Acute Undifferentiated Fever: Management Algorithm

*Rajneesh Joshi, MD, MPH, PhD **
*SP Kalantri, MD, MPH***

What is acute undifferentiated fever?

Acute undifferentiated fever (AUF) is a common cause of patients seeking healthcare in India, especially between June and September. (1, 2) Unlike fever of unknown origin (FUO), which enjoys a standard definition, AUF, also known as "acute febrile illness", "short febrile illness", or "acute fever" lacks an international consensus definition. Since FUO requires duration of fever to be longer than three weeks, some authors have defined AUF as fever that resolves within three weeks. (3) More traditionally however, AUF has been defined as fever of two weeks or shorter in duration. (4, 5) Thus the term AUF is used to denote fevers that typically do not extend beyond a fortnight, and lack localizable or organ-specific clinical features. (6)

AUF poses a diagnostic and therapeutic challenge to the health workers, particularly in limited resource settings. A number of viruses, bacteria, protozoa and rickettsia can cause FUO. The non-specificity of symptoms and signs and lack of availability of accurate diagnostics not only test the clinical mettle of even astute physicians but often leads to irrational use of antibiotics and antimalarials. Some fever syndromes have a more clear localization to skin and soft tissue (abscess or cellulitis), meninges or neural tissue (headache, neck-stiffness, altered sensorium with or without focal neurological signs), respiratory tract (cough, breathlessness), or urinary tract (dysuria, hematuria). These syndromes have better developed guidelines for their management. On the other hand, AUF-syndromes (such as fever-rash, fever-myalgia, fever-arthralgia, fever-hemorrhage, and fever-jaundice) have overlapping etiologies, which makes their diagnosis and management even more challenging. (7)

Fevers with proven diagnoses are known as diagnosed-AUFs; those that defy diagnosis are called undiagnosed undifferentiated fevers (UUF). (3) Because malaria is an important and treatable cause of AUFs in the tropics and ranks number one in the differential diagnosis of acute fevers, patients who test negative for malaria are assigned a diagnosis of non-malarial AUFs.(6, 12) Many UUFs often resolve either on their own or in response to empiric therapies. Those AUFs which persist, and total duration of illness becomes longer than three weeks are classified as FUO. (See Figure 1)

Diagnosis of many etiologies of AUF in the tropics can be established with help of simple tests, such as peripheral smear examination or rapid diagnostic tests (RDTs) for malaria or dengue. (6, 8, 9) Some other etiologies need more sophisticated tests such as ELISA for rickettsial infections, MAT or ELISA for leptospirosis or PCR based tests for paramyxoviruses. (4, 10, 11) Studies that have assessed the cause of AUF in Asia have indicated that depending on the nature of available laboratory support, between a quarter and half of AUFs may remain undiagnosed. (3, 8) We review here case definitions, diagnostic options, treatment strategies of FUO and suggest an algorithm based approach for managing AUF.

What causes acute undifferentiated fever in the tropics?

According to a systematic review on etiology of FUO in Asia (1), most FUO s are caused by malaria, dengue, leptospirosis, rickettsial infections especially scrub typhus, typhoid fever, Japanese encephalitis and influenza. The common blood isolates are Salmonella sp, Escherichia coli, and Staphylococcus aureus. Table 1 shows a few recent studies that have evaluated AUFs. The cause of AUF is driven by the regional disease burden, seasonality of infectious diseases, spectrum and severity of disease, availability of diagnostics and access to health care facilities. Overall different studies reported diagnosis of malaria in 5 to 50% cases; scrub typhus/ Rickettsial fevers in 4 to 49% cases; Enteric fever in 7 to 30% cases, dengue in 4 to 19% cases; leptospirosis in 3 to 10% cases; and influenza in 8 to 12% cases. A recent study from Cambodia Reported that at least one pathogen was identified in 73.3% (874/1193) of febrile patient samples. Most frequent pathogens detected were *P.vivax* (33.4%), *P.falciparum* (26.5%), *Influenza* viruses(8.9%), Dengue viruses(6.3%),*O.tsutsugamushi* (3.9%), Rickettsia (0.2%), *P. knowlesi* (0.1%) and pathogenic Leptospira (9.4%). (8) Based on median prevalence of individual etiologies, 20% of all acute febrile cases have malaria, 10% have rickettsia and influenza and 5 to 10% have dengue, enteric fever, leptospirosis or Japanese encephalitis. Contrary to the prevailing popular perception among doctors and public, other bacteria and viruses contribute little to the AUF in tropics. Even after applying a broad test battery for the detection of pathogens causing fever a causative agent may not be detected in in as many as third to a quarter of febrile patients. According to a 2014 systematic review, the proportion of undiagnosed AUF ranges between 8% and 80%. (1)

What should be management algorithm in acute undifferentiated fever?

We present a management algorithm based on scientific rationale, logic, and prevalent clinical practices. Pretest probability of infectious diseases (prevalence), severity of febrile illnesses, availability of specific diagnostics, and response to drug therapies guide this algorithmic approach. This algorithm also takes into account countrywide heterogeneity in incidence and epidemiology of infectious disease.

Step 1: Assess severity of symptoms and recognize sepsis

Because patients, their attendants or doctors cannot accurately detect the presence of a fever without using a thermometer, doctors should confirm a history of fever by recording temperature (13). The next step is to take history and do a focused physical examination to quickly assess the severity of disease and to rule out sepsis. Although fever, tachycardia, tachypnea, or hypotension can provide key clues for systemic inflammatory response syndrome (SIRS) or sepsis, severe falciparum malaria, hemorrhagic dengue, or adult respiratory distress syndrome can also share these characteristics. Blood cultures (prior to initiation of antimicrobial therapy) in whom there is suspicion of bacteremia and judicious use of C- reactive protein are important initial steps for management of sepsis. (14) The number of blood cultures sets (two, three or four) depends on the pretest probability of bacteremia in a febrile patient; the optimum volume should be at least 20 ml. The technique, number of

cultures, and volume of blood are more important factors for detection of bacteremia than timing of culture collection. Recent guidelines have provided algorithmic approach to their management. (15)

Step 2: History and clinical examination to assess for localization of fever

History and physical examination, the traditional tools used by health workers, worldwide, can provide important clues for the etiology of AUF. And yet, symptoms and physical signs lack accuracy and precision to rule in or rule out a specific infectious disease causing AUF. Clinical features specific to organ involvement are outlined in figure 2. Unfortunately neither history nor physical examination is accurate enough to distinguish the etiologies of acute undifferentiated fevers. For example, a third of patients with dengue present with cough, nasal stuffiness or sore throat- symptoms traditionally associated with upper respiratory infections. An enlarged liver and spleen could be found in malaria, dengue, typhoid fever and leptospirosis. Similarly, headache, neck stiffness and other signs of meningeal inflammation are traditionally associated with meningitis, but these signs lack accuracy for ruling in or ruling out meningitis. (16) The warning signs of severe dengue (severe abdominal pain or tenderness, persistent vomiting, lethargy or restlessness, abrupt change from fever to hypothermia, bleeding, pallor, cold/clammy extremities, liver enlargement on physical exam, or abnormal mental status) are noted in a minority of patients with severe dengue and, in most cases, develop less than one day prior to hospitalization. (17)

Clinical features can help in syndrome diagnosis of AUF, though. As an example, fever-rash syndrome, fever-jaundice syndrome, fever-altered syndrome, and fever-arthralgia syndrome can help physicians fine tune their differential diagnosis. Vesicular exanthemas (associated with varicella, herpes zoster or herpes simplex) or maculopapular rash (associated with measles or rubella) are usually well evident; what is often missed by patients and physicians alike is macular rashes associated with typhoid fever or dengue fever. Half the patients with dengue present with a transient macular or maculopapular rash that typically appears between two and five days after the onset of fever. A convalescent rash may appear a few days after defeverence.(18) Eschar- a localized necrotic skin lesion at the site of their infecting chigger bite is diagnostic of scrub typhus; between a third and two-thirds of patients with scrub typhus present with skin sign. The eschar may develop before the onset of systemic symptoms, and can be seen in multiple locations. (11) Thrombocytopenia, a non-specific feature of AUF can present with skin or mucous membrane bleeding; leptospirosis may also be associated with petechial hemorrhages in the skin or mucous membranes. Presence of icterus (Fever-Jaundice syndrome) needs different approach. Almost all AUFs lead to non-specific elevation in liver aminotransferases (ALT and AST). Approximately 40 percent of patients have minimal to moderate elevations of hepatic transaminases (usually <200 IU/L). AST and ALT >25 times the upper limit of normal are often found in acute viral hepatitis; patients with acute leptospirosis have modestly elevated AST and ALT enzymes. (19)

Step 3: Use Rapid diagnostic tests for early diagnosis of Malaria and Dengue

WHO recommends that patients with suspected malaria must have a rapid diagnostic test for malaria (RDTs) and only those who test positive should be treated with antimalarials. This approach can reduce unnecessary malaria treatment, help health workers initiate specific therapies and increase correct diagnosis in patients suffering from other febrile illnesses. The most useful RDT - HRP-II based test for diagnosis of malaria due to Plasmodium falciparum has very high sensitivity and specificity. (20) The pLDH based test for diagnosis of Plasmodium vivax infection has a high specificity but its relatively lower sensitivity (75-80%) mandates that a peripheral smear examination should follow a negative RDT. (21) Peripheral smear, coupled with complete blood counts, also gives useful information: leukocytosis may suggest sepsis, leptospirosis and leucopenia may indicate dengue; thrombocytopenia is an important indicator of severe malaria or dengue fever. All patients who test positive for malaria by HRP-II or pLDH based RDT or peripheral smear examination must receive guideline-based care for malaria. (22)

Unfortunately, the empirical treatment of NMAUFs with antimalarial drugs continues even in the era of highly specific rapid diagnostic tests (RDTs) for malaria. In a study from central India, despite one or more negative tests for malaria, many patients without malaria (39.9%, 95% CI 37.0–43.3) received antimalarial drugs. (6)

NS-1 antigen based test is the next step for detection for Dengue fever. NS-1 antigen positivity appears on the first day of fever, and may last till ninth day. When NS-1 antigen based rapid test is combined with IgM ELISA, the sensitivity of diagnosis of early dengue reaches 93% and the specificity hovers around 83%. (23) RDT for IgM antibody detection against dengue is useful after the fifth day of fever, as the test is negative early in the course of disease. (23) If NS-1 or IgM based RDT for dengue is positive, patients must receive guideline-based care for dengue. (24)

Step 4: Use anti-pyretics alone if fever is less than three days in duration and initial RDTs are negative

If initial RDTs are negative, and duration of fever is <3 days, patients with self-limiting fevers such as influenza should receive no more than paracetamol. Recent studies have shown that outcomes are similar in most individuals with influenza-like-illnesses, with or without allopathic drugs. (25, 26) If fever persists longer, symptoms and signs that suggest organ-specific fever or complicated AFU or sepsis should be looked for.

Step 5: Investigations and management if fever persists for longer duration and initial RDTs are negative

If initial RDTs are negative, and duration of fever is > three days, enteric fever, leptospirosis and scrub typhus are common bacterial or rickettsial etiologies that need to be investigated and treated. Specific investigations such as serologic tests, blood cultures, polymerase chain reaction (PCR) assays are often ordered for evaluating fevers at this step. Aerobic blood culture

is necessary before initiating empiric antibiotic therapy. (27) Despite a lower yield of blood culture for enteric fever, it remains an investigation of choice, as it will also help detect other gram-positive or gram-negative bacterial infections. Serology based tests for typhoid fever lack diagnostic accuracy, and PCR assays for detection of salmonella are not universally available. (28)

Simple tests for diagnosis of leptospirosis or scrub typhus do not exist. Compared to microscopic agglutination test (MAT), the reference standard for diagnosing leptospirosis, IgM antibodies have poor sensitivity. MAT is not available outside reference laboratories and rapid tests for leptospirosis have poor sensitivity as well as specificity. (29, 30) Because accurate diagnostics for leptospirosis either do not exist or are not easily available, leptospirosis may be empirically treated with simple oral antibiotics instead of spending time and efforts to detect it first and treat later. (31, 32) This approach differs from the one used in malaria where parasite-based diagnosis must precede treatment.

Indeed empirical treatment with doxycycline or azithromycin in patients with non-malarial acute undifferentiated fevers might be a clinically apt strategy for reducing morbidity and mortality. (33)Both the drugs have a comparable efficacy against salmonella, rickettsial organisms as well as leptospirosis. (31) In a study in Thailand, 296 patients with AUF (23% with leptospirosis, 19% with scrub typhus, 5% with murine typhus, 4% with leptospira and scrub typhus dual infection and 50% without a specific diagnosis) were randomized to either a three- day oral azithromycin or a seven- day oral doxycycline. Fever vanished equally quickly in both groups, but patients receiving oral doxycycline tended to have more frequent adverse events. (31) In a meta-analysis of 17 randomized controlled trials evaluating various drug treatments in management of scrub-typhus, doxycycline and azithromycin were comparable in reducing the symptom duration and resolution of fever; however doxycycline yielded more adverse effects than azithromycin. (34) Flouroquinolones should not be used for management of scrub typhus due to presence of gyrase A mutation in the organism. (35) In a meta-analysis comparing various drug therapies for enteric fever, azithromycin was found to be not only as good as cephalosporins for cure rates but was superior with respect to relapse rates. (36) While efficacy of azithromycin based regimens is well established in adults, its utility in children remains to be demonstrated. (37) Penicillins as well as doxycycline have been used in management of leptospirosis. (38, 39) Antibiotics other than penicillin were found to be as good or even better in a recent meta-analysis. (38)

Given these studies, Azithromycin is a reasonable empiric choice for enteric fever, leptospirosis, or scrub typhus, AUFs with overlapping clinical features. Dosage schedule as advised for enteric fever (1000 mg on day one, 500mg daily for next five days) is most likely to useful in both scrub typhus and leptospirosis. Many studies have reported a low proportion of confirmed enteric fever, amongst AUF cases in urban slums. (28, 40) Hence initiating doxycycline (100mg twice daily) as an empiric first antibiotic is also reasonable, given its low cost, and activity against leptospira as well as rickettsial organisms.

Step 6: Acute undifferentiated fever with negative culture that persists despite initial empiric antibiotics

About half the patients with AUF remain undiagnosed. (3) In a recent series of 193 patients with undiagnosed undifferentiated fever (UUF) most patients had normal total leukocyte counts, normal platelets, and normal liver enzymes. Fever resolved within three weeks in 187 of these 193 patients. A study has shown that AUF is likely to resolve in more than 95% instances, and progression to FUO happens in less than 5% of instances. (3)

How should the patients be treated when initial empiric therapy fails to resolve symptoms, and diagnosis is uncertain? There is no consensus on this issue. If fever apart there are no other criteria that meet definitions of severity, many clinicians choose to stop further antibiotics, and reinvestigate with cultures (blood and urine), imaging (chest radiographs, and abdominal ultrasounds), and clinical chemistry (liver enzymes) to evaluate potential focus of infection. Others prefer to initiate another three to five days of empiric antibiotic with a different agent (usually a beta-lactam, if not used earlier) before further investigations. Bone marrow examination and cultures are advised to evaluate for presence of hematological malignancies, granulomas, as well as salmonella, which has a better yield on bone marrow cultures. However, by this time duration of fever is already longer than three weeks, and extensive and intelligent investigations are warranted as part of FUO work-up. Antipyretics and supportive therapies are continued in this interim period.

Table 1: Etiologies of Acute undifferentiated fever in recent published studies (2010-2014) from Asia

Author Country (Publication Year)	Sample size Study base	Etiology in AUF cases (Percentage of total cases)									
		Malaria	Salmonella	Leptospira	Rickettsia	Other Bacteria	Dengue	Influenza	Other Viruses	Non-infectious	Un-known
Mueller Cambodia 2014 (8)	1193 Health facilities	51	<1	10	4	<1	6	8	0	0	37
Kumar India 2014 (11)	201 Hospital[c]	5	<1	<1	24	<1	4	0	2	3	60
Hisam Pakistan 2014 (41)	500 Hospital[d]	16	NE	NE	NE	NE	4	NE	NE	NE	80
Capeding South-East Asia 2013 (42)	1500 Various hopsitals[e]	NE	29	0	6	0	12	12	39	0	12
Reller Sri-Lanka 2013(43, 44)	859 Hospital [f]	NE	NE	13	NE	NE	3 to 11	NE	NE	NE	NE
Punjabi Indonesia 2013 (12)	226 Hospital	4	7	8	7	8	4	NE	NE	NE	64
Narvenkar India 2012 (45)	40 Hospital[g]	NE	NE	NE	15	NE	NE	NE	NE	NE	85
Sen Papua new Guinea 2011 (46)	546 OPD Clinics[h]	52	NE	NE	NE	NE	8	NE	NE	NE	40
Thai / Phuong Vietnam 2010 (47, 48)	1938 Clinics[i]	NE	NE	NE	NE	NE	19	10	NE	NE	71
Chrispal India 2010 (49)	898 Hospital	17	8	3	49	0	7	NE	<1	7	8

NE = Not evaluated; All values are in percentages that have been rounded off to nearest integer.

a. This was a retrospective hospital record study, where evaluation of AUF was based on tests employed in clinical practice

b. This study in three health centers used PCR to detect presence of malaria. Malaria positivity on RDT was 31%; remaining 20% were PCR positive. About 12% of cases had multiple detected pathogens hence the sum total of etiologies exceeds 100%.

c. This study was performed during a Scrub typhus epidemic at a tertiary care hospital. PCR was used as a diagnostic test for scrub typhus.

d. Patients were tested only for Dengue and Malaria

e. Malaria was not tested in this pediatric study. Purpose was to identify Dengue positivity.

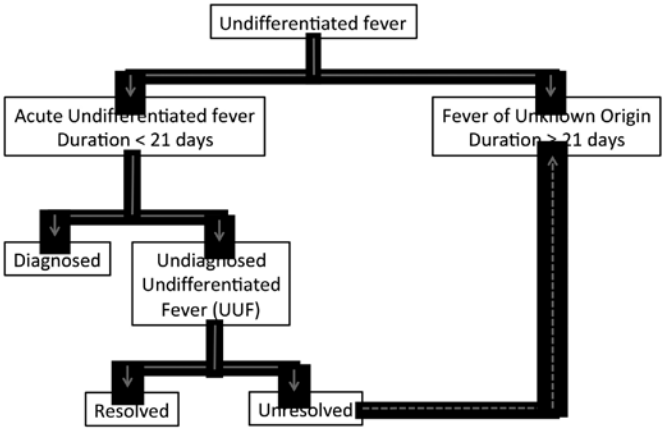
f. Results for Dengue positivity and Leptospirosis positivity were published as two separate studies and co-infections, and other diagnoses were not evaluated.

g. Scrub Typhus was diagnosed based on IgM ELISA

h. The study evaluated malaria based on RDT and rapid tests and Dengue serology only.

i. The studies were done over six years 2001-2006 and evaluated various dengue subtypes in one publication, and serology for Influenza in another publication.

Figure 1: Framework for evaluation of Acute Undifferentiated fever



Adapted from Reference (3)

Figure 2: Initial steps in assessment of Acute Undifferentiated fever

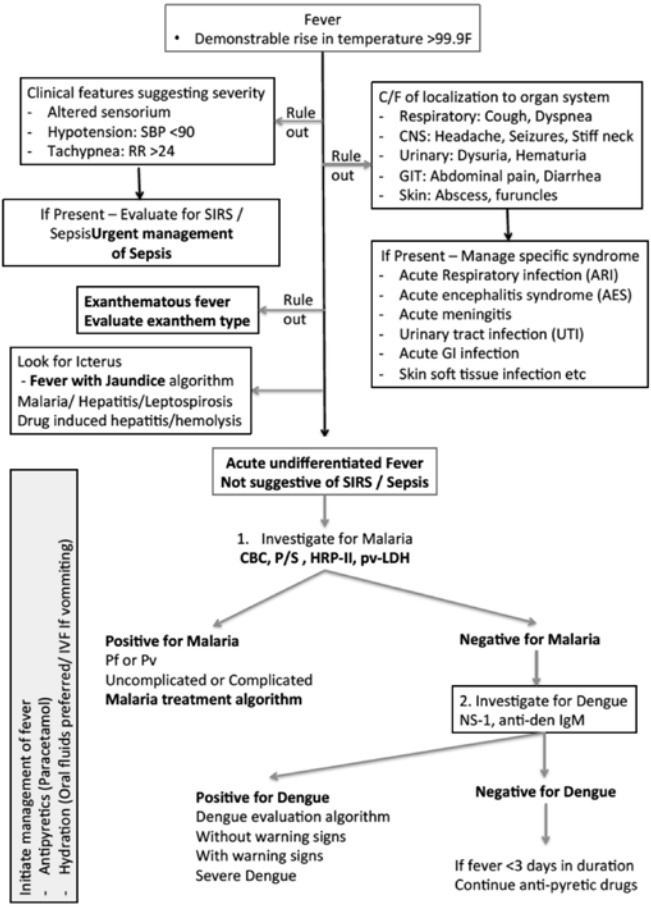
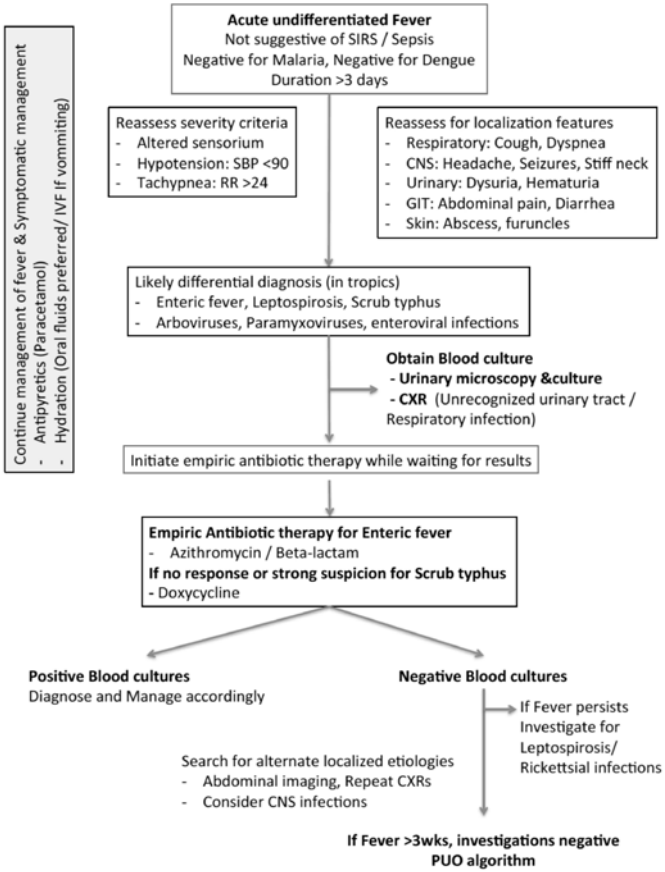


Figure 3: Assessment of Acute Undifferentiated fever when initial RDTs are negative



References

1. *Susilawati TN, McBride WJ. Acute undifferentiated fever in Asia: a review of the literature. The Southeast Asian journal of tropical medicine and public health. 2014;45(3):719-26.*

2. *Manocha H, Ghoshal U, Singh SK, Kishore J, Ayyagari A. Frequency of leptospirosis in patients of acute febrile illness in Uttar Pradesh. The Journal of the Association of Physicians of India. 2004;52:623-5.*

3. *Susilawati TN, McBride WJ. Undiagnosed undifferentiated fever in Far North Queensland, Australia: a retrospective study. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2014;27:59-64.*

4. *Phuong HL, de Vries PJ, Nagelkerke N, Giao PT, Hung le Q, Binh TQ, et al. Acute undifferentiated fever in Binh Thuan province, Vietnam: imprecise clinical diagnosis and irrational pharmaco-therapy. Tropical medicine & international health : TM & IH. 2006;11(6):869-79.*

5. Watt G, Jongsakul K. Acute undifferentiated fever caused by infection with Japanese encephalitis virus. The American journal of tropical medicine and hygiene. 2003;68(6):704-6.

6. Joshi R, Colford JM, Jr., Reingold AL, Kalantri S. Nonmalarial acute undifferentiated fever in a rural hospital in central India: diagnostic uncertainty and overtreatment with antimalarial agents. The American journal of tropical medicine and hygiene. 2008;78(3):393-9.

7. Crump JA. Time for a comprehensive approach to the syndrome of fever in the tropics. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2014;108(2):61-2.

8. Mueller TC, Siv S, Khim N, Kim S, Fleischmann E, Ariey F, et al. Acute undifferentiated febrile illness in rural Cambodia: a 3-year prospective observational study. PloS one. 2014;9(4):e95868.

9. Mbonye AK, Lal S, Cundill B, Hansen KS, Clarke S, Magnussen P. Treatment of fevers prior to introducing rapid diagnostic tests for malaria in registered drug shops in Uganda. Malaria journal. 2013;12:131.

10. Reller ME, Wunder EA, Jr., Miles JJ, Flom JE, Mayorga O, Woods CW, et al. Unsuspected leptospirosis is a cause of acute febrile illness in Nicaragua. PLoS neglected tropical diseases. 2014;8(7):e2941.

11. Kumar V, Kumar V, Yadav AK, Iyengar S, Bhalla A, Sharma N, et al. Scrub typhus is an under-recognized cause of acute febrile illness with acute kidney injury in India. PLoS neglected tropical diseases. 2014;8(1):e2605.

12. Punjabi NH, Taylor WR, Murphy GS, Purwaningsih S, Picarima H, Sisson J, et al. Etiology of acute, non-malaria, febrile illnesses in Jayapura, northeastern Papua, Indonesia. The American journal of tropical medicine and hygiene. 2012;86(1):46-51.

13. Singh M, Pai M, Kalantri SP. Accuracy of perception and touch for detecting fever in adults: a hospital-based study from a rural, tertiary hospital in Central India. Tropical medicine & international health : TM & IH. 2003;8(5):408-14.

14. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Critical care medicine. 2013;41(2):580-637.

15. From: The Indian Society of Critical Care Medicine Tropical fever G, Singhi S, Chaudhary D, Varghese GM, Bhalla A, Karthi N, et al. Tropical fevers: Management guidelines. Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine. 2014;18(2):62-9.

16. Waghdhare S, Kalantri A, Joshi R, Kalantri S. Accuracy of physical signs for detecting meningitis: a hospital-based diagnostic accuracy study. Clinical neurology and neurosurgery. 2010;112(9):752-7.

17. Rigau-Perez JG, Laufer MK. Dengue-related deaths in Puerto Rico, 1992-1996: diagnosis and clinical alarm signals. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2006;42(9):1241-6.

18. Vijayalakshmi AM, Jayavardhana A. Febrile rash and convalescent rash of dengue fever. Indian pediatrics. 2013;50(7):717.

19. Chang ML, Yang CW, Chen JC, Ho YP, Pan MJ, Lin CH, et al. Disproportional exaggerated aspartate transaminase is a useful prognostic parameter in late leptospirosis. World journal of gastroenterology : WJG. 2005;11(35):5553-6.

20. *Abba K, Deeks JJ, Olliaro P, Naing CM, Jackson SM, Takwoingi Y, et al. Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. The Cochrane database of systematic reviews. 2011(7):CD008122.*

21. *Meena M, Joshi D, Joshi R, Sridhar S, Waghdhare S, Gangane N, et al. Accuracy of a multispecies rapid diagnostic test kit for detection of malarial parasite at the point of care in a low endemicity region. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2009;103(12):1237-44.*

22. *Government of India. Guidelines for Diagnosis and Treatment of Malaria in India 2009. National Institute of Malaria Research, 2009.*

23. *lacksell SD, Jarman RG, Bailey MS, Tanganuchitcharnchai A, Jenjaroen K, Gibbons RV, et al. Evaluation of six commercial point-of-care tests for diagnosis of acute dengue infections: the need for combining NS1 antigen and IgM/IgG antibody detection to achieve acceptable levels of accuracy. Clinical and vaccine immunology : CVI. 2011;18(12):2095-101.*

24. *World Health Organization and the Special Programme for Research and Training in Tropical Diseases (TDR). Dengue guidelines for diagnosis, treatment, prevention and control: new edition. In: Organization WH, editor. 2009.*

25. *Danno K, Cognet-Dementhon B, Thevenard G, Duru G, Allaert FA, Bordet MF. Effectiveness of homeopathic medicine associated with allopathic medicine in the outpatient management of influenza-like illnesses or ear, nose, and throat disorders by pharmacists. Journal of managed care pharmacy : JMCP. 2013;19(8):631-41.*

26. *World Health Organization. WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and Other Influenza Viruses. WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and Other Influenza Viruses. WHO Guidelines Approved by the Guidelines Review Committee. Geneva2010.*

27. *Bhan MK, Bahl R, Bhatnagar S. Typhoid and paratyphoid fever. Lancet. 2005;366(9487):749-62.*

28. *Nizami SQ, Bhutta ZA, Siddiqui AA, Lubbad L. Enhanced detection rate of typhoid fever in children in a periurban slum in Karachi, Pakistan using polymerase chain reaction technology. Scandinavian journal of clinical and laboratory investigation. 2006;66(5):429-36.*

29. *Goris MG, Leeflang MM, Loden M, Wagenaar JF, Klatser PR, Hartskeerl RA, et al. Prospective evaluation of three rapid diagnostic tests for diagnosis of human leptospirosis. PLoS neglected tropical diseases. 2013;7(7):e2290.*

30. *Toyokawa T, Ohnishi M, Koizumi N. Diagnosis of acute leptospirosis. Expert review of anti-infective therapy. 2011;9(1):111-21.*

31. *Phimda K, Hoontrakul S, Suttinont C, Chareonwat S, Losuwanaluk K, Chueasuwanchai S, et al. Doxycycline versus azithromycin for treatment of leptospirosis and scrub typhus. Antimicrobial agents and chemotherapy. 2007;51(9):3259-63.*

32. *Suttinont C, Losuwanaluk K, Niwatayakul K, Hoontrakul S, Intaranongpai W, Silpasakorn S, et al. Causes of acute, undifferentiated, febrile illness in rural Thailand: results of a prospective observational study. Annals of tropical medicine and parasitology. 2006;100(4):363-70.*

33. *Mayxay M, Castonguay-Vanier J, Chansamouth V, Dubot-Peres A, Paris DH, Phetsouvanh R, et al. Causes of non-malarial fever in Laos: a prospective study. The Lancet Global health. 2013;1(1):e46-54.*

34. *Fang Y, Huang Z, Tu C, Zhang L, Ye D, Zhu BP. Meta-analysis of drug treatment for scrub typhus in Asia. Internal medicine. 2012;51(17):2313-20.*

35. *Jang HC, Choi SM, Jang MO, Ahn JH, Kim UJ, Kang SJ, et al. Inappropriateness of quinolone in scrub typhus treatment due to gyrA mutation in Orientia tsutsugamushi Boryong strain. Journal of Korean medical science. 2013;28(5):667-71.*

36. *Trivedi NA, Shah PC. A meta-analysis comparing the safety and efficacy of azithromycin over the alternate drugs used for treatment of uncomplicated enteric fever. Journal of postgraduate medicine. 2012;58(2):112-8.*

37. *Ohnishi K, Kobayashi K, Iwabuchi S, Nakamura-Uchiyama F. Treatment of Japanese patients with enteric fever using azithromycin and MIC levels for causative organisms. The Southeast Asian journal of tropical medicine and public health. 2013;44(1):109-13.*

38. *Charan J, Saxena D, Mulla S, Yadav P. Antibiotics for the treatment of leptospirosis: systematic review and meta-analysis of controlled trials. International journal of preventive medicine. 2013;4(5):501-10.*

39. *Edwards CN, Levett PN. Prevention and treatment of leptospirosis. Expert review of anti-infective therapy. 2004;2(2):293-8.*

40. *Brooks WA, Hossain A, Goswami D, Nahar K, Alam K, Ahmed N, et al. Bacteremic typhoid fever in children in an urban slum, Bangladesh. Emerging infectious diseases. 2005;11(2):326-9.*

41. *Hisam A, Mahmood ur R, Khan MB, Kadir E, Azam N. Frequency of co-existence of dengue and malaria in patients presenting with acute febrile illness. JPMA The Journal of the Pakistan Medical Association. 2014;64(3):247-51.*

42. *Capeding MR, Chua MN, Hadinegoro SR, Hussain, II, Nallusamy R, Pitisuttithum P, et al. Dengue and other common causes of acute febrile illness in Asia: an active surveillance study in children. PLoS neglected tropical diseases. 2013;7(7):e2331.*

43. *Reller ME, Bodinayake C, Nagahawatte A, Devasiri V, Kodikara-Arachichi W, Strouse JJ, et al. Unsuspected dengue and acute febrile illness in rural and semi-urban southern Sri Lanka. Emerging infectious diseases. 2012;18(2):256-63.*

44. *Reller ME, Bodinayake C, Nagahawatte A, Devasiri V, Kodikara-Arachichi W, Strouse JJ, et al. Leptospirosis as frequent cause of acute febrile illness in southern Sri Lanka. Emerging infectious diseases. 2011;17(9):1678-84.*

45. *Narvencar KP, Rodrigues S, Nevrekar RP, Dias L, Dias A, Vaz M, et al. Scrub typhus in patients reporting with acute febrile illness at a tertiary health care institution in Goa. The Indian journal of medical research. 2012;136(6):1020-4.*

46. *Senn N, Luang-Suarkia D, Manong D, Siba PM, McBride WJ. Contribution of dengue fever to the burden of acute febrile illnesses in Papua New Guinea: an age-specific prospective study. The American journal of tropical medicine and hygiene. 2011;85(1):132-7.*

47. *Thai KT, Phuong HL, Thanh Nga TT, Giao PT, Hung le Q, Van Nam N, et al. Clinical, epidemiological and virological features of Dengue virus infections in Vietnamese patients presenting to primary care facilities with acute undifferentiated fever. The Journal of infection. 2010;60(3):229-37.*

48. *Phuong HL, Nga TT, van Doornum GJ, Groen J, Binh TQ, Giao PT, et al. Viral respiratory tract infections among patients with acute undifferentiated fever in Vietnam. The Southeast Asian journal of tropical medicine and public health. 2010;41(5):1116-26.*

49. *Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JA, Thomas EM, et al. Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors - an experience from a tertiary care hospital in South India. Tropical doctor. 2010;40(4):230-4.*