Adult Undifferentiated Acute Fever Pathway

Definition

- Symptoms of fever (2 consecutive temperature elevations > 38.3°C (100.9 °F) or a single oral temperature > 38.3°C (100.9°F) in neutropenic persons without evidence of an environmental cause OR a temperature elevation > 38°C for > 1 hour) for a period of 3-14 days
- No clear localizable symptoms to suggest immediate diagnosis

Background

Infectious Diseases are the leading cause of morbidity and mortality in India.
Undifferentiated acute febrile syndromes vary by season, location and may present a challenge to the general practitioner. They are overwhelmingly caused by infectious

Fever episodes in rural tropical areas may be 4 per person per year in rural and 0.5 per person per year in urban areas.

Early presentation may be nonspecific and overlapping for many infections and may make distinguishing self-limited illness from more severe illness difficult.

Early recognition and appropriate specific antimicrobial therapy may lead to decreased morbidity and mortality for some infections. However indiscriminate empiric antibiotic therapy should be avoided in conditions where there may be limited role to avoid emergence of antimicrobial resistance. PMID: 28356302, 27139474, 29581252

Local context

What causes AUFI?

Can broadly be malarial or non-malarial.

Infection	Epidemiology		Clinical features	Diagnostic test
	Areas	Seasonality		
Malaria	All over but higher Eastern, NE (falciparum predominant), central and South India (vivax predominant)	Higher 2 months after start of monsoon season	Paroxysmal fevers, chills, sweats. Hyperparasitemia with P falciparum can cause shock, renal failure, hemolysis	RDT Malarial smear (sensitivity may be low and user dependent) 2nd line- malaria PCR
Dengue fever	All over and more cases in south, west,	Also, in monsoon period	Fever + headache, retroorbital pain, myalgia, arthralgia,	NS1 Ag and IgM/IgG

	NE, east. Urban>rural		rash. Platelets <150k. Symptoms last 2-7 days. 3-7 days after initial symptoms pt can develop dengue shock or hemorrhagic fever with purpura, bleeding and hypotension.	(Sn 75-93% and Sp 88-100%). Detectable 1-9 days post fever, higher in primary infection. IgM band cross reacts with Chikungunya 2nd line Dengue PCR or IgM capture ELISA (MAC-ELISA)
Typhoid/enteric fever	All over; Urban predominance	Endemic but higher Jul-Oct, occasional food borne epidemic	Fever malaise. Diarrhea <50%. Splenomegaly. Secondary worsening in week 2. Could lead to encephalopathy and intestinal perforation	Blood cultures (pos 40-80%). Need higher volume of cultured blood
Leptospirosis	South, west and eastern India	Urban slums after flooding, a/w rodent exposure. In rural areas work in paddy fields or having pets at home	Fever, malaise, headache. Conjunctival suffusion and myalgias prominent. Jaundice, hepatitis and renal failure, pulmonary hemorrhage (5-15%)	IgM ELISA 2nd line microscopic agglutination test >200 Sn of both tests low (≤50%) in first week and may be improved when tested in week 2 (PMID10586903)
Scrub Typhus	Northeast, east and south India Majority rural, agricultural laborers	Higher in Aug to January	Fever, headache, myalgias, rash, lymph node swelling, confusion. May have eschar (22%) at site of mite bite which predates symptoms by around 7-10 days.	IgM ELISA 2nd line PCR or IFA
Chikungunya	All over but max KA, MH, TL, UK	Rainy season through winter.	Fever, polyarthralgia, rash, headache, conjunctivitis, back pain, nausea, rash. 30-	IgM ELISA

			40% can have chronic peripheral arthritis	
Influenza or other viral URI	All over	Post monsoon season and second peak in Jan-Mar	Close contact history. Fever, cough, myalgia, sore throat, headache	Flu Ag, COVID Ag on nasal or nasopharyngeal swab
Other causes include focal infection with bacteremia e.g pyelonephritis or abdominal abscess or acute meningoencephalitis: Japanese B encephalitis, HSV encephalitis, Nipah virus disease				

Other challenges

- Patients in many parts of India do not need to see a doctor to obtain antibiotics for fever
- Access to reliable clinical bacteriology laboratory for identification and antimicrobial susceptibility testing on specimens (blood cultures, urine cultures) is an important part of the clinical evaluation and treatment in the AUFI pathway but may be limited in low resource location or have an unacceptable turnaround time within the clinical context of such patient encounters. A follow up encounter may be necessary to make therapy changes based on antimicrobial susceptibility results and may not be feasible. (PMID: 29519767)
- Burden of multidrug resistant organisms as a cause of community onset acute febrile illness is high and may lead to higher mortality unless antibiotic therapy is guided by antimicrobial susceptibility testing. (PMID 28329303; 35065702)
- Patients and clinicians may be reluctant to undergo invasive procedures including blood sampling due to perceptions that tests may be expensive or irrelevant. The post analytical laboratory clinician interaction may not be timely or in person
- Prior antibiotic therapy may render a blood culture sample sterile and decrease yield.
- Cross reactivity as well as background positivity from prior infections in endemic areas are limitations of serologic tests used to diagnose some infections (Dengue, Leptospirosis and Chikungunya) and convalescent testing to confirm diagnosis may not be feasible. Hence clinical diagnosis should guide therapy in cases where test results are discordant to presentation
- In endemic areas, background seroprevalence may be high for antibody-based tests (example >50% Leptospira Ab in Andamans, slum dwellers or sewer workers)
- Sensitivity of serologic tests for Dengue, Leptospirosis and Scrub typhus are limiting, but remember the clinical suspicion may increase predictive value of a positive test.
- The Widal test for typhoid is widely used but is not recommended due to low sensitivity and specificity. However, if it is performed elsewhere, or is the only test available, it should be used in clinical decision making only for its negative predictive value which is around 95% even in high prevalence settings. (PMID 24995178)
- Patients may not present to CSA partner sites with mild-moderate symptoms (can present directly to pharmacy for antibiotics)

Key questions to answer

- What to test/when to test

- How to treat/what to treat with

Resources

- UpToDate
- National Centre for Disease Control in India (NCDC): National Treatment Guidelines for Antimicrobial Use in Infectious Diseases
- WHO report on fever management in peripheral healthcare settings (2013)
- WHO: Good clinical diagnostic practice: a guide for clinicians in developing countries to the clinical diagnosis of disease and to making proper use of clinical diagnostic services. http://apps.who.int/iris/bitstream/10665/119735/1/dsa236.pdf (2005)
- National Vector Borne Disease Control Program guidelines (2013)
- MSF

Proposed Pathway

- Early assessment of severity and SIRS response
    - If unstable, resuscitate
- Define clinical syndrome and identify clinical cues. This is guided by history and physical exam. A good practice is to conduct a system-based review of symptoms (negative history). Clinical history would include assessment for
    - Sore throat runny nose
    - ear pain, sinus pain, dental pain,
    - headache, photophobia, vomiting, altered consciousness,
    - cough, sputum, shortness of breath, wheezing
    - diarrhea (blood, mucus) and abdominal pain
    - painful urination, hematuria, flank pain
    - skin rash, ulcer
    - joint pain, swelling or bone pain
    - bleeding from mucus membranes, rash

  Physical examination would assess for
    - rapid pulse, rapid respiratory rate (exception: slow pulse in typhoid fever)
    - pallor, jaundice
    - stiff neck, photophobia
    - red throat, pus on tonsils, red bulging eardrums,
    - sinus tenderness decayed teeth
    - respiratory distress (use of accessory muscles, chest indrawing, grunting, nasal flaring), rhonchi, bronchial breathing, pleural rub
    - abdominal tenderness, liver or spleen enlargement, masses, ascites loin/pelvic tenderness
    - skin rash, ulcer,
    - lymphangitis swollen tender joints bone tenderness, swelling bleeding, petechiae lymphadenopathy.
- Underlying risk factors or comorbidity which may either increase severity of condition or impact management- diabetes mellitus, sickle cell disease, malignancy, pregnancy, HIV, alcoholic liver disease, prior antibiotic therapy (may increase risk of MDR organisms)
- Appropriate initial investigations

- Appropriate empiric therapy awaiting results of clinical investigations
- Consider overlapping diagnoses

Severity Assessment

Temperature – high grade fever, associated rigors	May be associated with bacteremia, abscesses, malaria, pyelonephritis or cholangitis.	Assess for dehydration esp in summer months. Blood cultures have higher yield with rigors
HR -tachycardia out of proportion to fever (expect 10 beats increase per deg F rise, or 18 bts/deg C)	May be a sign of myocarditis. (COVID or viral illness)	Reassess after fluid administration/rehydration
RR- tachypnoea out of proportion to fever (Normal RR 16-24/min. Any RR above 30 /min- view with caution)	May be a sign of pneumonia or sepsis	Assess with pulse oximetry if available Chest X ray if available.
BP	Low BP may be a sign of sepsis or shock/dehydration	Administration of intravenous fluids or rehydration. 30ml/kg over 30 minutes Repeat bolus if severe dehydration persists/pulses remain weak Then 70ml/kg over 2.5 hours Reassess after fluid administration
Hydration- assess tongue/oral mucosa, skin turgor, urine output by history	Can occur due to diarrheal illness, or from nausea/vomiting, low PO intake	Administration of intravenous fluids or rehydration with ORS if due to fluid losses. 2.2 – 4 litres of ORS over 4 hours
Mental status	May be from sepsis, cerebral malaria, typhoid encephalopathy, scrub typhus, meningitis	Assess neck stiffness, need for lumbar puncture. Assess for ability to protect airway Assess for focal weakness, periodic breathing, directional gaze

Initial clinical evaluation

Defining the initial syndrome can be useful to narrow down the possible infectious agent.

- Fever – Malaria, leptospirosis, dengue, typhoid, scrub typhus, other rickettsial illness, chikungunya, pyelonephritis
- Fever with thrombocytopenia/rash: dengue, malaria,leptospirosis,
- Fever with rash -dengue, measles, typhoid, rubella, HIV, viral illness, scrub typhus, meningococcal infection
- Fever with respiratory symptoms- influenza, community acquired pneumonia, COVID-19
- Fever with hepatorenal syndrome: falciparum malaria, leptospirosis, scrub typhus and hepatitis E or A with fulminant hepatic failure. Modest elevation in leptospirosis and malarial hepatitis. Higher in viral hepatitis.
- Fever with mental status change- meningitis, encephalitis (HSV, Japanese B, enterovirus) cerebral malaria, typhoid encephalopathy, scrub typhus

General supportive care

- Antipyretics to control fever- paracetamol in most cases. 500-1000mg PO q8h. Max 4g/day.
- Tepid sponging
- Assess hydration status. If able to take PO, allow for water, lime juice, kanji or ORS solution, especially if diarrheal symptoms or vomiting.
- IV fluids if unable to take orally, ongoing dehydration due to vomiting or diarrhea with severe dehydration, ileus or shock or confusion. Normal saline for most patients.
- Oxygen if respiratory symptoms and low oxygen saturation. Assess for need for higher level of care
- Mask for contacts if respiratory viral syndrome suspected

Initial investigations

- Fever with URI symptoms of duration <3 days should be managed with supportive care unless convincing signs of pneumonia exist or conditions like purulent tonsillitis
- Complete blood count, differential, platelet count. Leukocytosis in sepsis, leptospirosis. Leucopenia in Dengue. Thrombocytopenia in malaria and Dengue.
- Creatinine, liver function tests (SGPT, SGOT, bilirubin and alkaline phosphatase)
- POC glucose
- Urinalysis if urinary symptoms present. A reflex sample for urine culture should be drawn by clean catch midstream sample.
- Malaria rapid antigen card test [HRP- P falciparum (high Sn and Sp)/LD antigen (lower Sn and high Sp)]. If available malarial smear. Negative RDT should be followed by smear (or repeat RDT) if suspicion high. Malaria less likely if 2 neg RDTs. Malarial RDTs may stay positive for >3-4 weeks in highly endemic areas.
- Dengue card test for NS1 Ag, IgM and IgG
- Influenza or COVID antigen test

Focused work up

- If initial RDTs are negative, and fever >3 days, enteric fever, leptospirosis and scrub typhus or other etiologies may need to be investigated.

- Elevated transaminases may suggest enteric fever or rickettsiosis vs other cause of AUFI (PMID 35491421)
- Blood cultures should be a high priority to rule out typhoid/enteric fever or other infections where severe presentation could be due to bacteremia. At least 20-30 ml of blood should be collected and inoculated in aerobic bottles. Anaerobic cultures may be drawn where resources exist.
- A chest X ray may reveal occult pneumonia and could be an ordered test if respiratory symptoms are prominent
- IgM antibodies for leptospirosis and scrub typhus could be ordered. Sensitivity of such tests is poor, especially earlier in illness. Microscopic agglutination test (MAT), the reference standard for diagnosing leptospirosis but may not be available.
- IgM ELISA for scrub typhus may be available. The indirect fluorescent Ab (IFA) is a mainstay but may not be available. Most common cutoff titer is 1:50

Anti-microbial treatment of AUFI

In non-malarial AUFI, when patient has moderate to serious severity of illness, empirical treatment may be indicated while awaiting results of tests including blood cultures. Doxycycline or azithromycin may be appropriate initial therapy for those who are not seriously ill and do not need parenteral antimicrobial therapy. (PMID 24748368). Both the drugs have a comparable efficacy against rickettsia organisms and Leptospira. Azithromycin may be a better option if enteric fever suspected and may have lower incidence of adverse effects (PMID 17638600, 22975540, 22718054). For those needing parenteral antimicrobial therapy a combination of ceftriaxone and doxycycline may be appropriate.

Treatment for malaria

- P vivax: Chloroquine X3 days [10mg/kg on day 1 (4 tabs) , 10mg/kg on day 2 (4 tabs) and 5 mg /kg on day 3 (2 tabs)] + primaquine 0.25 mg/kg/d (6 tabs/d) X14 days*
- P falciparum:
    - NE: Artemether-Lumefantrine [80mg/480mg (4 tabs) BID] X3 days and primaquine 0.75 mg/kg on day 2
    - Other states: Artesunate 200 mg X3 days + sulfadoxine-pyrimethamine (750 mg/37.5 mg X1 dose) plus primaquine 0.75 mg/kg on day 2

(* Primaquine is contraindicated in infants, pregnant women and individuals with G6PD deficiency)

Suggested Treatment Regimens for Enteric fever

Severe illness or inpatient care (confusion, prolonged fever, organ dysfunction)

- Ceftriaxone 2g IV daily (50-100 mg/kg/d) for 10-14 days*
- Cefotaxime 1-2g IV q 8h (150-200mg/kg/d) for 10-14 days*

Ambulatory care

- Azithromycin: 1g PO daily (10-20 mg/kg/d) for 7 days
- Cefixime 400 mg PO twice daily (20mg/kg in 2 divided doses) for 10-14 days#

Fluoroquinolones should not be used. TMP/SMX 960 mg BID may be considered if susceptibility testing confirms no drug resistance.
(*antimicrobial susceptibility testing to rule out XDR S typhi)
(# may be used for de-escalation from initial IV therapy. May be associated with slower defervescence and higher rate of on treatment failure)

Treatment for leptospirosis
Mild disease:

- Doxycycline 100 mg BID (2 mg/kg/d in 2 doses) X 7 days
- Azithromycin 500 mg PO daily for 3 days or 10 mg/kg on day 1 f/b 5 mg/kg/d for 2 days

Severe disease

- Penicillin G (1.5 -3 million U IV q 6h), OR Ceftriaxone 1-2 g IV daily/ Cefotaxime1 g IV every six hours*

(*Penicillin and cephalosporins lack activity against rickettsiae and so should be avoided when rickettsial infection cannot be ruled out)

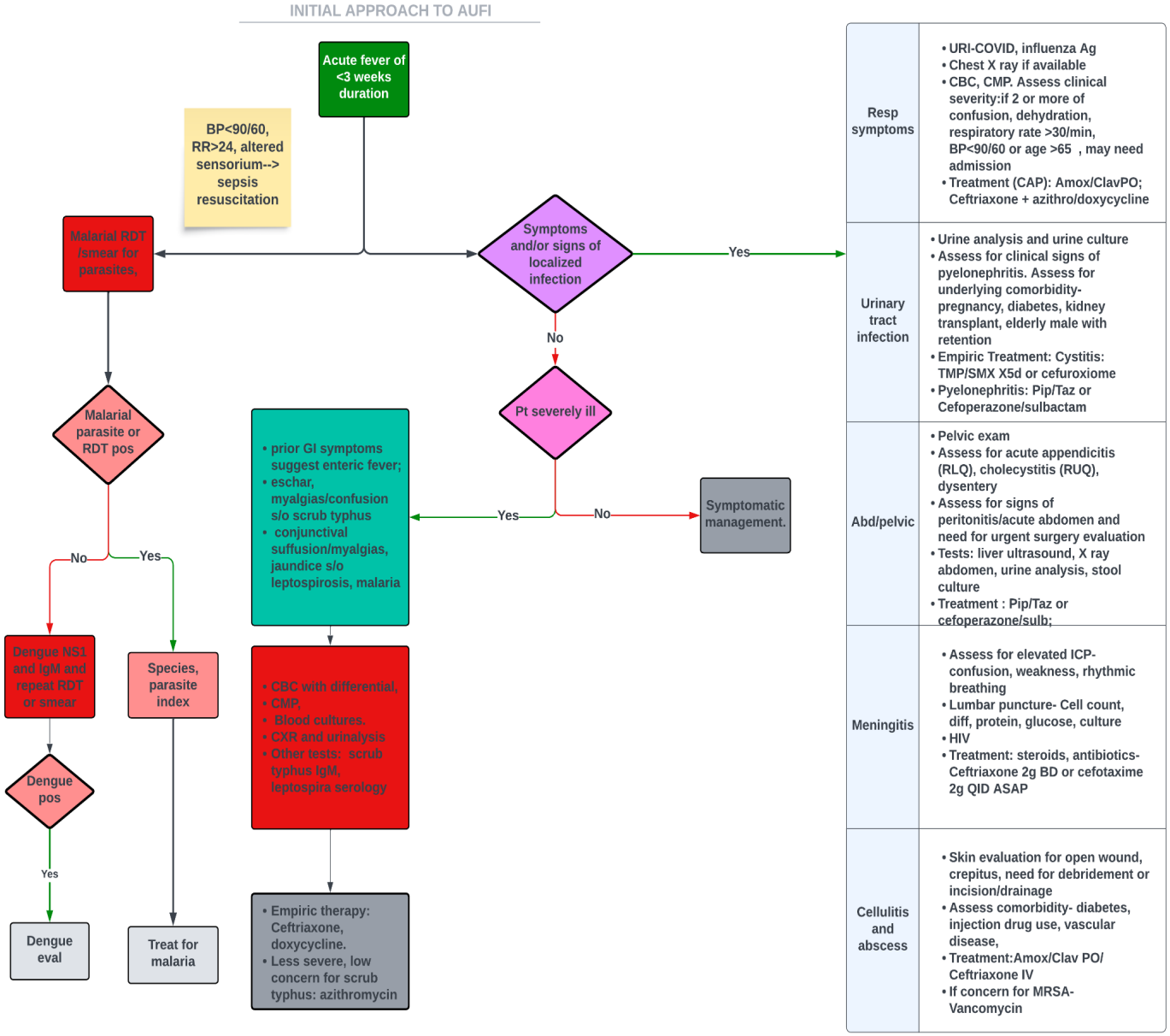
Treatment for scrub typhus

- Doxycycline 100 mg PO/IV BID (2 mg/kg/d in 2 doses) X 7 days
- Azithromycin 500 mg PO/IV daily for 3

Follow up activities

- Reassess for
  - Not improving in the expected time frame
  - Getting worse in spite of appropriate treatment
  - New symptoms appear- e.g., rash, seizures, altered sensorium, jaundice, reduced urine output, etc.

- Isolation of patient from other household contacts if possible


INITIAL APPROACH TO AUFI
Acute fever of <3 weeks duration
BP<90/60, RR>24, altered sensorium--> sepsis resuscitation
Malarial RDT /smear for parasites,
Symptoms and/or signs of localized infection
Yes
No
Malarial parasite or RDT pos
Pt severely ill
• prior GI symptoms suggest enteric fever;
• eschar, myalgias/confusion s/o scrub typhus
• conjunctival suffusion/myalgias, jaundice s/o leptospirosis, malaria
Yes
No
Symptomatic management.
No
Yes
Dengue NS1 and IgM and repeat RDT or smear
Species, parasite index
• CBC with differential,
• CMP,
• Blood cultures.
• CXR and urinalysis
• Other tests: scrub typhus IgM, leptospira serology
Dengue pos
Yes
Dengue eval
Treat for malaria
• Empiric therapy: Ceftriaxone, doxycycline.
• Less severe, low concern for scrub typhus: azithromycin
Resp symptoms
• URI-COVID, influenza Ag
• Chest X ray if available
• CBC, CMP. Assess clinical severity:if 2 or more of confusion, dehydration, respiratory rate >30/min, BP<90/60 or age >65 , may need admission
• Treatment (CAP): Amox/ClavPO; Ceftriaxone + azithro/doxycycline
Urinary tract infection
• Urine analysis and urine culture
• Assess for clinical signs of pyelonephritis. Assess for underlying comorbidity- pregnancy, diabetes, kidney transplant, elderly male with retention
• Empiric Treatment: Cystitis: TMP/SMX X5d or cefuroxiome
• Pyelonephritis: Pip/Taz or Cefoperazone/sulbactam
Abd/pelvic
• Pelvic exam
• Assess for acute appendicitis (RLQ), cholecystitis (RUQ), dysentery
• Assess for signs of peritonitis/acute abdomen and need for urgent surgery evaluation
• Tests: liver ultrasound, X ray abdomen, urine analysis, stool culture
• Treatment : Pip/Taz or cefoperazone/sulb;
Meningitis
• Assess for elevated ICP- confusion, weakness, rhythmic breathing
• Lumbar puncture- Cell count, diff, protein, glucose, culture
• HIV
• Treatment: steroids, antibiotics- Ceftriaxone 2g BD or cefotaxime 2g QID ASAP
Cellulitis and abscess
• Skin evaluation for open wound, crepitus, need for debridement or incision/drainage
• Assess comorbidity- diabetes, injection drug use, vascular disease,
• Treatment:Amox/Clav PO/ Ceftriaxone IV
• If concern for MRSA- Vancomycin