Assessment and initial management of acute undifferentiated fever in tropical and subtropical regions

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Acute undifferentiated febrile illnesses (AUFI) are characterised by fever of less than two weeks' duration without organ-specific symptoms at the onset.[1] These may begin with headache, chills, and myalgia. Later, specific organs may be involved. AUFIs can range from mild and self limiting disease to progressive, life threatening illness. A mortality rate of 12% has been reported in severely ill hospitalised patients in tropical regions.[2]

AUFIs are classified into malaria and non-malarial illnesses with the help of microscopy or rapid diagnostic tests for malaria.[3] The overlap of epidemiological and clinical features often renders clinical diagnosis difficult. There is greater focus on non-malarial AUFIs with the decline of malaria in many regions of the world.[4] They account for 20-50% of all fevers in children over 5 years of age and adults in Asia and Africa.[5] Laboratory confirmation is difficult—in contrast to malaria and dengue, for which high accuracy rapid diagnostic tests are now available. Current guidelines do not comprehensively address undifferentiated infections, which can fuel indiscriminate use of antimalarials and antibiotics.[6 7]

In this clinical update, we present an approach to the diagnosis and initial management of common AUFIs in children older than 5 years and in adults in tropical regions, taking into consideration availability of limited resources in some settings.

Sources and selection criteria
We searched PubMed for studies published in English between January 1990 and August 2018 using the MeSH terms: "(epidemiology, diagnosis, therapy, guideline) and (fever, bacteremia, typhoid fever, scrub typhus, rickettsial infections, spirochetal infections, arbovirus infections, malaria, brucellosis, melioidosis)." We also searched the Cochrane Database for related systematic reviews. Key references identified in review articles and textbooks were hand searched.

What are the causes of non-malarial AUFI?
Studies from Asia and Africa report arboviral infections (17.5% of severe febrile illnesses), bacterial bloodstream infections (mainly enteric fever) (10.5%), and bacterial zoonoses such as leptospirosis and rickettsioses (4.0% each) as major causes of non-malarial AUFI.[6 8-13] Box 1 presents the mnemonic "MA-ESR" as an aid to recall the common AUFIs, and figure 1 gives an overview of how undifferentiated fever is classified. Enteric fever affects an estimated 11.9 million people annually in Asia and Africa.[14] Globally, over one million cases each of leptospirosis and scrub typhus occur annually.[15 16]

Rarer infections include viral haemorrhagic fevers such as Ebola virus disease and Lassa fever seen in Africa, and Crimean-Congo haemorrhagic fever (CCHF) with a wider distribution. Outbreaks of CCHF (also sometimes referred to as Asian Ebola virus) have been documented in Pakistan and India in recent years with high mortality.[17-20] Timely recognition of these illnesses is important as they cause high mortality and spread rapidly.

How is it diagnosed?
Follow a typical stepwise approach to synthesise information from history and epidemiology. A careful history and physical examination can provide vital clues. Clinicians in settings with limited access to testing may have rely solely on these to formulate a probable diagnosis and start treatment (see fig 2).

Consider local pathogens, what season it is (some infections are particularly prevalent around rainy season), and activities or specific events that might give clues to the cause. Ask out about the onset, nature and features of the illness

Locally prevalent pathogens
The infographic lists common infections to consider by region (also see appendix 1 on bmj.com).[21] Within regions considered endemic, the epidemiology of AUFIs is continuing to evolve. Scrub typhus and leptospirosis, once considered rural diseases, now affect urban populations too. Urban parks, and flooding in slums have emerged

WHAT YOU NEED TO KNOW

- Malaria, arboviral infections (such as dengue), enteric fever, and bacterial zoonotic diseases (such as scrub typhus and leptospirosis) are common causes to consider in patients presenting with acute fever and no localising symptoms in tropical regions

- A step-wise approach—with a careful interpretation of local disease patterns, possible exposures and risk factors, clinical features, and basic laboratory data—can help clinicians recognise specific diseases

- Request testing for malaria and a full blood count in all patients with acute undifferentiated fever

- Early presumptive antibiotic therapy may be started for suspected bacterial zoonoses if diagnostic confirmatory tests are awaited or not available, as these infections may progress rapidly into a life threatening illness with multi-system involvement

- Treatment for enteric fever needs to account for increasing drug resistance, especially in South Asia

Box 1 | Mnemonic MA-ESR lists the five main disease groups that cause acute undifferentiated febrile illnesses
- **Malaria**—Including all malaria due to *Plasmodium falciparum*, *P vivax*, *P ovale*, *P malariae*, *P knowlesi*
- **Arboviral infections**—Such as dengue, chikungunya, Japanese encephalitis, Zika, yellow fever
- **Enteric fever**—Due to *Salmonella enterica* serovar Typhi and Paratyphi A, B, C
- **Spirochaete infections**—Such as leptospirosis and tick-borne or louse-borne relapsing fever
- **Rickettsial infections**—Including scrub typhus, murine typhus, spotted fevers
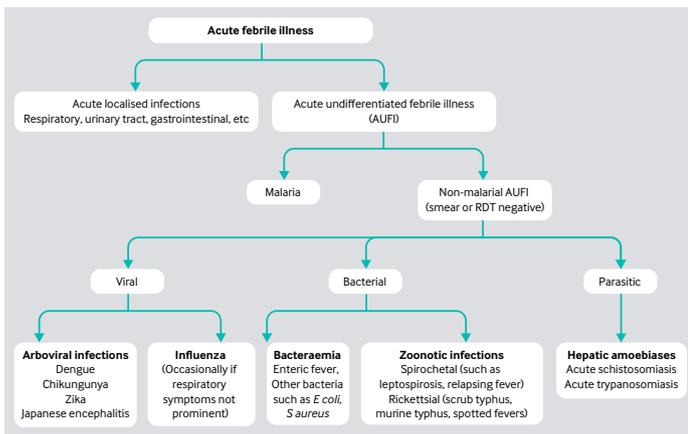
RDT = rapid diagnostic test. E coli = Escherichia coli. S aureus = Staphylococcus aureus.

Fig 1 | Broad classification of acute febrile illness. In patients with high fever and rhinorrhoea, consider ruling out influenza

as risk factors for these respectively.[22] [23] Dengue, once considered an urban disease, is increasingly observed in rural and peri-urban areas in India.[24] Melioidosis is an important cause of community-acquired sepsis in northern Thailand and northern Australia, and is now recognised to be endemic in many countries of the Indian subcontinent, East Asia, sub-Saharan Africa.[8] [25]

Seasonality
Arboviral infections, scrub typhus, leptospirosis, and melioidosis peak during the rainy season, similar to malaria. In many tropical areas, malaria occurs round the year. Seasonal dynamics of enteric fever are variable, with peaks after rainfall seen in northern latitudes.[26] Information on ongoing outbreaks or a cluster of cases in a family or neighbourhood are useful clues to guide diagnosis.

Potential exposures
Consider asking about:
- Insect or mosquito bites, which are involved in transmission of several infections (malaria, dengue, chikungunya, Zika, CCHF, scrub typhus, murine typhus, spotted fevers, relapsing fever).
- Ingestion of contaminated food and water, implicated in enteric fever.
- Contact with body fluids or products of animals or contaminated water and soil, through skin abrasions or conjunctiva, which is linked to leptospirosis.
- Walking barefoot, working in paddy fields, and flooding in urban areas, which are risk factors for scrub typhus and leptospirosis. In rural areas, the risks of exposure to a contaminated environment,
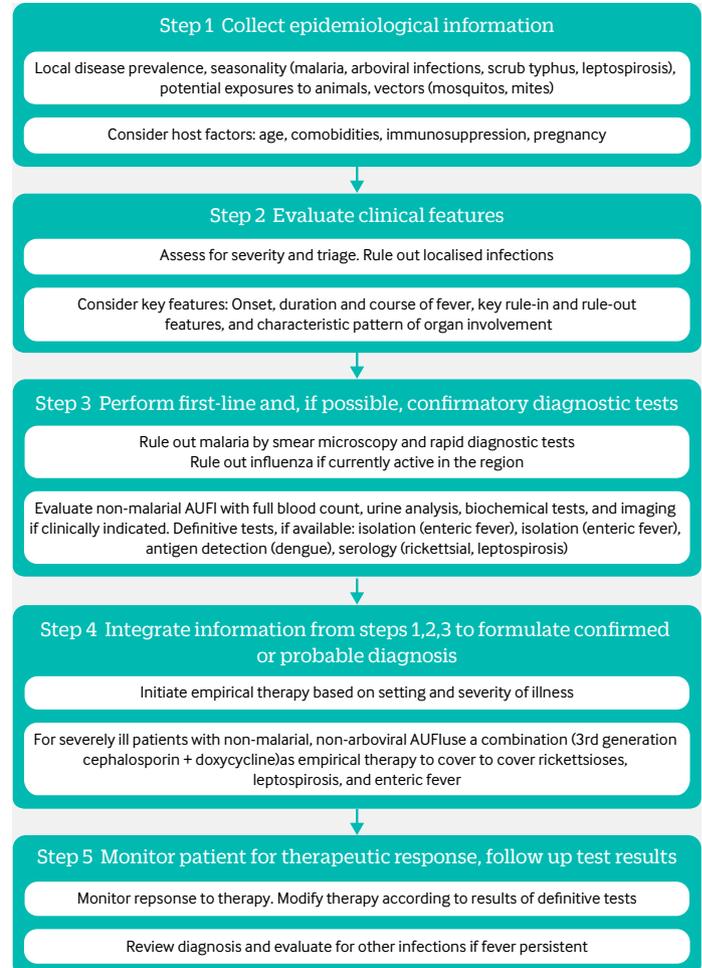
Fig 2 | The diagnostic and management approach for acute undifferentiated febrile illnesses in low resource settings

contact with animals, and exposure to multiple vectors can coexist, making it difficult to estimate the risk of any particular disease.

Onset, duration and pattern of fever and illness
The pattern of fever can be disrupted by fever medications such as paracetamol and ibuprofen but may sometimes be typical of a specific infection.
- Malaria, arboviral infections, scrub typhus, and leptospirosis have an abrupt onset and can rapidly progress to complications in the first week. A peak in temperature every other day is seen in malaria due to *Plasmodium vivax* or *P ovale*.[27]
- Enteric fever has a more insidious onset. Fever >39°C (102.20°F) for more than three days with abdominal pain and diarrhoea or constipation can suggest enteric fever.
- Dengue has a self limiting course with fever for up to 7-12 days.
- Fever in influenza classically lasts three days but may persist for up to eight days.[28]
- Fever may be absent or low grade in Zika infection.
- Tropical borrelioses cause relapsing fever lasting 3-5 days between afebrile periods of 4-10 days.

Patient related factors
Age, comorbidities, immunosuppression, and pregnancy can help narrow the differential diagnosis, and also affect outcomes. For example, patients with diabetes have a higher risk of

melioidosis.[8] [25] Bloodstream infection due to non-typhoidal Salmonella, disseminated tuberculosis, and deep mycoses are more commonly observed in adults with HIV infection.[29] Pregnancy related immunosuppression is associated with increased severity of infections, in particular with more severe falciparum malaria.

Examination

Assess severity of illness

Look for signs of severe disease (see box 3) which indicate the need for urgent referral and hospitalisation.

Rule out localised infections

Figure 3 indicates examination features consistent with a possible localised infection. Evaluate patients with fever, especially severe infection, for both localised infections and AUFIs. Influenza may be confused with AUFIs as fever and myalgia can initially overshadow respiratory symptoms, which may be absent in older people.[28] Complicated AUFIs may also evolve and mimic localised infections—such as falciparum malaria (encephalitis), scrub typhus (severe pneumonia), or icteric leptospirosis (hepatobiliary infections).

Look for diagnostic clues of AUFIs

Certain clues on examination, which we term rule-in signs, help narrow the differential diagnoses (see infographic and appendix 2 on bmj.com). Rule-in signs, if present singly or in combination, indicate a moderate to high likelihood of a particular AUFI—that is, they are good predictors of a particular disease. There is limited evidence, however, on the diagnostic value of these signs.

Scrub typhus has a characteristic skin lesion—an eschar (fig 4)—seen in 17-57% of patients as per recent reports from India,[33] [34] and in 56-86% of patients in reports from elsewhere in Asia.[33-35] Examine the neck, chest, axilla, abdomen, and groin for such lesions not associated with pain, pruritus, or oedema. A similar lesion in a patient with a milder illness in Africa is suggestive of African tick-bite fever, seen often in travellers returning from game parks. The lack of pain and oedema in eschars of rickettsial origin distinguish them from those of rarer causes such as tularaemia, anthrax, or East African trypanosomiasis.

Conjunctival suffusion (red eyes and oedema without exudate) and haemorrhage, jaundice, and marked muscle tenderness suggest
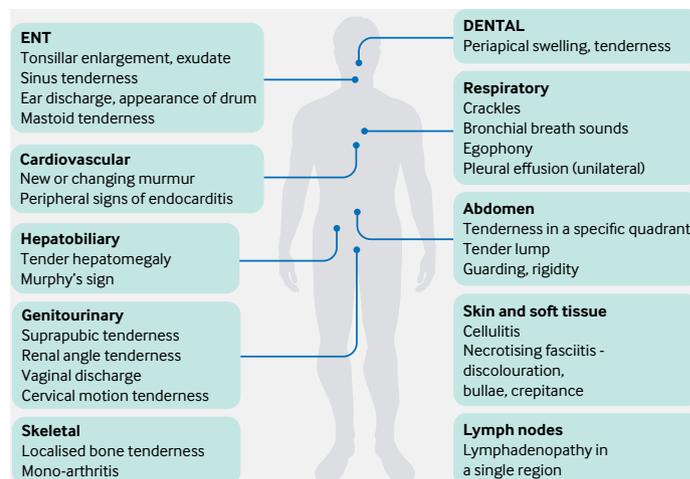

Fig 3 | Potential diagnostic clues to causes of acute localised infections

leptospirosis (fig 5).[36] A non-purulent conjunctivitis is also frequently seen in Zika virus infection, but not in other arboviral infections.

Rash and/or polyarthritis are suggestive of arboviral infections such as dengue, Zika or chikungunya. In Zika virus infection, a maculopapular rash appears typically on the first day with a cephalocaudal distribution and is intensely pruritic (worse in sleep). In contrast, the rash in dengue appears first on the trunk around five days after onset of fever.[37]

Symmetric arthritis of small joints with oedema is typical of chikungunya.[37]

Conversely, rule-out signs exclude a particular disease. For example, the presence of rash or lymphadenopathy renders malaria highly unlikely.[38] Likewise, generalised lymphadenopathy is uncommon in enteric fever.[39] [40] Jaundice with high fever makes a diagnosis of viral hepatitis less likely and instead suggests leptospirosis or other AUFIs with hepatic involvement.

What are the first investigations?

In endemic areas, request a complete blood count, urine analysis, and smear microscopy and/or rapid diagnostic test (RDT) for malaria in all patients with fever. Urine examination may reveal urinary tract infection, especially in women and older people as they may not present with localised symptoms. Biochemical tests (such as liver and renal function tests) and imaging (x ray and ultrasound) are useful in patients with

Box 3 | Red flag signs in patients with acute undifferentiated febrile illnesses indicating need for hospitalisation and urgent treatment

- *Prostration*—Unable to stand, sit, or walk without support[30]
- *Temperature*—Hyperpyrexia (temperature >41.5°C) or hypothermia (temperature <36°C) or rigors
- *Respiration*—Shortness of breath, respiratory rate >22 breaths/minute, cyanosis, arterial oxygen saturation <92% on room air[31]
- *Circulation*—Blood pressure <100 mm Hg systolic,[31] cold clammy extremities, capillary refill >3 seconds
- *Neurological*—Altered mental status (Glasgow coma scale <13), convulsions, positive meningeal signs (such as neck stiffness and Kernig's sign)[31]
- *Abdominal pain*—Severe or persistent vomiting[32]
- *Severe conjunctival or palmar pallor*[30]
- *Jaundice on examination of sclera*[30]
- *Petechial or purpuric rash*
- *Bleeding*—From nose, gums, or venepuncture sites; haematemesis, melaena[30]

Fig 4 | An eschar on abdomen. Note the characteristic punched-out ulcer with a central black scab (often missing in eschars in moist areas)

Fig 5 | Characteristic eye signs of leptospirosis: conjunctival suffusion, jaundice, and sub-conjunctival haemorrhage

localised symptoms and in patients with severe illness to detect complications. Table 1 describes the diagnostic value of findings on initial investigations.

Based on the suspected diagnosis, confirmatory tests for specific infections are requested (table 2). Spirochetal and rickettsial infections are confirmed by demonstration of either a IgM seroconversion (appearance of IgM in specimens about 10 days apart), or a fourfold elevation of IgG titre in a pair of specimens at least two weeks apart. This precludes their use in the immediate clinical decision making. Further, these tests have limitations in availability and sensitivity. The sensitivity of blood culture and PCR is influenced by duration of illness (highest in the first week), specimen type (highest with eschar in the case of scrub typhus), and by previous antibiotic treatment.

The specificity of serological tests is affected by cross-reactions among pathogens, and by persistence of IgM antibodies after infections. In practice therefore, diagnostic certainty eludes the physician dealing with a non-malarial AUFI, and the demonstration of IgM antibody in a single acute-phase specimen contributes, at best, to a "probable diagnosis" of leptospirosis and scrub typhus.

What are the possible complications?
Malaria, scrub typhus and leptospirosis can progress rapidly to multi-organ dysfunction within the first week. Severe scrub typhus and leptospirosis can present as bilateral pneumonia or pulmonary haemorrhage respectively, and evolve to acute respiratory distress

Table 1	Findings on investigations in patients with acute undifferentiated febrile illnesses (AUFI)	
Basic investigations	**Diagnostic value***	**Suggests severe illness***
Complete blood count:	Perform in all patients	
• Haematocrit	—	Anaemia in patients with malaria, rising haematocrit in severe dengue.
• Leucocytosis	Seen often in leptospirosis, enteric fever in children, and in scrub typhus. Seen in the majority of patients of hepatic amoebiasis.	Leucocytosis may occur in enteric fever in adults with onset of complications (intestinal perforation); associated with severe forms of leptospirosis, scrub typhus, malaria and dengue fever.
• Leukopenia	Leukopenia occurring early in illness and in association with thrombocytopenia is suggestive of dengue.[41] Seen later in course of typhoid fever.	Falling TLC + thrombocytopenia + rising haematocrit seen with severe dengue
• Lymphocytosis	May be seen in rickettsial and viral infections	—
• Thrombocytopenia	Thrombocytopenia may be seen in all common AUFIs, so poor discriminatory value. Thrombocytopenia + splenomegaly suggestive of malaria, Thrombocytopenia + bleeding is seen in dengue and other VHFs, but is unusual in malaria.	Dengue fever: in association with bleeding
• Eosinophilia	Seen in filariasis, acute schistosomiasis, Loeffler's syndrome	—
Peripheral blood smear examination	Perform in all patients if facilities for microscopy available	
	Malaria, borreliosis, filariasis, Acute trypanosomiasis can be diagnosed on smear	Parasite density correlates with severity in malaria
Urine examination	Perform in severely ill patients. May be performed, especially in women and elderly, since UTIs may not have localising symptoms	
	Proteinuria and haematuria seen in leptospirosis	Haemoglobinuria in patients with severe malaria
Biochemistry	Perform in severely ill patients to assess organ dysfunction. Hepato-renal involvement is common in leptospirosis, scrub typhus, and malaria, while pulmonary-renal syndrome is seen in scrub typhus and leptospirosis	
Liver enzymes	Raised in several AUFIs, so no discriminatory value[42]	WHO has defined ALT or AST >1000 as suggestive of severe dengue
Bilirubin	Raised bilirubin distinguishes malaria from dengue[43] Raised bilirubin + modest rise in transaminases (<200 IU/L) + raised CPK seen in leptospirosis[44]	In severe leptospirosis, hyperbilirubinaemia may be marked (up to 300-400 mg/L)
Renal function	AKI common in malaria, scrub typhus, leptospirosis. Non-oliguric renal failure with potassium wasting seen in leptospirosis[45]	Correlate with prognosis especially when patient has multiorgan dysfunction syndrome
Imaging:	Perform in patients with tachypnoea and/or severe illness	
• Chest x ray	Scrub typhus: pneumonia is most common systemic involvement.[33][46] Bilateral opacities progressing to ARDS may be seen in scrub typhus, leptospirosis, and occasionally in malaria. Pneumonia occurs occasionally in enteric fever. Pleural effusion occasional in dengue fever (sign of capillary leakage). Others: Bilateral nodular opacities or upper lobe cavitating pneumonia in melioidosis	
• Ultrasound scan of abdomen	May be done in severely ill patients, especially those with jaundice, shock, abdominal pain, or persistent fever without obvious cause	
	May be helpful in diagnosing infections such as hepatic amoebiasis, melioidosis (liver and splenic abscesses). Findings such as mesenteric lymphadenopathy may help in diagnosis of enteric fever[47]	Ascites, pleural effusion, and gallbladder wall oedema are associated with severe dengue infection and are signs of plasma leakage. Acute acalculous cholecystitis and acute pancreatitis has been reported in all common causes of AUFI

TLC: total leucocyte count; UTI: urinary tract infections; AUFI: acute undifferentiated febrile illness; VHF: viral haemorrhagic fevers; WHO: World Health Organization; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CPK: creatine phosphokinase; ARDS: acute respiratory distress syndrome; AKI: Acute kidney injury

*Alone or in combination with other abnormalities. If confirmatory tests are not available, then the diagnosis may be "suspected" at best, if the epidemiological and clinical features and results of basic laboratory investigations are compatible. As such, treatment may be started on clinical grounds.

Table 2 | Confirmatory tests for select pathogens causing AUFI

Tests	Findings	Test performance	Advantages	Disadvantages
Malaria[48-51]				
RDT for malarial antigens (ICT format): histidine-rich protein 2 (HRP-2), *Plasmodium* lactate dehydrogenase (pLDH), *Plasmodium* aldolase (pAldolase)	Parasite antigens in blood. HRP-2 antigen is unique to *P falciparum*. pLDH can be common to genus *Plasmodium* or specific to *P falciparum* or *P vivax*	~95% sensitive and specific for *P falciparum*. Acceptable as standalone test for *P falciparum*. HRP-2 kits are the most sensitive	Results in minutes, no need for laboratory, little technical skill needed. pLDH can be used to monitor treatment response.	Low sensitivities for low level parasitaemia (<100 parasites/µL). RDTs of different brands vary greatly in performance. Cannot quantify parasitaemia. Kits deteriorate above 35°C. In areas where HRP-2 deletion *P falciparum* exist, only pLDH based tests are effective.
Confirmatory test: microscopy	Presence of parasites in blood. Presence of only gametocytes suggests that current illness is not malaria	Detects as few as 5-10 parasites per µL of blood. Turnaround time 20-30 minutes	Current gold standard: inexpensive, quantifies parasitaemia, identifies species	Needs skilled staff. Asymptomatic parasitaemia in hyperendemic areas can confound diagnosis
Dengue[52-55]				
RDT NS1 antigen	NS1 antigen in blood collected within 6 days of onset	Pooled sensitivity 66%, pooled specificity 97.9%	Results in minutes, no need for laboratory, little technical skill needed	Reduced sensitivity in dengue serotype 4 infection, and in case of previous infection with any serotype
RDT IgM	Dengue-specific IgM antibody in blood. Many RDT kits test NS1 antigen and dengue IgM in same cassette.	Pooled sensitivity 83%, pooled specificity 86% (if taking either NS1 or IgM as proof of infection)	Results in minutes, no need for laboratory facilities, little technical skill needed	IgM can persist for months and may not appear at all in secondary infections. Prior exposure to WNV, JE, or YF dampens dengue IgM response
Confirmatory test: culture	Isolation of virus from blood or tissue collected within 5 days of onset of fever	Sensitivity ~40%, specificity 100%	—	Turnaround time 1-2 weeks, expensive
Confirmatory test: NAA	Detection of dengue RNA in blood or tissue collected within 5 days of onset.	Sensitivity 60-100%, specificity >95%	Same-day diagnosis with nearly 100% sensitivity and specificity	Expensive
Confirmatory test: serology	≥4-fold rise in titre.* Seroconversion*	Specificity 100% for ≥4-fold increased titre or seroconversion*	Less expensive than culture or NAA	Results are retrospective and of no use in management
Enteric fever[40 56-58]				
RDT for antibody	Detection of antibody against salmonellae in single serum specimens	Sensitivity 69-78%, specificity 77-90%	Turnaround time 2-4 hours	Test performance of kits has varied widely among studies. No RDT for enteric fever is accurate enough to replace reference tests.
Confirmatory test: Culture	Isolation of enteric fever *Salmonella* from blood and bone marrow	Sensitivity 40-87% in blood and 80% in marrow, specificity 100%	Isolation allows drug sensitivity testing	Turnaround time 3-6 days. High level of expertise needed. Decreased sensitivity with prior therapy
Widal test†	≥4-fold rise in titre*	Sensitivity depends on local prevalence, specificity 100%	Affordable	≥4 fold increase may not occur in partially treated patients, ≥4-fold rise can be missed if antibody level peaks before first specimen is collected.
Scrub typhus[59-63]				
RDT for specific IgM (ICT format)	Detection of IgM in single specimens	Pooled sensitivity 66.0%, pooled specificity 92.0%[59]	Rapid	IgM can remain elevated over diagnostic cut-off for 12 months post-infection.[64] IgM may not appear in second or subsequent attacks. Higher specificity means test is more useful for ruling in a diagnosis of scrub typhus than for ruling out.
ELISA for specific IgM using recombinant antigens	≥4-fold rise in titre or seroconversion.* IgM OD reading above a predetermined cut-off in a single specimen	Sensitivity variable (91% seen in a study in northern Thailand), specificity 100% for paired sera, ≥90% for single sera	Simpler, cheaper, and more reproducible than IFA test	Same limitations as for rapid IgM tests
Confirmatory test: IFA or IPA for antibodies	≥4-fold rise in titre, seroconversion*	Specificity 100%	Current gold standard	Expensive, laborious, endpoints can be subjective
Confirmatory test: Weil-Felix test	≥4-fold rise in titre or seroconversion* for heterophile antibodies against *Proteus mirabilis* OX-K strain	Sensitivity variable, specificity high for paired specimens, low for single specimens	Inexpensive, easy to perform, turnaround time 1 day	Low sensitivity and specificity
Leptospirosis[65-70]				
RDT for IgM	Specific IgM in serum	Sensitivity 13-22% in 1st week, ~60% in 2nd week, ~80% afterwards; specificity low	Short turnaround time of hours, no special expertise needed	IgM can persist for months. False positive IgM possible in co-infection with HIV, EBV, hepatitis B or A, and *Salmonella* and *Plasmodium* spp
IgM ELISA	Specific IgM in serum	Sensitivity 84% in acute phase and 86% overall, specificity 91% in acute phase and 90% overall	Short turnaround time, specific enough to rule in leptospirosis in presence of compatible clinical picture	IgM can persist for months after infection.

(Continued)

Table 2 | (Cont.)

Tests	Findings	Test performance	Advantages	Disadvantages
Confirmatory test: Microscopic agglutination test for antibody	≥4-fold rise in titre or seroconversion*	Sensitivity 41% in 1st week, 82% in 2nd-4th week; specificity depends on cut-off titre adopted	Highly sensitive and specific	Expensive, high technical skill needed. Need to include local serotypes in antigen pool to ensure satisfactory sensitivity
Confirmatory test: Nucleic acid amplification	Detection of *Leptospira* DNA in blood, CSF, and urine after amplification	Analytical sensitivity ~10^5 bacilli/mL sample, diagnostic sensitivity no data, specificity >95%	NAA is only test with high sensitivity in 1st week of illness	Expensive, high technical skill needed.
Confirmatory test: Culture	Isolation of *Leptospira* spp from blood, CSF, dialysate in first 10 days, and from urine afterwards	Sensitivity low, specificity 100%	Gold standard. Identifies pathogenic serovars prevalent in the locality	Expensive, very slow

RDT: Rapid diagnostic test; ELISA: Enzyme-linked immunosorbent assay; HRP-2 Histidine-rich protein 2; ICT: Immunochromatographic test; NAA: Nucleic acid amplification; IgG: Immunoglobulin G; IgM: Immunoglobulin M; NS-1: Non-structural antigen 1; IFA: Immunofluorescent assay; IPA Immunoperoxidase assay. WNV: West Nile virus; JE: Japanese encephalitis; YF: Yellow fever.
*Fourfold or higher rise of specific antibody level in the 2nd of two serum specimens collected 10-14 days apart compared to the 1st specimen. Seroconversion is presence of antibody above a fixed level in the second of two serum specimens collected 10-14 days apart when none is detectable in the first specimen.
†Performing Widal test on a single serum specimen has very poor sensitivity and specificity.

syndrome.[33 34 71] Scrub typhus is an important cause of fever in pregnant women in Asia,[72 73] and has been associated with high rates of miscarriage (17%) and poor neonatal outcomes (42%).[74]

Dengue usually resolves within a week. Complications such as shock or bleeding characteristically occur 3-5 days after the onset of fever. Enteric fever typically has a subacute onset with complications such as encephalopathy, intestinal perforation, and bleeding only in the second or third week of illness.

Untreated, case fatality ratios range from 2.49% in enteric fever,[75] 0-39.7% in icteric leptospirosis,[76] and 0-33% in scrub typhus.[77]

How is it managed?
Clinically stable patients
Patients who are clinically stable with no red-flag features can be managed in the community. Treat patients with a confirmed diagnosis of malaria or dengue as per national guidelines or your local formulary.[78 79]

For suspected bacterial AUFIs with characteristic clinical features it is prudent to start early presumptive antibacterial therapy if diagnostic confirmatory testing is awaited or not available. Infections such as rickettsioses and leptospirosis are rapidly progressive, and delay in treatment can increase severity and mortality.[80-82]

Choose an appropriate antibiotic based on local disease and resistance patterns. In regions which are co-endemic for rickettsial infections and leptospirosis, especially in South-East Asia, doxycycline is an appropriate choice.[83] Oral azithromycin is effective for uncomplicated enteric fever, scrub typhus, leptospirosis, and relapsing fever, and is another possible choice in regions co-endemic for these infections.[84] Oral doxycycline is not advised in pregnancy, and azithromycin is an alternative.[85]

Severely ill patients
These patients must be immediately referred to a hospital and managed as inpatients. Empirical therapy with a combination of parenteral third generation cephalosporin (ceftriaxone) along with doxycycline or azithromycin is appropriate while diagnostic confirmation is awaited.[86 87] Ceftriaxone provides coverage for enteric fever, and leptospirosis; while doxycycline provides coverage for rickettsial infections. This combination is also appropriate for AUFIs complicated by pneumonia or acute respiratory distress syndrome, encephalopathy, and liver involvement[87] and does not require dose modification in renal failure[79 88] and multi-organ failure. Finally, this combination may also be administered to patients suspected of, or diagnosed with, severe malaria, in addition to intravenous artesunate. Doxycycline would serve as a companion antimalarial drug to artesunate, and ceftriaxone and would address

concomitant bacterial sepsis frequently seen in such patients.[89]

It is important to be aware of local resistance patterns. For example, extensively resistant typhoid fever has been documented in Pakistan since 2016, requiring the use of carbapenems or azithromycin.[84] Additionally, local disease patterns guide choice of treatment. For example, in patients with AUFI followed by a severe pneumonia, if there is an influenza epidemic, it would be prudent to add oseltamivir pending confirmation of influenza by antigen test or RT-PCR, if available.[90] In regions where melioidosis is common ceftazidime or meropenem may be an appropriate initial choice.

Further management
The response of fever to antibiotics can vary: rickettsial infections usually respond within 48 hours, while it may take up to a week in enteric fever, and longer in conditions such as melioidosis. The results of blood culture or serological tests may confirm the diagnosis and guide further therapy. Even if the fever responds to empirical therapy, a repeat specimen may be tested at follow-up a few weeks later to demonstrate IgM seroconversion or a fourfold rise in titre (see table 2) to confirm the probable diagnosis.

Review the diagnosis if fever persists after appropriate antibiotic therapy for other infectious causes of persistent fever.[91] Clinical features of other causes of acute undifferentiated fever are mentioned in appendix 3.

EDUCATION INTO PRACTICE

From your practice records, identify the five most common causes of acute undifferentiated fever you have seen in your practice in the past six months?

How would you investigate a person presenting with acute undifferentiated fever?

What signs would prompt you to refer a patient with fever for hospitalisation?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

No patients were involved in the creation of this article.

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Infographic: Fever identification charts: A quick guide to differentiation and diagnosis in low resource settings
Appendices 1-3: Prevalence of main causes of AUFIs by geographic region; Clinical features of the main causes of AUFIs; Clinical features of other important causes of AUFIs