are screened. Proper application of mosquito repellents containing 20% to 30% DEET as the active ingredient on exposed skin and clothing decreases the risk of being bitten by mosquitoes. The risk of dengue infection for international travelers appears to be small, unless an epidemic is in progress.

The emphasis for dengue prevention is on sustainable, community-based, integrated mosquito control, with limited reliance on insecticides (chemical larvicides and adulticides). Preventing epidemic disease requires a coordinated community effort to increase awareness about dengue/DHF, how to recognize it, and how to control the mosquito that transmits it. Residents are responsible for keeping their yards and patios free of sites where mosquitoes can be produced.

## **Typhoid fever**

Typhoid fever, also known as enteric fever, is an illness caused by the bacterium *Salmonella enterica serovar typhi*. Common worldwide, it is transmitted by the fecal-oral route — the ingestion of food or water contaminated with feces from an infected person. The bacteria then multiply in the blood stream of the infected person and are absorbed into the digestive tract and eliminated with the waste. The organism is a Gram-negative

short bacillus that is motile due to its peritrichous flagella. Optimal temperature for multiplication is 37 degrees Celsius.

### **Symptoms**

Typhoid fever is characterized by a sustained fever as high as 40°C (104°F), profuse sweating, gastroenteritis, and diarrhea. Less commonly a rash of flat, rose-colored spots may appear early in the course. This rash is not commonly seen in India because of our dark complexion.

Classically, the course of untreated typhoid fever is divided into four individual stages, each lasting approximately one week.

1. In the first week, there is a slowly rising temperature with relative bradycardia, malaise, headache and cough. Epistaxis is seen in a quarter of cases and abdominal pain is also possible. There is leukopenia with eosinopenia and relative lymphocytosis, a positive diazo reaction and blood cultures are positive for *Salmonella typhi* or *paratyphi*. The classic Widal test is negative in the first week.
2. In the second week of the infection, the patient lies prostrated with high fever in plateau around 40°C and bradycardia (Sphygmo-thermic dissociation), classically with a dicrotic pulse wave. Delirium is frequent, frequently calm, but sometimes agitated. This delirium gives to typhoid the nickname of "nervous fever". Rose spots appear on the lower chest and abdomen in around 1/3 patients. There are rhonchi in lung bases. The abdomen is distended and painful in the right lower quadrant where borborygmi can be heard. Diarrhea can occur in this stage: six to eight stools in a day, green with a characteristic smell, comparable to pea-soup. However, constipation is also frequent. The spleen and liver are enlarged (hepatosplenomegaly) and tender and there is elevation of liver transaminases. The Widal reaction is strongly positive with antiO and antiH antibodies. Blood cultures are sometimes still positive at this stage.
3. In the third week of fever, a number of complications can occur:
  - Intestinal hemorrhage due to bleeding in congested Peyer's patches; this can be very serious but is usually non-fatal.
  - Intestinal perforation in distal ileum: this is a very serious complication and is frequently fatal. It may occur without alarming symptoms until septicaemia or diffuse peritonitis sets in.
  - Encephalitis
  - Metastatic abscesses, cholecystitis, endocarditis and osteitis

The fever is still very high and oscillates very little over 24 hours. Dehydration ensues and the patient is delirious (typhoid state). By the end of third week defervescence commences that continues itself in the fourth week.

### **Diagnosis**

Diagnosis is made by blood, bone marrow or stool cultures and with the Widal test (demonstration of salmonella antibodies against antigens O-somatic and H-flagellar). The positivity of the test depends on the week of fever as shown above.

When untreated, typhoid fever persists for three weeks to a month. Death occurs in between 10% and 30% of untreated cases. Vaccines for typhoid fever are available and are advised for persons traveling in regions where the disease is common (especially Asia, Africa and Latin America). Typhim Vi is an intramuscular killed-bacteria vaccination and Vivotif is an oral live bacteria vaccination, both of which protect against typhoid fever. The vaccine does not offer 100% protection against typhoid fever.

### **Resistant Typhoid Fever**

Resistance to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole and streptomycin is now common, and these agents have not been used as first line treatment now for almost 20 years. Typhoid that is resistant to these agents is known as multidrug-resistant typhoid (MDR typhoid).

Ciprofloxacin resistance is an increasing problem, especially in the Indian subcontinent and Southeast Asia. Many centres are therefore moving away from using ciprofloxacin as first line for treating suspected typhoid originating in India, Pakistan, Bangladesh, Thailand or Vietnam. For these patients, the recommended first line treatment is ceftriaxone.

There is a separate problem with laboratory testing for reduced susceptibility to ciprofloxacin: current recommendations are that isolates should be tested simultaneously against ciprofloxacin (CIP) and against nalidixic acid (NAL), and that isolates that are sensitive to both CIP and NAL should be reported as "sensitive to ciprofloxacin", but that isolates testing sensitive to CIP but not to NAL should be reported as "reduced sensitivity to ciprofloxacin". However, an analysis of 271 isolates showed that around 18% of isolates with a reduced susceptibility to ciprofloxacin (MIC 0.125–1.0 mg/l) would not be picked up by this method. It not certain how this problem can be solved, because most laboratories around the world (including the West) are dependent disc testing and cannot test for MICs .

### **Transmission**

Flying insects feeding on feces may occasionally transfer the bacteria through poor hygiene habits and public sanitation conditions. Public education campaigns encouraging people to wash their hands after toileting and before handling food are an important component in controlling spread of the disease. According to statistics from the United States Center for Disease Control, the chlorination of drinking water has led to dramatic decreases in the transmission of typhoid fever in the U.S..

A person may become an asymptomatic carrier of typhoid fever, suffering no symptoms, but capable of infecting others. According to the Centers for Disease Control

approximately 5% of people who contract typhoid continue to carry the disease after they recover. The most famous asymptomatic carrier was Typhoid Mary. She was a young cook that was responsible for infecting about 25 people in Oyster Bay, New York, in 1915. This was the first time a perfectly healthy person was known to be responsible for an "epidemic".

## **Malaria**

Malaria is both preventable and curable. A child dies of malaria every 30 seconds. More than one million people die of malaria every year, mostly infants, young children and pregnant women and most of them in Africa.

### **Infection and transmission**

Malaria is a disease which can be transmitted to people of all ages. It is caused by parasites of the species *Plasmodium* that are spread from person to person through the bites of infected mosquitoes. The common first symptoms – fever, headache, chills, and vomiting – appear 10 to 15 days after a person is infected. If not treated promptly with effective medicines, malaria can cause severe illness that is often fatal.

There are four types of human malaria – *Plasmodium falciparum*, *P.vivax*, *P.malariae*, and *P.ovale*. *P.falciparum* and *P.vivax* are the most common. *P.falciparum* is by far the most deadly type of malaria infection. In India only infection with *P. falciparum* and *P.vivax* is seen.

Malaria transmission differs in intensity and regularity depending on local factors such as rainfall patterns, proximity of mosquito breeding sites and mosquito species. Some regions have a fairly constant number of cases throughout the year – these are *malaria endemic* – whereas in other areas there are “malaria” seasons, usually coinciding with the rainy season.

Large and devastating epidemics can occur in areas where people have had little contact with the malaria parasite, and therefore have little or no immunity. These epidemics can be triggered by weather conditions and further aggravated by complex emergencies or natural disasters.

### **Clinical Features:**

1. Sequential fever, chills, sweating (Hot stage followed by cold and then the wet stage.)
2. Nausea, vomiting
3. Headache
4. Muscle pain
5. Diarrhoea
6. Pallor
7. Mild Jaundice
8. Breathlessness, Cough

9. Oliguria
10. Altered Sensorium, Convulsions, Coma
11. Bleeding manifestations

**Physical Findings:**

1. Fever
2. Anaemia
3. Jaundice (usually mild)
4. Hepato-splenomegaly
5. Purpura, petechial hemorrhages

**Complications:**

1. Cerebral malaria: Patient may present with convulsions, coma, cranial nerve palsies, hemiplegia, extra pyramidal signs, raised intracranial tension, decerebrate rigidity
2. **Black water fever:** There is a massive hemolysis of RBC; presents as hemoglobinuria i.e. cola coloured urine or acute renal failure.
3. **Algid malaria:** Patient has diarrhoea, vomiting.
4. **ARDS:** due to increased in capillary permeability in lungs; presents with severe breathlessness, cyanosis
5. Hepatitis: There are Kupffer cell hyperplasia causing jaundice & minimal rise of enzymes with hepatomegaly.
6. Hypoglycemia: There has excess consumption of glucose by malaria parasite.
7. Thrombocytopenia & DIC: Platelets are used in small thrombus formations; manifests as purpura, petechial hemorrhages or bleeding into internal organs.
8. Severe Anaemia: It is due to haemolysis RBC's.
9. Splenomegaly & hypersplenism: There may be small to large splenomegaly and few patient may present as hypersplenism (pancytopenia)
10. Lactic acidosis: There may be severe acidosis.
11. Renal Failure: Presents as oliguria, acidosis

**Laboratory Diagnosis of Malaria:**

The diagnostic tests can be divided into the microscopic tests and the non-microscopic tests.

**The microscopic tests**

Peripheral smear  
Quantitative buffy coat (QBC)

**Non microscopic tests**

Antigen Detection tests

**Non-microscopic tests (Antigen Detection Tests):**

Para Sight F, Paracheck Pf and Malaquick – detects P. falciparum only.  
OptiMAL – Detects both P.vivax as well as P. falciparum  
SD Malaria Pf/Pv – Detects all species of Plasmodia.

Useful in field settings where facilities for microscopy and technical expertise is not available.

### **Other Investigations:**

1. CBC:
  - Hemoglobin may be decreased
  - Thrombocytopenia
2. Liver function tests
  - Bilirubin increased
  - Enzymes increased
3. Kidney function tests:
  - BUN may be raised
  - S.Creatinine may be raised
  - Electrolyte disturbances
4. G-6PD deficiency carried out for treatment purpose.
5. ECG to monitor QT interval along with Quinine therapy.
6. X-Ray chest : bilateral fluffy shadows in presence of ARDS
7. ABG:
  1. Hypoxia in ARDS
  2. Metabolic acidosis

### **Baseline Investigation Panel – Day 1:**

- Peripheral smear for malarial parasites
- Hb., CBC, Platelets
- Blood for G6PD assay

### **Follow-up Investigation Panel – Day 3:**

**If the fever persists and/or there is suspicion of complications**

- Peripheral smear for malarial parasites
- Hb, Platelets
- S.Bilirubin, SGOT, SGPT
- BUN,S. Creatinine
- ECG
- X-Ray Chest

## **TREATMENT OF MALARIA**

### **Vivax Malaria**

#### **Rx. objectives**

1. Cure of acute infection
2. Clearance of hypnozoites to prevent future relapses

**Recommendations on the treatment of uncomplicated vivax malaria**

Chloroquine 25 mg base/kg bw divided over 3 days, combined with primaquine 0.25 mg base/kg bw, taken with food once daily for 14 days is the treatment of choice for chloroquine-sensitive infections.

In Oceania and South-East Asia the dose of primaquine should be 0.5 mg/kg bw.

In moderate G6PD deficiency, primaquine 0.75 mg base/kg bw should be given once a week for 8 weeks. In severe G6PD deficiency, primaquine should not be given.

Where ACT has been adopted as the first-line treatment for *P. falciparum* malaria, it may also be used for *P. vivax* malaria in combination with primaquine for radical cure. Artesunate + sulfadoxine-pyrimethamine is the exception as it will not be against *P. vivax* in many places

**Drug resistant P.Vivax**

T. Quinine (10mg/kgbw TDS x 7 days)

OR

Amodiaquine (25 – 30mg base/kgbw) given over 3 days + Primaquine

OR

Mefloquine (15 mg base/kgbw) as single dose

Higher dose of Primaquine (0.5 – 0.6 mg/kg once daily for 14 days) recommended in areas where there are presumed Primaquine resistant hypnozoite infections.

**Resistance in Vivax Infections:**

The interval between Primary and repeat infection can serve as a guide.

	<b><u>Recurrence</u></b>	<b><u>Inference</u></b>
1.	Within 16 days of starting treatment For primary infection	Recrudescence
2.	Between 17 – 28 days	Recrudescence by Chloroquine Resistant parasites/relapse
3.	Beyond 28 days	Relapse in an infection of Chloroquine sensitive P.Vivax

Rx. of severe and complicated Vivax malaria – same as for Falciparum Malaria.

### **Mild G6PD Deficiency**

A primaquine regimen of 0.75 mg base/kgbw once per week for 8 weeks is recommended as antirelapse therapy for P.vivax and P.Ovale malaria.

### **Moderate G-6PD deficiency**

Primaquine 0.75 mg/kgbw once a week for 8 weeks.

### **Severe G-6PD deficiency**

Primaquine is contraindicated.

## **FALCIPARUM MALARIA**

Hyperparasitemia carries an increased risk of mortality in Falciparum malaria. Hyperparasitemic patients with no signs of severe disease may be treated with oral artemesinin derivatives provided that the following apply.

1. The patients must be monitored closely for the first 48 hours after initiation of treatment.
2. They must tolerate the drugs well i.e. without diarrhea or vomiting.
3. For regimens containing Mefloquine, Tab Mefloquine should be given on day 2 when it is better tolerated with a lower incidence of early vomiting rather than day 0.
4. If possible additional oral artemesinin derivative should be given so that the total treatment course is 5-7 days.

The first dose of artemesinin derivative can be given parenterally / rectally to ensure adequate absorption.

### **Treatment Objectives – Uncomplicated Falciparum Malaria**

Cure of infection so as to prevent progression to severe disease and prevent additional morbidity associated with treatment failure.

### **Severe Malaria**

- ❖ Primary objective is to prevent death
- ❖ Prevention of recrudescence and avoidance of minor side effects
- ❖ Prevention of neurologic deficit
- ❖ In treatment of severe malaria in pregnancy – saving the life of the mother is the primary objective.

Antimalarial treatment policies will vary between countries depending on the epidemiology of the disease, transmission, patterns of drug resistance and political and economic contexts.

### **Recommendations on treatment for uncomplicated falciparum malaria**

The treatment of choice for uncomplicated falciparum malaria is a combination of two or more antimalarials with different mechanisms of action.

ACTs are the recommended treatments for uncomplicated falciparum malaria.

The following ACTs are currently recommended:

- artemether-lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, artesunate + sulfadoxine-pyrimethamine.

The choice of ACT in a country or region will be based on the level of resistance of the partner medicine in the combination:

- in areas of multidrug resistance (South-East Asia), artesunate + mefloquine or artemether-lumefantrine
- in Africa, artemether-lumefantrine, artesunate + amodiaquine; artesunate + sulfadoxine-pyrimethamine.

### **Global and regional risk**

Approximately, 40% of the world's population, mostly those living in the world's poorest countries, are at risk of malaria. Every year, more than 500 million people become severely ill with malaria. Most cases and deaths are in sub-Saharan Africa. However, Asia, Latin America, the Middle East and parts of Europe are also affected. Travellers from malaria-free regions going to areas where there is malaria transmission are highly vulnerable – they have little or no immunity and are often exposed to delayed or wrong malaria diagnosis when returning to their home country.

### **Drug resistance**

The rapid spread of antimalarial drug resistance over the past few decades has required more intensive monitoring of drug resistance to ensure proper management of clinical cases and early detection of changing patterns of resistance so that national malaria treatment policies can be revised where necessary. Surveillance of therapeutic efficacy over time is an essential component of malaria control. Recent efforts to scale-up malaria control in endemic countries throughout the world including increased support for commodities and health systems, as well as the proposed price subsidy on artemisinin-based combination therapies (ACTs) is resulting in greater access to and a vastly increased use of antimalarial medicines, in particular ACTs. This is leading to a much higher degree of drug pressure on the parasite which will almost certainly increase the likelihood of selecting for resistant parasite genotypes. There are currently no effective

alternatives to artemisinins for the treatment of *P. falciparum* malaria either on the market or towards the end of the development pipeline.

The parasite's resistance to medicines continues to undermine malaria control efforts. WHO has therefore called for continuous monitoring of the efficacy of recently implemented ACTs, and countries are being assisted in strengthening their drug resistance surveillance systems. In order to preserve the efficacy of artemisinins as an essential component of life-saving ACTs, WHO has called for a ban on the use of oral artemisinin monotherapies, at various levels, including manufacturers, international drug suppliers, national health authorities and international aid and funding agencies involved in the funding of essential antimalarial medicines.

### **Prevention: vector control and intermittent preventive therapy in pregnant women**

The main objective of malaria vector control is to significantly reduce both the number and rate of parasite infection and clinical malaria by controlling the malaria-bearing mosquito and thereby reducing and/or interrupting transmission. There are two main operational interventions for malaria vector control currently available: Indoor Residual Spraying of long-acting insecticide (IRS) and Long-Lasting Insecticidal Nets (LLINs). These core interventions can be locally complemented by other methods (e.g. larval control or environmental management) in the context of Integrated Vector Management (IVM). Effective and sustained implementation of malaria vector control interventions (IRS or LLINs) requires clear political commitment and engagement from national authorities as well as long-term support from funding partners.

Pregnant women are at high risk of malaria. Non-immune pregnant women risk both acute and severe clinical disease, resulting in up to 60% fetal loss and over 10% maternal deaths, including 50% mortality for severe disease. Semi-immune pregnant women with malaria infection risk severe anaemia and impaired fetal growth, even if they show no signs of acute clinical disease. An estimated 10 000 of these women and 200 000 of their infants die annually as a result of malaria infection during pregnancy. HIV-infected pregnant women are at increased risk. WHO recommends that all endemic countries provide a package of interventions for prevention and management of malaria in pregnancy, consisting of (1) diagnosis and treatment for all episodes of clinical disease and anaemia and (2) insecticide-treated nets for night-time prevention of mosquito bites and infection. In highly endemic falciparum malaria areas, this should be complemented by (3) intermittent preventive treatment with sulfadoxine–pyrimethamine (IPT/SP) to clear the placenta periodically of parasites.

### **Insecticide resistance**

In spite of increased national and international efforts to scale up cost-effective malaria vector control interventions and maximize the protection of populations at risk, significant challenges continue to threaten these objectives and the sustainability of achievements. Challenges include increasing resistance of vector mosquitoes to

insecticides, the behaviour and ecology of local malaria vectors – which often change as a result of vector control interventions -- and the diminishing number of available insecticides that can be used against malaria vectors (adulticides).

There are currently no alternatives to DDT and pyrethroids and the development of new insecticides will be an expensive long-term endeavour. Therefore, immediate sound vector resistance management practices are required to assure the continued utility of the currently available insecticides. At present there is only limited evidence of the impact of various resistance mechanisms on the efficacy of vector control interventions, whether they are implemented singly or in combination.

Recent evidence from Africa indicates that pyrethroid and DDT resistance is more widespread than anticipated. It is believed that the same level of resistance will have a more detrimental impact on the efficacy of IRS than on that of LLINs, but evidence for this is very limited. Networks for vector resistance monitoring still need greater strengthening in order to make resistance detection a routine operational feature of national programmes, particularly in countries in Africa and the Eastern Mediterranean region. Regional level databases feeding into a global database accessible by governments, scientists and policy-makers would greatly assist in the rational use and deployment of vector control interventions.

### **Socioeconomic impact**

Malaria causes an average loss of 1.3% annual economic growth in countries with intense transmission. When compounded over the years, this loss has led to substantial differences in GDP between countries with and without malaria. Malaria traps families and communities in a downward spiral of poverty, disproportionately affecting marginalized populations and poor people who cannot afford treatment or who have limited access to health care. Malaria's direct costs include a combination of personal and public expenditures on both prevention and treatment of disease. In some countries with a very heavy malaria burden, the disease may account for as much as 40% of public health expenditure, 30-50% of inpatient admissions and up to 60% of outpatient visits. Malaria has lifelong effects through increased poverty, impaired learning and decreases attendance in schools and the workplace.

### **Chikungunya**

Chikungunya fever is a viral disease transmitted to humans by the bite of infected mosquitoes. Like Malaria and Dengue, this infection has almost become endemic in India, especially central and south India.

The term “chikungunya” is derived from the Makonde root verb kungunyala, meaning “to become contorted” or more specifically as "that which bends up". This refers to the stooped posture adopted by the patient as a result of symptoms of arthritis that the patient develops. This disease is almost always self-limited and rarely fatal.

Symptoms of sudden onset of fever, chills, headache, nausea, vomiting, joint pain with or without swelling, low back pain, and rash are very similar to those of dengue but, unlike dengue, there is no hemorrhagic or shock syndrome form.

### **Etiology**

Chikungunya virus (CHIKV) is a member of the genus *Alphavirus*, in the family *Togaviridae*. The vector for this disease is the Aedes Mosquito (sps. *egypti*) which is the same vector for the Dengue Fever and Yellow Fever. Recently the Pasteur Institute in Paris has claimed that the virus has suffered a mutation that enables it to be transmitted by *Aedes Albopictus* (Tiger mosquito) also.

### **Epidemiology**

The spread of Chikungunya in India is of unprecedented magnitude. There is no case of Chikungunya reported from the northern states like Delhi, Haryana, Punjab etc. However, except for Kerala in the southern India, other states like Tamil Nadu, Karnataka and Andhra Pradesh besides Orissa, Madhya Pradesh, Maharashtra, Gujarat and Rajasthan are under the onslaught of the infection since December 2005

In 2006, there has been a big outbreak in Andhra Pradesh which still continues. The initial cases were reported from Hyderabad-Secunderabad and Anantpur district as early as November and December 2005. In Hyderabad alone an average practitioner sees approximately 10 to 20 cases every day.

There have been reports of large scale outbreak of this virus in Southern India from Gulbarga, Tumkur, Bidar, Raichur, Bellary, Chitradurga, Davanagere, Kolar and Bijapur districts in Karnataka state since December 2005. A separate outbreak of Chikungunya fever was reported from Malegaon town in Nasik district, Maharashtra state and also Orissa in early March 2006. The latest outbreaks seem to be from Bangalore and Tamil Nadu in May-June 2006 in Salem and Chennai.

Outbreak of Chikungunya has also been reported from Hong and Malaysia. Analysis of the recent outbreak has suggested that the increased severity of the disease may be due to a change in the genetic sequence, altering the virus' coat protein, which potentially allows it to multiply more easily in mosquito cells.

Chikungunya is closely related to O'nyong'nyong virus.

### **Clinical features**

The incubation period can be 2-12 days, but is usually 3-7 days. "Silent" CHIKV infections (infections without illness) do occur; but how commonly this happens is not yet known.

After an incubation period of 3-12 days there is a sudden onset of flu-like symptoms including a severe headache, chills, fever (>40°C,104°F), arthralgia or arthritis,

conjunctival suffusion and mild photophobia, nausea and vomiting. The joints of the extremities in particular become swollen and painful to the touch. Some patients have incapacitating joint pain, or arthritis which may last for weeks or months. A petechial or maculopapular rash usually involving the limbs may occur. Hemorrhage is rare.

Dermatological manifestations observed in a recent outbreak in Karnataka<sup>3</sup>, were maculopapular rash, nasal blotchy erythema, freckle-like pigmentation over centro-facial area, flagellate pigmentation on face and extremities, lichenoid eruption and hyperpigmentation in photodistributed areas, multiple aphthous-like ulcers over scrotum, crural areas and axilla, unilateral or bilateral lymphoedema in acral distribution, multiple ecchymotic spots in children, vesiculobullous lesions in infants, and subungual hemorrhage. Histopathological examination revealed perivascular lymphocytic infiltrate.

Acute chikungunya fever typically lasts a few days to a couple of weeks, but as with dengue, West Nile fever, O'nyong-nyong fever and other arboviral fevers, some patients have prolonged fatigue lasting several weeks. In the present epidemic in the state of Andhra Pradesh in India, high fever and crippling joint pain is the prevalent complaint. Fever typically lasts for two days and abruptly comes down, however joint pain, intense headache, insomnia and an extreme degree of prostration lasts for a variable period, usually for about 5 to 7 days.

Chikungunya is a self-limiting illness. The major cause of morbidity is due to severe dehydration, electrolyte imbalance and loss of glycemic control. Recovery is the rule except for about 3 to 5% incidence of prolonged arthritis. Few deaths have been reported<sup>3</sup>. It was thought to be due mainly to the inappropriate use of antibiotics and anti-inflammatory tablets. As this virus can cause thrombocytopenia, injudicious use of these drugs can cause erosions in the gastric epithelium leading to exsanguinating upper GI bleed (due to thrombocytopenia). Also the use of steroids for the control of joint pains and inflammation is dangerous and completely unwarranted.

### **Diagnostic Tests**

The tests available are: detection of antigen and antibody in blood by serology, ELISA test. An IgM capture ELISA is necessary to distinguish the disease from dengue fever.

### **Treatment**

There is no specific treatment for Chikungunya. Vaccine is also not available. The illness is usually self-limiting and will resolve with time. Symptomatic treatment is recommended. Rest, fluids, and ibuprofen, naproxen, acetaminophen, or paracetamol may relieve symptoms of fever and aching. Aspirin should be avoided

Chloroquine phosphate (250 mg/day) has been tried in the treatment of arthralgia associated CHIK with promising results.

### **Information to Travellers**

Travellers visiting the above mentioned countries should be careful and take precautions to see that they are not bitten by mosquitoes, especially pregnant women, immunosuppressed and people suffering from a severe chronic illness.

### **Chikungunya Infection and Pregnancy**

There have been cases of mother-to-fetus infection which have occurred between 3 and 4.5 months into pregnancy. Before and after that period in pregnancy, cases have not been recorded. IgG that is produced around day 15 passes through the placenta and confers immunity to the fetus. However, there is a 48 percent risk of infection at birth if the virus is present in the mother's blood. Such an infection in the fetus is rarely serious and more than 90 percent of the infected newborns recover quickly without sequelae.

## **Avian Influenza**

### **Avian Influenza A Virus Infections of Humans**

Avian Influenza or “Bird Flu” is caused by human influenza A (H5N1) virus. Most human cases of H5N1 virus infection are thought to have occurred during direct contact with sick or dead infected poultry.

### **Symptoms of Avian Influenza in Humans**

The reported symptoms of avian influenza in humans have ranged from eye infections (conjunctivitis) to influenza-like illness symptoms (e.g., fever, cough, sore throat, muscle aches) to severe respiratory illness (e.g. pneumonia, acute respiratory distress, viral pneumonia) sometimes accompanied by nausea, vomiting and neurologic changes.

### **Antiviral Agents for Avian Influenza A Virus Infections of Humans**

CDC and WHO recommend oseltamivir, a prescription antiviral medication, for treatment and chemoprophylaxis of human infection with avian influenza A viruses. Analyses of available H5N1 viruses circulating worldwide suggest that most viruses are susceptible to oseltamivir. However, some evidence of resistance to oseltamivir has been reported in H5N1 viruses isolated from some human H5N1 cases. Ongoing monitoring for antiviral resistance among avian influenza A viruses is critical.

### **Prevention of Avian Influenza A Virus Infections of Humans**

Persons exposed to avian influenza A-infected or potentially infected poultry are recommended to follow good infection control practices including careful attention to

hand hygiene, and to use personal protective equipment. In addition, they should be vaccinated against seasonal influenza and should take influenza antiviral agents for prophylaxis. Exposed persons should be carefully monitored for symptoms that develop during and in the week after exposure to infected poultry or to potentially avian influenza-contaminated environments.

## The Febrile Patient with Rash

Evaluation of a patient who presents with fever and a rash can be challenging because the differential diagnosis is extensive and includes minor and life-threatening illnesses. In addition, the clinical picture can vary considerably, and the family physician may need to quickly decide about initiating empiric therapy or isolation.

Brief descriptions of common primary skin lesions are presented in Table 4.

**Table 4**  
**Causes of Fever and Rash**

<b>Disease</b>	<b>Etiology</b>	<b>Description of Rash</b>
Rubeola	Measles Virus	Macular-papular rash that may become confluent; begins on face, neck and shoulders and spreads centrifugally and inferiorly; fades in 4 to 6 days
Rubella	Rubella Virus	Pink macules and papules that develop on forehead and spread inferiorly and to extremities within one day; fading of macules and papules in reverse order by third day
Erythema infectiosum (fifth disease)	Human parvovirus B 19	Begins as classic bright-red facial rash ("slapped cheek") and progresses to lacy reticular rash; may wax and wane for 6 to 8 weeks
Roseola	Human Herpes virus 6	Diffuse maculopapular eruption, usually sparing face
Secondary Syphilis	<i>Treponema pallidum</i>	Various presentations; brownish-red or pink macules and papules; generalized eruption or localized eruption on head, neck, palms or soles; condyloma lata common
Erythema multiforme		Dull-red macules developing into papules with central vesicles or bullae; common on dorsa of hands, palms, soles, arms, knees, penis and vulva; often bilateral and symmetric
Acute meningococemia	<i>Neisseria meningitidis</i>	Variety of lesions but, characteristically, petechial lesions distributed on the trunk and extremities (although the lesions can be located

		anywhere); petechiae on mucous membranes
Chronic meningococemia	<i>Neisseria meningitidis</i>	Intermittent maculopapular lesions, often on a painful joint or pressure point; may have nodules on calves
Toxic Shock Syndrome	<i>Staphylococcus aureus</i>	Diffuse "sunburn" rash that desquamates over 1 to 2 weeks
Chicken pox	<i>Varicella zoster</i>	Initially, papules, which evolve into vesicles ("dewdrops on a rose petal") and eventually into pustules and crusts; rash beginning on face and spreading inferiorly to trunk and extremities
Erythema nodosum		Bright-red nodules (3 to 20 cm in diameter) scattered bilaterally but not symmetric; most frequently on lower legs but also found on knees and arms; rarely found on face and neck; lesions often tender and indurated

## History

A detailed history can be quite helpful in identifying the cause of fever and a rash. A history of recent travel, woodland or animal exposure, drug ingestion or contact with ill persons should be noted. The time of year can be a clue to certain diagnoses.

A complete medical history can help to determine whether the patient is at increased risk for specific conditions associated with valvular heart disease, sexually transmitted diseases or immunosuppression from chemotherapy. Immune status is particularly important because many of the diseases that result in fever and a rash present differently in immunocompromised patients.

Details about the rash should include site of onset, rate and direction of spread, presence or absence of pruritus, and temporal relationship of rash and fever.<sup>2-5</sup> It is also important to know whether any topical or oral therapies have been attempted.

## Physical Examination

A basic understanding of the various types of rashes is essential in making an accurate assessment and determining the severity and acuteness of the patient's illness. The physician should identify the primary lesion but also note the presence of secondary lesions. Important features include the distribution, configuration and arrangement of the lesions.<sup>2</sup>

In addition to evaluating the patient's vital signs and general appearance, the physician should look for the following: signs of toxicity, adenopathy, oral, genital or conjunctival lesions, hepatosplenomegaly, evidence of excoriations or tenderness, and signs of nuchal rigidity or neurologic dysfunction.

## **Laboratory Data**

Laboratory data are not usually available during the initial evaluation. The complete blood count with differential, an erythrocyte sedimentation rate, a chemistry panel, liver function tests, and blood and urine cultures may prove useful in identifying organisms or disease processes.

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 should be obtained from nonhealing or persistent purpuric lesions. Biopsy of inflammatory dermal nodules and ulcers should also be considered.

Specific diagnoses that may be confirmed histologically include Rocky Mountain spotted fever, herpetic infections, systemic lupus erythematosus, erythema multiforme, allergic vasculitis, secondary syphilis and deep fungal infections.

Although serologic tests are not helpful in the acute setting, they can be used to confirm or support the diagnosis of conditions such as systemic lupus erythematosus, syphilis, rheumatoid arthritis and human immunodeficiency virus infection.

Diseases that present with fever and rash are discussed by rash type in the following sections.

## **Maculopapular Rashes**

Maculopapular eruptions are most frequently seen in viral illnesses (Figure 1) and immune-mediated syndromes. These eruptions can have many causes, including drug reactions and bacterial infections. Infectious exanthems are common and are defined as generalized cutaneous eruptions associated with a systemic infection. It is helpful to consider centrally and peripherally distributed eruptions separately because each type has its own differential diagnosis.

### **Centrally Distributed Eruptions**

Centrally distributed maculopapular eruptions are more common than peripheral eruptions. These eruptions include rashes that begin centrally, first affecting the head and neck, and then progress peripherally.

*Viral Exanthems.* Viral etiologies of rashes include rubeola, rubella, erythema infectiosum (Figure 2) and roseola.



**FIGURE 1.** Maculopapular rash in a nonspecific viral exanthem.



**FIGURE 2.** Maculopapular rash of erythema infectiosum (fifth disease).

*Drug-Related Eruptions.* Drug reactions can present as any dermatologic morphology and show no predilection for age, gender or race. Exanthematous eruptions most commonly occur in association with the administration of penicillins or cephalosporins. The rash usually appears within the first week after the offending drug is started and typically resolves within days after the drug is discontinued. Drug-related reactions can be difficult to distinguish from viral exanthems, but they may be more intensely erythematous and pruritic.

### **Peripheral Eruptions**

The most common peripheral eruptive maculopapular rash is erythema multiforme (Figure 3). Although erythema multiforme has a number of known etiologies like drugs, viral infections, salmonella, tuberculosis, histoplasma, mycoplasma, Chlamydia, it is idiopathic in more than 50 percent of affected patients.

*Others.* Secondary syphilis, meningococemia, Rocky Mountain spotted fever and dengue fever--all potentially life-threatening infections--may initially present with erythematous maculopapular lesions before advancing to a petechial exanthem.

### **Petechial Eruptions**

Petechial rashes warrant immediate evaluation to rule out severe, life-threatening illness. For proper assessment of an acutely ill patient with a petechial rash, the physician must be familiar with the common infectious and noninfectious etiologies. Prompt, accurate diagnosis and early treatment can be life-saving in patients with meningococemia, rickettsial infections and bacteremia.



**FIGURE 3.** Erythema multiforme associated with sulfa drug administration.

## Meningococemia

Meningococcal infections are a worldwide concern. These infections occur sporadically or in epidemics, most commonly in the midwinter months. Seeding of *Neisseria meningitidis* from the nasopharynx may result in acute meningococcal septicemia, meningococcal meningitis or chronic meningococemia. The risk of meningococcal disease is highest in infants, asplenic patients, alcoholics and patients with a complement deficiency (especially C5 to C8).

In some patients, the typical prodrome of cough, headache, sore throat, nausea and vomiting may be of short duration. Patients with acute meningococemia appear ill and usually present with a characteristic petechial rash (Figure 4), a high, spiking fever, tachypnea, tachycardia and mild hypotension. In the early stages of disease, the rash may be maculopapular. Signs and symptoms of meningeal irritation may be helpful, given that up to 88 percent<sup>1</sup> of patients with meningococemia develop meningitis.



Chronic meningococemia is a rare condition. Patients may present with intermittent rash, fever, arthritis and arthralgias occurring over a period of weeks to several months. In some patients, the chronic form advances to acute meningococemia. The rash may be polymorphous, with maculopapular lesions usually located around a painful joint or pressure point, nodules on the lower extremities and petechiae of variable size.

## Other Causes

Viral illnesses known to cause petechial rashes include coxsackievirus A9, echovirus 9, Epstein-Barr virus and cytomegalovirus infections, atypical measles and viral hemorrhagic fevers caused by arboviruses and arenaviruses. Coxsackievirus and echovirus infections in children can produce severe illness and, at times, are difficult to distinguish from meningococemia.

Included in the differential diagnosis of petechial rash are disseminated gonococcal infections, bacteremia, staphylococemia and thrombotic thrombocytopenic purpura.

## Diffuse Erythema with Desquamation

## Toxic Shock Syndrome and Scalded Skin Syndrome

*Staphylococcus aureus* is the organism responsible for classic toxic shock syndrome and scalded skin syndrome. Toxic shock syndrome can present with hypotension, erythema, fever and multisystem dysfunction. Most cases of nonmenstrual toxic shock syndrome occur in the postoperative setting.



**FIGURE 5.** Diffuse erythema in toxic shock syndrome.

Several different staphylococcal exotoxins have been implicated. The syndrome may result from infection, or it may occur because of simple colonization with *S. aureus*. Staphylococcal scalded skin syndrome occurs in infants, young children and adults with immunosuppression or renal impairment.

The rash is usually diffuse and can present as bullous impetigo, scarlatiniform lesions or diffuse erythema (Figure 5). The mucous membranes are spared in most patients. During the physical examination, the physician should attempt to elicit Nikolsky's sign (shearing of the skin with gentle lateral pressure).

### Other Causes

Ehrlichiosis, a rickettsial-like infection, can occasionally be associated with a clinical picture similar to toxic shock syndrome, including diffuse erythema. *Streptococcus viridans* bacteremia is another rare cause of generalized erythema. Finally, enteroviral infections, toxic epidermal necrolysis, graft-versus-host reaction, erythroderma and generalized pustular psoriasis (von Zumbusch's psoriasis) may present with diffuse erythema.

## Vesiculobullous-Pustular Eruptions

### Varicella-Zoster Virus Infections

Varicella-zoster virus is the most infectious of the human herpesviruses. It is responsible for varicella (chickenpox) and herpes zoster (shingles).

### Other Causes

Staphylococcal bacteremia may present with a widespread pustular eruption. Gonococcemia may also produce a pustular rash, although other lesion types, such as macules, petechiae and papules, are usually present.

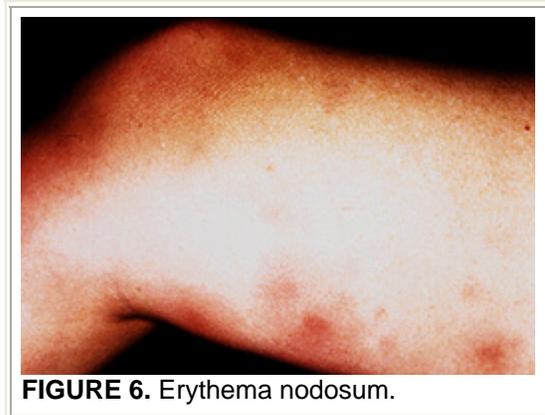
In immunocompromised patients, disseminated herpes simplex virus infection must be considered. Patients with underlying liver disease, renal dysfunction or diabetes are particularly susceptible to infection with *Vibrio vulnificus*, which is acquired from eating seafood, exposure to sea water or injury when handling crabs. *Rickettsia akari*, transmitted by a house mite, is the cause of rickettsialpox, a mild disease characterized by a local eschar, a papulovesicular rash and a mild clinical course.

## Nodular Eruptions

### Erythema

Erythema nodosum is an acute inflammatory and immunologic process involving the panniculus adiposus (the fatty tissue layer underlying the skin). A number of etiologies have been identified. This condition is more common in women than in men.

Presenting features often include fever, malaise and arthralgias. The characteristic nodules are painful and tender. The lesions most often develop on the lower legs, knees and arms



**FIGURE 6.** Erythema nodosum.

(Figure 6). The course of erythema nodosum depends on the specific cause, but spontaneous resolution can be expected within six weeks.

### Other Causes

In immunocompromised patients, disseminated fungal infections may produce nodular lesions. Disseminated candidiasis may present with diffuse nonerythematous nodules in an immunocompromised patient who has fever and myalgias. Other fungal infections to consider include cryptococcosis, blastomycosis, histoplasmosis, coccidioidomycosis and sporotrichosis.

Rarely, bacteria such as *Nocardia*, *Pseudomonas* and *Mycobacterium* species may produce nodular lesions.

## Summary

Fever is a symptom which indicates disease, from mild upper respiratory tract infections to serious sepsis and cancer. All patients of fever should be promptly dealt with. Viral upper respiratory tract infections require no treatment. But early recognition and treatment of most conditions will avert complications, morbidity and mortality

## RECOMMENDED READING

1. Fever and Hyperthermia. Harrison's Principles of Internal Medicine, 16<sup>th</sup> Edn, 2005; 104-8.
2. Fever and Rash. Harrison's Principles of Internal Medicine, 16<sup>th</sup> Edn, 2005; 108-116.
3. Fever of Unknown Origin. Harrison's Principles of Internal Medicine, 16<sup>th</sup> Edn, 2005; 116-121.
4. Approach to Fever or Suspected Infection in the Normal Host. Cecil Medicine, 23<sup>rd</sup> Edn. 2007;2112-17.
5. <http://www.who.int/malaria/docs/TreatmentGuidelines2006>.
6. Chikungunya. JAPI, 2006; 54:725-26.
7. <http://en.wikipedia.org/wiki/Chikungunya>.
8. Centres for Disease Control and Prevention: Chikungunya Virus Factsheet. <http://www.cdc.gov/ncidod/dvbid/chikungunya/chickvfact.htm>
9. [http://www.who.int/csr/disease/avian\\_influenza/guidelines/ClinicalManagement07](http://www.who.int/csr/disease/avian_influenza/guidelines/ClinicalManagement07).
10. <http://www.aafp.org/afp/20000815/804.html>