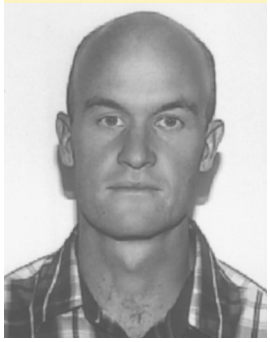
UNEXPLAINED FEVER — AN APPROACH TO DEFINING THE AETIOLOGY

The cause of an unexplained fever needs to be found before treatment can be started.



GRAEME MEINTJES
MB ChB, MRCP (UK), FCP (SA)
Senior Registrar
Infectious Diseases Unit
University of Cape Town
Consultant
Department of Medicine
GF Jooste Hospital
Manenberg

Dr Meintjes' research interests include immune reconstitution inflammatory syndromes, delay in TB diagnosis and cryptococcosis.

KEVIN REBE
MB ChB, FCP (SA)
Senior Registrar
Infectious Diseases Unit
University of Cape Town
Consultant
Department of Medicine
GF Jooste Hospital
Manenberg

Dr Rebe's research interests include Pneumocystis carinii *pneumonia.*

Patients at all levels of the health care system will often have a fever on initial presentation. The cause may be obvious; most will have a simple viral upper respiratory tract infection (URTI) and others will have signs and symptoms pointing to the site and aetiology of the fever. Sometimes, however, a patient will present with fever without obvious localising clinical features. A systematic approach is needed to elucidate the cause of the fever in these situations, in which the cause of the fever is often a common disease with an uncommon presentation, rather than a rarity.

In this article, we suggest 10 questions that should be asked when an adult patient has an unexplained fever on initial presentation. This article is not intended to deal with the separate, but related, issue of a fever of unknown origin (FUO), which is defined as documented fever of > 38.3°C for more than 3 weeks with no established diagnosis despite appropriate investigation for 1 week.[1]

1. IS THERE A FOCUS OF BACTERIAL SEPSIS?

A thorough history and examination and directed special investigations will usually elucidate a focus of bacterial sepsis. Particular attention should be paid to focal pain and tenderness (e.g. pleuritic, renal angle, over sinuses), purulent secretions (e.g. sputum, nasal discharge, dysentery, vaginal discharge) and other features of acute inflammation (e.g. erythema, swelling, limitation of movement of a joint). Other specific symptoms (such as tachypnoea in the case of pneumonia) will point to an organ system. A checklist of sites of bacterial sepsis is given in Table I.

Investigations should be directed by the suspected site of sepsis, but if bacterial sepsis is suspected without an obvious site, the initial investigations should include a chest X-ray, urine Dipstix, urine microscopy and culture, and blood culture.

In elderly or immunosuppressed patients, for example diabetics, HIV-positive patients, those on chemotherapy and alcoholics, the clinical signs of bacterial sepsis may be subtle. These patients may even fail to mount a febrile response. An example is the elderly patient with pneumonia presenting with confusion, but without a cough, and with minimal fever. Tachypnoea is often the major clue to the diagnosis in this scenario. Another example is the diabetic patient with a renal abscess presenting with constitu-

Table I. **Sites of bacterial infection**

Upper respiratory tract
- Tonsillitis
- Sinusitis
- Otitis media
- Retropharyngeal abscess

Lower respiratory tract
- Bronchitis
- Pneumonia
- Empyema
- Lung abscess

Abdominal
- Cholecystitis
- Appendicitis
- Diverticulitis and diverticular abscess
- Liver abscess
- Other intra-abdominal collection (e.g. subphrenic abscess)
- Peritonitis

Urinary tract
- Pyelonephritis
- Renal abscess

Perineum
- Ischiorectal abscess

Skin and soft tissue
- Cellulitis
- Erysipelas
- Soft-tissue abscess including psoas abscess

Central nervous system
- Meningitis
- Brain abscess
- Extradural abscess

Cardiovascular
- Infective endocarditis
- Septic pericarditis
- Arteritis and mycotic aneurysms
- Septic thrombus

Pelvic
- Pelvic inflammatory disease
- Prostatitis

Musculoskeletal
- Septic arthritis
- Osteomyelitis
- Pyomyositis

Dental
- Dental abscess

Prostheses and grafts
- Sepsis of vascular grafts, joint prostheses, artificial valves, intravascular lines, etc.

Surgical wound infections

tional symptoms and weight loss but minimal urinary tract symptoms.

Diverticulitis and diverticular abscesses are an easily missed cause of fever in elderly patients. Clinicians should be alerted by a history of rectal bleeding or loose bowel motions, evidence of rectal bleeding on examination, and lower abdominal pain and tenderness.

Always look for stigmata of infective endocarditis, particularly in patients with a murmur or who are known to have valvular or congenital heart disease, or a prosthetic valve. The examination should include urine Dipstix. Blood cultures and echocardiography are indicated if the diagnosis is entertained.

2. IS THIS PATIENT SEPTICAEMIC?

There is no single clinical sign to warn that a patient is septicaemic, but clues include hypotension, poor peripheral perfusion, confusion, marked tachycardia and tachypnoea (representing metabolic acidosis) in the absence of pneumonia. Immediate hospital referral and admission is advised.

Two important causes of septicaemia are:

Salmonella septicaemia

The classic syndrome associated with salmonella infection is enteric fever. This is an acute illness that initially presents with fever, headache and abdominal pain. Other signs may include a relative bradycardia and splenomegaly. The syndrome is usually due to infection with *Salmonella typhi,* but may also be caused by other salmonella species such as *S. paratyphi* and shigella or campylobacter.

The fever is initially remitting but becomes sustained. Diarrhoea and constipation are both described. The majority of patients with enteric fever will have some disturbance of gastrointestinal function. Rose spots occur in 2 - 46% of patients, but may be difficult to see in patients with dark skin.

Definitive diagnosis is made by culturing the organism, with the highest yield from blood cultures early in the course of the disease. Stool and urine cultures may become positive only later, and their yield is under 50%. A decreased leukocyte count is a useful pointer. The Widal test is of limited value in diagnosis.[2]

Studies from sub-Saharan Africa looking at bacteraemia in HIV-positive patients admitted with a fever have shown that salmonella species are commonly isolated. Non-typhi salmonella bacteraemia is an AIDS-defining illness.

It is also important to consider shigella or campylobacter colitis if there is a short history of fever with abdominal cramps, even in the absence of diarrhoea, as these features may precede the diarrhoea or dysentery.

Staphylococcal septicaemia

Staphylococcus aureus septicaemia may present in the absence of a clinically identifiable source (up to 58% of cases of community-acquired *S. aureus)*.[3] The most common identified source is skin sepsis. A quarter of patients with community-acquired staphylococcal septicaemia are diabetic. Intravenous drug abuse and the use of intravenous indwelling catheters increase the risk of staphylococcal septicaemia and endocarditis.

Common presenting features are fevers, sweats, rigors and confusion. Staphylococcal septicaemia tends to result in seeding out of infection, giving rise to endocarditis, septic arthritis, abscesses, osteitis and meningitis. Community-acquired staphylococcal septicaemia carries a mortality of 35%. Management includes aggressive antibiotic therapy and surgical drainage of sites of metastatic infection.

3. IS THERE A HISTORY OF RECENT TRAVEL?

The list of tropical diseases that can cause fever is extensive. Many patients with a travel history and fever will be suffering from unrelated and simple diseases such as a viral URTI, but it is important to exclude travel-acquired diseases that are serious, treatable, or might require isolation.

The first diagnosis to consider in any patient who has been travelling is malaria. This requires a detailed history of their travel itinerary, concentrating on destinations and duration of travel, as well as airport lay-overs, as 'airport-acquired' malaria is not unheard of. The travel history should include domestic travel to malarial areas of South Africa. Always ask about chemoprophylaxis for malaria, as well as any self-treatment with antimalarials or antibiotics. Smears for malaria should be sent (Fig.1) and antigen testing is also useful. If the diagnosis is strongly suspected, repeat smears should be sent if the initial one is negative. Clues to the diagnosis include splenomegaly and thrombocytopenia. It is also worth remembering that cases of malaria do rarely occur outside endemic malaria areas without a history of travel, and are probably related to the transportation of the mosquito vector to the non-endemic area.

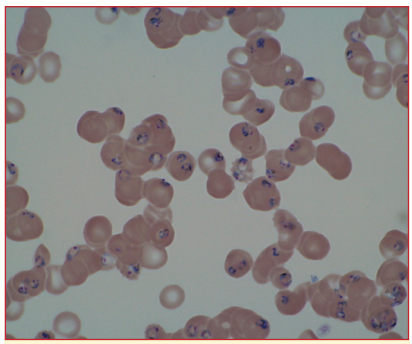


Fig. 1. Smear showing Plasmodium falciparum *infection.*

Once malaria has been excluded the following approach may be useful:

- consider the incubation period of common pathogens (Table II)
- consider the patient's travel history, specifically duration and destination
- consider the likely pathogens that occur at the destinations visited.

These factors can then be combined to find a 'best fit' differential diagnosis and appropriate investigations can then be requested for confirmation. Certain diseases also have a predilection for specific organ systems (e.g. viral hepatitis), and clinical findings may guide investigation and management.[4]

4. IS THERE A RASH?

In any patient who has a rash with a fever, the aetiology must initially be assumed to be infectious or drug-related. The rash may be a clue to a specific diagnosis.

Considerations in the patient with fever and a rash include:

- drug exposure in the last month
- travel and outdoor exposure
- occupational exposure
- animal exposure
- possibility of sexually transmitted infection.

When considering a rash, the following factors are important:

- timing of the rash
- type of skin lesions
- distribution
- progression
- associated clinical findings (e.g. meningism).

A few important examples of diseases causing fever and a rash are cited below.[5]

Meningococcus

Rash occurs in 50 - 90% of patients with fulminant disease. The rash begins as small irregular petechiae, which may coalesce to form palpable purpura, which often have a gun metal-grey colour. They may occur anywhere on the body. A Gram stain from a deroofed skin lesion frequently reveals the causative organism.

Tick bite fever

Rash is a hallmark of this disease. Initially the rash is maculopapular and then becomes more petechial. It occurs classically 4 - 6 days after the bite. History of tick exposure is important, as the onset of the rash may be delayed. The rash typically begins on the extremities, often around the wrists or ankles and affects the palms and soles. It then spreads to involve the

Table II. **Travel-related pathogens classified according to incubation period**

Long (> 2 weeks)	Short (< 2 weeks)
Malaria	Arboviral infections
Tuberculosis	Viral haemorrhagic fevers
Viral hepatitis	Enteric bacteria and viruses
Amoebae and worms	Rickettsia
HIV	Plague
Schistosomiasis	Seafood poisoning
Filariasis	Pneumonia
Leishmaniasis	Influenza
Trypanosomiasis	Anthrax

trunk, often sparing the face. Headache occurs in over 90% of cases.

Toxic shock syndrome

This syndrome may occur following colonisation or localised infection with toxin-producing *S. aureus*. Patients may present severely ill, with an acute febrile illness, hypotension, and symptoms and signs of multi-organ involvement. A generalised erythematous reaction occurs due to staphylococcal toxin production. The rash is a diffuse erythroderma with desquamation occurring 1 - 2 weeks after the onset of the illness. It is important to look for the site of localised infection (e.g. carbuncle or retained tampon).

Other infections due to staphylococcal and streptococcal infection may also present with a rash. Examples include staphylococcal scalded skin syndrome, impetigo, cellulitis and erysipelas.

Bacterial endocarditis

This diagnosis may be suggested by a variety of skin lesions. These include Osler's nodes, Janeway lesions and splinter haemorrhages.

Viral exanthems

Many viral illnesses are associated with rash. They classically produce a maculopapular rash. Included in this group are all the common childhood viruses such as rubella, measles and roseola.

Secondary syphilis

Rash is the most characteristic finding in secondary syphilis. It is classically a papular erythematous eruption involving the trunk and extremities including palms and soles. Other features are constitutional (including fever), condylomata lata and generalised lymphadenopathy.

5. IS THE PATIENT HIV-POSITIVE?

The aetiological possibilities are obviously wider if a patient has HIV infection. If the patient's HIV status is not known, clinical features that suggest HIV infection should be sought — the most common clinical pointers are generalised lymphadenopathy, significant wasting, oral candidiasis, oral hairy leukoplakia, shingles (old or current), molluscum contagiosum, fungal infections, Kaposi's sarcoma, papular pruritic eruption or post-inflammatory scarring.

Consented HIV testing with pre- and post-test counselling is indicated if these features are present, or an HIV-related opportunistic infection (e.g. *Pneumocystis carinii* pneumonia (PCP)) is suspected.

The common causes of fever in HIV-positive patients are outlined in Table III.

The work-up of a fever in an HIV-positive patient may include: a chest X-ray, blood cultures (including TB and fungal blood cultures), urine and sputum for TB, lymph node fine needle aspiration biopsy (FNAB), abdominal and cardiac ultrasound, bone marrow biopsy (especially if patient is pancytopenic), serum cryptococcal latex agglutination test (CLAT) and lumbar puncture.

Patients with advanced HIV infection may present with a fever within 3 months of starting antiretroviral therapy, owing to development of an immune reconstitution syndrome. This is an overexuberant immune response to an infection that was clinically occult while the patient was profoundly immunosuppressed. Immune reconstitution syndromes may develop in relation to most of the infections listed in Table III. Immune reconstitution syndrome may also manifest as a paradoxical deterioration with fever in a

Table III. **Common causes of a fever in HIV-positive patients[6]**

CD4 > 200
- Bacterial pneumonia
- Upper respiratory tract infection
- Pulmonary tuberculosis (PTB)

CD4 < 200
- PTB and extrapulmonary TB
- PCP
- Cryptococcosis, histoplasmosis
- Cytomegalovirus (CMV)
- *Mycobacterium avium*-intracellulare
- Salmonella non-typhi
- Nocardiosis
- Bacillary angiomatosis
- Lymphoma

Note: HIV itself can cause fever (as part of seroconversion or of the HIV wasting syndrome).

condition for which the patient is on treatment, typically TB.

6. COULD THIS BE AN HIV SEROCONVERSION ILLNESS?

This is obviously a common cause of fever in South Africa today. Features can be nonspecific, and HIV seroconversion is probably often misdiagnosed as a viral URTI or infectious mononucleosis due to Epstein Barr virus (EBV) infection. Between 40% and 90% of new HIV-1 infections are associated with symptomatic illness. The presence of generalised lymphadenopathy, orogenital ulceration and a morbiliform or fine maculopapular rash (mainly involving the trunk) should alert the clinician. It is important to note that the rash may be minimal, especially in dark-skinned individuals, the nodes small and other features absent, making fever the predominant sign.

The importance of diagnosing acute HIV lies in the opportunity to prevent further infection through appropriate counselling. The common clinical features are listed in Table IV. It is also important to remember that because patients develop transient profound lymphopenia during seroconversion, it is possible that they may develop opportunistic infections such as oral thrush or even PCP during this time.

Symptoms tend to occur days to weeks after the infection. The acute illness may persist from a few days to 10 weeks, but in most subsides within 2 weeks.

Differential diagnosis is acute EBV or cytomegalovirus (CMV), but these are rare in adults, as most acquire immunity after childhood infection.

The diagnosis is confirmed with either p24 antigen or viral RNA testing and subsequently HIV antibody testing. Antibody tests become positive 22 - 27 days after infection and once symptoms have subsided.

7. COULD THIS BE TB?

The diagnosis of TB is invariably considered when there is a history of chronic cough or haemoptysis, together with night sweats, malaise and weight loss. However, TB may not always present with respiratory features. In patients with advanced HIV (CD4 < 200) cavitation in the lung may not occur, and dissemination and extrapulmonary TB are more common than in HIV-negative patients. The presentation of TB in these patients may be atypical, with constitutional and non-pulmonary symptoms predominating. For example, if the patient has abdominal TB, this may present with abdominal pain and fever.

In addition, miliary TB may affect HIV-negative individuals, especially those who are immunosuppressed for another reason such as alcoholism. Miliary TB in this context will usually give a distinctive appearance on a chest radiograph (CXR) (Fig. 2), but the CXR may be clear initially (in 22% in a series at Groote Schuur Hospital the CXR did not reveal miliary nodules). Common symptoms of miliary TB are constitutional (92%), respiratory (72%), neurological (25%) and abdominal (21%). The median symptom duration of miliary TB in HIV-negative individuals when they are admitted to a tertiary care facility is 4 weeks (range 1 - 52 weeks).[8]

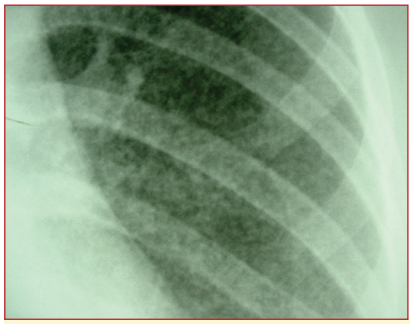


Fig. 2. Chest radiograph appearance of miliary TB.

8. COULD THIS BE THE PRE-ICTERIC PHASE OF VIRAL HEPATITIS?

Acute viral hepatitis is most often a self-limiting febrile illness. Many different hepatitis viruses have been isolated, and early in their course there is little to differentiate them clinically. The presentation of viral hepatitis is variable and ranges from asymptomatic infection to fulminant liver failure.

The illness is divided into four phases:
- incubation phase
- pre-icteric phase
- icteric phase
- convalescence.

Importantly, the patient feels well during incubation. The pre-icteric phase often presents as a flu-like illness with weakness, headaches, myalgias, chills and fever. Fever rarely persists into the icteric phase and thus jaundice with a high fever is not characteristic of viral hepatitis. Fever is also not an invariable feature of viral hepatitis prodromes.

When this diagnosis is considered, a careful history should be obtained to determine possible exposure. Supportive clinical features such as right upper quadrant tenderness may be useful. The diagnosis is confirmed by serological tests.

Table IV. **Clinical features of HIV seroconversion illness**[7]

Fever	> 80 - 90 %
Fatigue	> 70 - 90%
Rash (usually maculopapular)	> 40 - 80%
Headache	32 - 70%
Lymphadenopathy	40 - 70%
Pharyngitis	50 - 70%
Myalgia or arthralgia	50 - 70%
Oral ulcers	10 - 20%
Genital ulcers	5 - 15%
Aseptic meningitis	24%

9. DOES THIS PATIENT HAVE CHRONIC LIVER DISEASE?

Patients with chronic liver disease and excessive alcohol intake are immunosuppressed and this may mask the site of sepsis causing fever. These patients are at increased risk of both bacterial and fungal infections. One of the most common causes of sepsis is spontaneous bacterial peritonitis (SBP). This may occur in the absence of clinically identifiable ascites, and signs of peritonism are usually absent. When present, ascites should be tapped and sent for analysis to confirm or exclude SBP.

10. COULD THE CAUSE OF THIS FEVER BE NON-INFECTIVE?

The list of non-infective causes of fever is extensive. The important categories are listed in Table V.

An important cause of fever in elderly patients is giant cell arteritis. Patients typically present with symptoms of polymyalgia rheumatica, unilateral headache and fever. Other granulomatous diseases such as sarcoidosis and Wegener's granulomatosis may also present with fever.

Many commonly used drugs (especially antibiotics) can cause a drug fever. Diagnosis of a drug fever is confirmed by resolution of the fever within 3 - 4 days of stopping the drug, and recurrence of fever on rechallenge. Even medication that a patient has taken for years may cause a drug fever.

The commonest malignancies to present with fever are Hodgkin's and other lymphomas. Others to consider are multiple myeloma, leukaemia and certain solid tumours (e.g. renal cell carcinoma and atrial myxoma).

Inflammatory bowel disease may present with fever prior to the onset of gastrointestinal symptoms.

Finally, other rare infective causes of fever to consider are brucellosis, Q fever, leptospirosis, amoebic liver abscess and pseudomembranous colitis. Pseudomembranous colitis occurs after antibiotic exposure and may initially present with fever and abdominal pain prior to diarrhoea.

References available on request.

Table V. **Categories of non-infective causes of fever**[1]

Connective tissue and granulomatous diseases
Drugs
Malignancy
Deep-vein thrombosis (DVT) or pulmonary embolism (PE)
Haematoma
Hyperthyroidism
Factitious
Miscellaneous (e.g. pancreatitis, thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, acute rheumatic fever, inflammatory bowel disease)

IN A NUTSHELL

A thorough history and examination will often elucidate a focus of bacterial sepsis.

The signs and site of bacterial sepsis may be masked in elderly and immunocompromised patients.

Clues to a septicaemic illness are hypotension, poor peripheral perfusion, confusion, marked tachycardia and tachypnoea in the absence of pneumonia.

The most important community-acquired septicaemic illnesses to consider are: staphylococcal, salmonella, meningococcal and septicaemia secondary to pneumonia or pyelonephritis.

The presence of a rash may point to a specific aetiology such as tick bite fever or meningococcaemia.

A history of recent travel to a malaria area should be sought.

In HIV-positive patients the diagnostic possibilities are wider, and include pulmonary and extrapulmonary TB, cryptococcosis and PCP.

HIV seroconversion illness is frequently missed. Signs that suggest it are a morbiliform rash, orogenital ulcers and generalised lymphadenopathy.

The most important diagnoses not to miss initially are: the septicaemic illnesses mentioned above, malaria, a pus collection, infective endocarditis, thrombotic thrombocytopenic purpura and acute leukaemia.