

# Fever and Serology

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## ABSTRACT

Fever is a common symptom encountered in the clinical practice. This can provide vital clues about the underlying condition. This is a brief report on the role of serological investigations in a patient with fever.

**Keywords:** Fever, Infections, Serology.

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## INTRODUCTION

Fever can be referred to a Pandora's box, as it is surrounded by so many mysteries. The proper investigation of fever is important, as it provides important diagnostic clues. This review discusses the microbiological experiences with fever from the perception of a physician, which could assist in fever investigation.

## EPIDEMIOLOGY AND CAUSES

Fever is highly variable. In Western countries, inflammatory causes are more common and infection plays a major role in causing fever in low- and middle-income countries. The most commonly reported infections are enteric fever, brucellosis, tuberculosis, endocarditis, and intra-abdominal abscesses.<sup>1</sup>

The infectious etiologies of fever include enteric fever, tuberculosis, dengue/viral fever, malaria, leptospirosis, brucellosis, typhus fever, focal abscesses, infectious mononucleosis, and infective endocarditis. The noninfectious etiologies include connective tissue disorders, autoimmune disorders, and malignancies.<sup>1</sup>

## HISTORY COLLECTION

The methodology to investigate a fever starts from the history. A careful history should be comprised of previous infectious illnesses, family history of infection, exposure to similar infections, residence and country of origin, recent travel, zoonotic exposure, and leisure activities. Physical examination requires special attention to the eyes, heart, spinal tenderness point, liver/spleen, lymphadenopathy, skin lesions, and oropharynx.<sup>1</sup>

## BASIC LABORATORY AND RADIOLOGICAL INVESTIGATIONS

The basic laboratory investigations include complete blood count (CBC), peripheral blood smear, erythrocyte sedimentation rate, C-reactive protein (CRP), liver function tests, and blood and urine culture. Radiological investigations such as the chest radiograph, CT, and MRI scans of the abdomen and pelvis are performed, if required.<sup>1</sup>

The CBC is the most important nondefinite investigation performed in cases with fever. The observations from CBC are suggestive of the following diseases:

- Leukopenia: Enteric fever, TB, HIV, SLE
- Leukocytosis: Pyogenic infection, vasculitis
- Reactive lymphocytosis: EBV, CMV

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- Eosinophilia: Drug reactions, parasitic infections
- Eosinopenia: Enteric fever
- Thrombocytosis: Pyogenic infection, inflammation
- Thrombocytopenia: Malaria, SLE, HIV
- Pancytopenia: Bone marrow infiltration, SLE

The liver function test also plays a vital role in the investigation. Elevated alanine transaminase (ALT)/aspartate transaminase (AST) indicates viral hepatitis or infectious mononucleosis. Elevated alkaline phosphatase and gamma glutamyl transpeptidase indicate granulomatous hepatitis, sepsis, or cholangitis.<sup>2</sup>

Segal et al. have reported CRP as the most useful marker in children to differentiate bacterial and viral infections. The CRP increases during the first 36 hours of fever and declines more rapidly with viral infections. In a patient with fever duration > 24 hours, if CRP is >11 mg/dL, the probability of having a bacterial infection is 75%; whereas if CRP is ≤5 mg/dL, the chance of a bacterial infection is unlikely (>95% accuracy).<sup>3</sup>

Procalcitonin is more specifically elevated in bacterial infections and the levels can correlate with the severity of sepsis. It can be used as a trend to monitor a sepsis patient, rather than a single diagnostic marker.<sup>4</sup>

## Enteric Fever

Timing of tests is very important in the investigation of enteric fever.

**Week 1:** Isolation of Salmonella from blood/bone marrow. Automated culture systems do better. The success of a culture lies in the blood volume and proper timing of the collection of the sample.

**Week 2:** The Widal by tube method is preferred. The slide method can also be used, but there are chances of false-positive results.

**Week 3:** Stool culture.

**Week 4:** Urine culture.

As per the WHO, there is no definitive role for rapid typhoid antibody tests like tubex, typhidot, typhidot rapid, and IgM dipstick, and there are no other molecular tests in the market for routine diagnosis. Culturing remains the gold standard.<sup>5</sup>

### Brucellosis

IgM raises first and peaks at around 3 months of the infection. IgM ELISA is usually preferred, followed by the *Brucella* agglutination test. However, blood culture remains the gold standard, but prolonged incubation is required.<sup>6</sup>

### Dengue

The NS1 antigen level elevates during the first 5 days of fever, followed by IgM and IgG in a primary infection. Secondary infection witnesses an accelerated IgG response. The serological markers include ELISA for NS1, IgM, and IgG.<sup>7</sup> Real-time PCR is helpful during an acute viremic phase. The rapid test does not have any role.

### Chikungunya

Markers include IgM, IgG, and circulating viruses. According to the testing algorithm by CDC, if the disease onset is <6 days, PCR should be performed and if it is >6 days, IgM ELISA should be carried out.<sup>8</sup>

### Leptospirosis

Around 90% of the infection is presented as undifferentiated febrile illness. It is often misdiagnosed at onset as aseptic meningitis, influenza, hepatic disease, or fever (pyrexia) of unknown origin. The tests available for the diagnosis of leptospirosis include dark field microscopy, IgM ELISA, microscopic agglutination test, and PCR. Dark field microscopy requires 104 leptospires/mL to be visible under the microscope. However, it lacks sensitivity and specificity. IgM ELISA has chances of false positivity. The gold standard is the microscopic agglutination test, followed by PCR.<sup>9</sup>

### Infectious Mononucleosis

The immune response of infectious mononucleosis involves several antigens and antibodies, and they include early antigens, followed by heterophile antibodies and later viral capsid antigens (VCA IgM, VCA IgG, and Epstein–Barr nuclear antigen (EBNA)-1 IgG). A positive VCA IgM and negative VCA IgG and EBNA-1 IgG and a positive VCA IgM and IgG and negative EBNA-1 IgG indicate acute infection. A positive EBNA-1 IgG and VCA IgG indicate past infection. A late primary infection is indicated when all three markers are positive.<sup>10</sup>

### Malaria

The target antigens are *P. falciparum*-specific proteins like histidine-rich protein II or lactate dehydrogenase and pan-specific antigens (aldolase or pan-malaria pLDH). The PCR, generally used to confirm malaria infection, detects only 1–5 parasites/μL of blood. However, peripheral smear and rapid tests can detect 50–100 parasites/μL of blood.<sup>11</sup> Recently the Ministry of Health and Family Welfare prohibited the use of antibody-detecting rapid diagnostic tests for the diagnosis of malaria.<sup>12</sup>

### Typhus Fever

Scrub typhus and Indian tick typhus predominate in India. The Weil-Felix test can be used only after 1 week and has low sensitivity and specificity due to cross-reactivity of *Proteus* antigens used. However, ELISA has good sensitivity and specificity. IgM ELISA and the *R. conorii* ELISA IgG/IgM kit are used correspondingly for the detection of scrub typhus and Indian tick typhus.<sup>13</sup> Scrub typhus

IgM should be interpreted with caution, as IgM levels persist for a longer duration and there are possibilities for false-positive results when single serum samples are interpreted.<sup>11</sup> Therefore, further research should focus on antigen detection assays.<sup>14</sup>

### Tuberculosis

The Ministry of Health and Family Welfare, Government of India, has banned the use of inaccurate serological blood tests for the diagnosis of TB.<sup>15</sup> The Quantiferon TB gold test (QFT) measures the release of interferon gamma produced in whole blood in response to stimulation by the purified protein derivative. The Centers for Disease Control and Prevention (CDC) recommends initial and serial testing of persons with an increased risk for latent TB (recent immigrants, injection drug users, residents, and employees of prisons and jails) and also for individuals who are, by history, at low risk for latent TB but whose future activity might place them at increased risk for exposure (healthcare workers and military personnel).<sup>16</sup> However, Quantiferon gold is contraindicated in the evaluation of suspected active tuberculosis; assessment of contacts of persons with infectious tuberculosis; screening of children aged <17 years, pregnant women, or for persons with clinical conditions that increase the risk for progression of latent to active TB; detection of latent TB after suspected exposure; confirmation of tuberculin skin test results; and diagnosis of *M. avium* complex disease.<sup>17</sup>

### Invasive Fungal Infections

Biologic markers include galactomannan *Aspergillus* antigen and the fungal wall component (1–3)-β-D-glucan. However, it is associated with a high negative predictive value. The 2016 Infectious Diseases Society of America (IDSA) guidelines for aspergillosis recommends that galactomannan and 1,3-β-D-glucan assays are useful in high-risk patients and are not recommended for routine blood screening in patients receiving antifungal therapy or prophylaxis, but can be applied to bronchoscopy specimens from these patients.<sup>18</sup> Invasive fungal infection should be tested in conjunction with other methods for the diagnosis of invasive fungal infections and should precede antifungal therapy. Positive test results should be confirmed with a second new specimen or repeated from the initial specimen.<sup>19</sup>

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