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

Anurag Bhargava,1,2,3 Ravikar Ralph,4 Biswaroop Chatterjee,5 Emmanuel Bottieau6

1Department of Medicine, Yenepoya Medical College, Mangalore, Karnataka, India
2Center for Nutrition Studies, Yenepoya (Deemed to be University), Mangalore, Karnataka, India
3Department of Medicine, McGill University, Montreal, Canada
4Department of Medicine, Christian Medical College, Vellore, Tamil Nadu, India
5Department of Microbiology, IQ City Medical College, Durgapur, West Bengal, India
6Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

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. AUFI 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 AUFI 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 AUFI 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 antimicrobials and antibiotics.6,7

In this clinical update, we present an approach to the diagnosis and initial management of common AUFI 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.6–13 Box 1 presents the mnemonic “MA-ESR” as an aid to recall the common AUFI, 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.15 Globally, over one million cases each of leptospirosis and scrub typhus occur annually.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 AUFI 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
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-an urban disease, is increasingly observed in rural and peri-urban subcontinent, East Asia, sub-Saharan Africa.\(^{8,25}\) 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,
Bloodstream infection due to non-typhoidal Salmonella, disseminated tuberculosis, and deep mycoses are more commonly observed in adults with HIV infection. 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. 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 AUIF—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,33-35 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 tularemia, anthrax, or East African trypanosomiasis.

Conjunctival suffusion (red eyes and oedema without exudate) and haemorrhage, jaundice, and marked muscle tenderness suggest leptospirosis (fig 5). A non-purulent conjunctivitis is also frequently seen in Zika virus infection, but not in other arboviral infections.

Rash and/or polyarthritides 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.

Symmetric arthritis of small joints with oedema is typical of chikungunya.

Conversely, rule-out signs exclude a particular disease. For example, the presence of rash or lymphadenopathy renders malaria highly unlikely. Likewise, generalised lymphadenopathy is uncommon in enteric fever. 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...
localised symptoms and in patients with severe illness to detect complications. Table 1 describes the diagnostic value of findings on initial investigations.

![Characteristic eye signs of leptospirosis: conjunctival suffusion, jaundice, and sub-conjunctival haemorrhage](image)

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)**

<table>
<thead>
<tr>
<th>Basic investigations</th>
<th>Diagnostic value*</th>
<th>Suggests severe illness*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count:</td>
<td>Perform in all patients</td>
<td>Anemia in patients with malaria, rising haematocrit in severe dengue</td>
</tr>
<tr>
<td><strong>Haematocrit</strong></td>
<td></td>
<td>Leucocytosis occurring early in illness and in association with thrombocytopenia is suggestive of dengue.</td>
</tr>
<tr>
<td><strong>Leucocytosis</strong></td>
<td>Seen often in leptospirosis, enteric fever in children, and in scrub typhus. Seen in the majority of patients of hepatic amoebiosis.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Leukopenia</strong></td>
<td>Leukopenia occurring early in illness and in association with thrombocytopenia is suggestive of dengue. Seen later in course of typhoid fever.</td>
<td>Falling TLC + thrombocytopenia + rising haematocrit seen with severe dengue</td>
</tr>
<tr>
<td><strong>Lymphocytosis</strong></td>
<td>May be seen in tick-bite and viral infections</td>
<td>—</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>Thrombocytopenia may be seen in all common AUFI, so poor discriminatory value. Thrombocytopenia + splenomegaly suggestive of malaria, Thrombocytopenia + bleeding is seen in dengue and other VHF's, but is unusual in malaria.</td>
<td>Dengue fever in association with bleeding</td>
</tr>
<tr>
<td><strong>Eosinophilia</strong></td>
<td>Seen in filariasis, acute schistosomiasis, Loeffler's syndrome</td>
<td>—</td>
</tr>
<tr>
<td>Peripheral blood smear examination</td>
<td>Perform in all patients if facilities for microscopy available</td>
<td>Parasite density correlates with severity in malaria</td>
</tr>
<tr>
<td><strong>Malaria, borreliosis, filariasis, Acute trypanosomiasis can be diagnosed on smear</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>Raised bilirubin distinguishes malaria from dengue</td>
<td>In severe leptospirosis, hyperbilirubinaemia may be marked (up to 300–400 mg/L)</td>
</tr>
<tr>
<td></td>
<td>Raised bilirubin + modest rise in transaminases (&lt;200 IU/L) + raised CPK seen in leptospirosis</td>
<td></td>
</tr>
<tr>
<td>Renal function</td>
<td>ATG common in malaria, scrub typhus, leptospirosis. Non-oliguric renal failure with potassium wasting seen in leptospirosis</td>
<td>Correlate with prognosis especially when patient has multiorgan dysfunction syndrome</td>
</tr>
<tr>
<td>Imaging:</td>
<td>Perform in patients with tachypnoea and/or severe illness</td>
<td></td>
</tr>
<tr>
<td><strong>Chest x-ray</strong></td>
<td>Scrub typhus: pneumonia is most common systemic involvement. 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).</td>
<td>Bilateral nodular opacities or upper lobe cavitating pneumonia in melioidosis</td>
</tr>
<tr>
<td>Ultrasound scan of abdomen</td>
<td>May be made in severely ill patients, especially those with jaundice, shock, abdominal pain, or persistent fever without obvious cause</td>
<td>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</td>
</tr>
</tbody>
</table>

---

*To view Table 1 in its entirety, please download the PDF from the BMJ website or view the online version.*

---

**Fig 5 | Characteristic eye signs of leptospirosis: conjunctival suffusion, jaundice, and sub-conjunctival haemorrhage**
Table 2 | Confirmatory tests for select pathogens causing AUIF

<table>
<thead>
<tr>
<th>Tests</th>
<th>Findings</th>
<th>Test performance</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malaria</strong>&lt;sup&gt;60-61&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDT for malarial antigens (ICT format): histidine-rich protein 2 (HRP-2), Plasmodium lactate dehydrogenase (pLDH), Plasmodium aldolase (pAldolase)</td>
<td>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 Pvivax.</td>
<td>~95% sensitive and specific for P falciparum. Acceptable as stand-alone test for P falciparum. HRP-2 kits are the most sensitive</td>
<td>Results in minutes, no need for laboratory; little technical skill needed. pLDH can be used to monitor treatment response.</td>
<td>Low sensitivities for low level parasitaemia (&lt;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.</td>
</tr>
</tbody>
</table>

| **Dengue**<sup>14 9</sup> | | | | |
| 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: 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 |

| **Confirmatory test: culture** | Isolation of virus from blood or tissue collected within 5 days of onset of fever | Sensitivity ~60%, specificity 100% | — | Turnaround time 1–2 weeks, expensive |

| **Confirmatory test: serology** | 4-fold rise in titre or 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 |

| **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** | 24-fold rise in titre* | Specificity 100% for 24-fold increased titre or seroconversion* | Less expensive than culture or NAA | Results are retrospective and of no use in management |

| **Enteric fever**<sup>59-63</sup> | | | | |
| RDT for antibody | Detection of antibody against salmonellae in single serum specimens | Sensitivity 69–79%, 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. |

| **Confirmeratory 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** | 24-fold rise in titre* | Sensitivity depends on local prevalence, specificity 100% | Affordable | 24 fold increase may not occur in partially treated patients, 24-fold rise can be missed if antibody level peaks before first specimen is collected. |

| **Scrub typhus**<sup>59-63</sup> | | | | |
| RDT for specific IgM (ICT format) | Detection of IgM in single specimens | Pooled sensitivity 66.0%, pooled specificity 92.0%.<sup>63</sup> | Rapid | IgM can remain elevated over diagnostic cut-off for 12 months post-infection.<sup>64</sup> 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 | 24-fold rise in titre or seroconversion* | 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 IPAS for antibodies** | 24-fold rise in titre, seroconversion* | Specificity 100% | Current gold standard | Expensive, laborious, endpoints can be subjective |

| **Confirmatory test: Weil-Felix test** | 24-fold rise in titre or seroconversion* | Sensitivity variable, specificity high for paired specimens, low for single specimens | Inexpensive, easy to perform, turnaround time 1 day | Low sensitivity and specificity |

| **Leptospirosis**<sup>49-57</sup> | | | | |
| 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.)**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Findings</th>
<th>Test performance</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmatory test: Microscopic agglutination test for antibody</td>
<td>24-fold rise in titre or seroconversion*</td>
<td>Sensitivity 41% in 1st week, 82% in 2nd-4th week; specificity depends on cut-off titre adopted</td>
<td>Highly sensitive and specific</td>
<td>Expensive, high technical skill needed. Need to include local serotypes in antigen pool to ensure satisfactory sensitivity</td>
</tr>
<tr>
<td>Confirmatory test: Nucleic acid amplification</td>
<td>Detection of <em>Leptospira</em> DNA in blood, CSF, and urine after amplification</td>
<td>Analytical sensitivity ~10^7 bacilli/ml sample, diagnostic sensitivity no data, specificity &gt;95%</td>
<td>NAA is only test with high sensitivity in 1st week of illness</td>
<td>Expensive, high technical skill needed.</td>
</tr>
<tr>
<td>Confirmatory test: Culture</td>
<td>Isolation of <em>Leptospira</em> spp from blood, CSF, dialysate in first 10 days, and from urine afterwards</td>
<td>Sensitivity low, specificity 100%</td>
<td>Gold standard. Identifies pathogenic serovars prevalent in the locality</td>
<td>Expensive, very slow</td>
</tr>
</tbody>
</table>


*Performing Widal test on a single serum specimen has very poor sensitivity and specificity.

†Performing Widal test on a single serum specimen has very poor sensitivity and specificity. Seroconversion is presence of antibody above a fixed level in the second of two serum specimens collected 10-14 days apart from the first specimen.

**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 involvement88 and does not require dose modification in renal failure.79 89 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.44 Additionally, local disease patterns guide choice of treatment. For example, in patients with AUIF 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.

We thank Dr Anand Zachariah for his comments on the manuscript, Dr Prashant Upadhyay for designing the infographics, and Dr Madhavi Bhargava, Dr Vineeth Nair, and Dr Sajjad Munaf for their help in preparing the manuscript for submission.

**Contributors:** AB formulated the approach and wrote the initial draft. All authors contributed equally.

**Funding:** None.

**Competing interests:** We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

**Patient consent:** Obtained.

**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.


Islam K, Sayed M, Hossen E, et al. Comparison of the Performance of the TTest, TubeX, Typhidot and Widal Immunodiagnostic Assays and Blood Cultures in Detecting


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