INVITED ARTICLE

Laboratory Diagnosis of Tropical Infections

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Abstract

Highlights: (1) Blood culture is the gold standard for the diagnosis of bacterial infections. (2) Bone marrow culture is more sensitive than blood culture even in patients with enteric fever receiving antibiotics. (3) Microscopic agglutination test is considered the gold standard for diagnosing leptospirosis; however, now IgM ELISA and polymerase chain reaction (PCR) are more frequently used for diagnosis. (4) Tuberculosis is diagnosed with the help of nucleic acid amplification tests like Xpert MTB/RIF Ultra which also detects rifampicin resistance. Other tests include microscopy, Lowenstein–Jensen and mycobacteria growth indicator tube culture, line probe assay. (5) Tropical rickettsial infections are diagnosed by serological reactions (Weil–Felix, ELISA for antibodies) and PCR. (6) For Brucellosis culture from blood, bone marrow or tissue specimens remain the mainstay in diagnosis. (7) Dengue, Zika, Crimean–Congo hemorrhagic fever, Ebola, hantavirus, rabies are diagnosed with reverse transcriptase-polymerase chain reaction. Serological tests like IgM ELISA or paired sera samples for IgG are also used for diagnosis.

Keywords: Brucellosis, Dengue, Ebola, Enteric fever, Leptospirosis, Rickettsial diseases, Tropical infections, Tuberculosis.

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Introduction

Tropical infections are those which are prevalent in tropical and subtropical regions. "Ending the neglect to attain Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030"—a 10 years plan was formally launched by WHO in January 2021.[1]

Bacterial Infections

- **Enteric fever**
  - *Blood culture:* It is considered the gold standard with maximum yield in the first week of illness. Sensitivity can be improved by increasing the volume and sets of blood culture collected prior to the initiation of antibiotics. The positivity rate is 60 – 80% if large volume of blood (15 mL in adults) is cultured.
  - *Bone marrow culture:* It is more sensitive than blood culture with a positivity rate of 80 – 95% even in patients on antibiotics for several days; regardless of the duration of illness.[2,3]
  - *Urine and stool culture:* Stool cultures are positive in 30% of patients with acute typhoid fever; however, the positivity rate increases with the duration of illness. Due to the irregular shedding of bacilli, several samples should be examined for the detection of carriers.
  - Leukopenia, eosinopenia, and raised transaminases.
  - *Widal:* detects antibodies against lipopolysaccharide (O) and flagellar (H) antigens of S. typhi and paratyphi A and B. Though used rampantly, it is poor on accuracy.
  - Rapid diagnostic tests (RDTs) (immunochromatographic assays, e.g., typhidot): Detect antibodies against antigens selected from S. typhi isolates (not for S. paratyphi) with sensitivity and specificity of 84% and 79%, respectively, for typhidot.[4]
- **Leptospirosis**
  - Leukocytosis with left shift, thrombocytopenia, impaired liver function tests, raised S. creatinine.
  - *Culture:* Tween-albumin media like Ellinghausen, McCullough, Johnson and Harris (EMJH) media is used. However, it is very laborious, difficult, can take months to grow and usually positive only in the acute phase, and not done routinely.
  - *Microscopic agglutination test (MAT):* It is considered the gold standard with a sensitivity of 86 to 96% and specificity of 100%. However, it is of no value in the early phase when antibodies are not present. It is labor intensive and complicated procedure as there is a need to maintain *Leptospira* strain for preparing live antigen with multiple serovars. A four-fold rise in titer between acute and convalescent specimens is considered to be positive. A single titer exceeding 1:200 or serial titers exceeding 1:100 also suggest leptospirosis.[5,6]
  - *ELISA for IgM antibodies:* These are most widely and routinely used. Though IgM antibodies against *Leptospira* start appearing in the first week. A convalescent sample taken after 2 weeks would confirm the diagnosis. However, the antibodies may persist for a long duration (at least 5 months) and give false-positive results.[7] Rapid diagnostics like dipstick tests for detecting IgM antibodies are also available.
  - *Polymerase chain reaction (PCR):* Helps in rapid and early detection of leptospiral DNA in the early phase of infection. Nested PCR and PCR/RFLP for 16S ribosomal RNA gene amplification can be used. Combining PCR with IgM ELISA would lead to improved sensitivity.
- **Tuberculosis (TB)**
  - *Microscopy:* Zeihl–Neelsen and fluorescent microscopy help rapid detection of TB bacilli. However, the sensitivity is poor with interobserver variation.

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- *Culture:* Solid culture on Lowenstein–Jensen (LJ) media and liquid culture by mycobacteria growth indicator tube (MGIT) help in accurate diagnosis. MGIT is the gold standard with 13% higher sensitivity than LJ. The turnaround time for solid LJ media is about 6 to 8 weeks while it is about 4 – 6 weeks for MGIT. Growth-based phenotypic drug susceptibility testing on MGIT is used for determining the appropriate antituberculous treatment.
- *Nucleic acid amplification tests (NAATs):* This forms the first line in the diagnosis of TB. WHO recommends the use of cartridge-based GeneXpert (Xpert MTB/RIF and Ultra) and chip-based TrueNat. In presumptive extrapulmonary TB, Xpert Ultra shows 6.3% better sensitivity than Xpert MTB/RIF when compared to culture (90.9% vs. 84.7%). However, specificity is reduced by 2.7% (95.6% vs. 98.4%).[8] The WHO technical expert group concludes that Ultra has a higher sensitivity than Xpert MTB/RIF particularly in smear-negative culture-positive specimens, extrapulmonary specimens, and testing specimens from HIV-infected patients and children. Among people without HIV infection, for sputum specimens, an initial "trace call" positive result should be confirmed by testing a fresh specimen with clinical and radiological correlation. This is due to the fact that Ultra can detecting even small numbers of nonreplicating or nonviable bacilli present, especially in patients with recent history of TB (treatment in last 2 years). However, it has similarly good accuracy (~100%) for rifampicin resistance detection.[9]
- *Line probe assay (LPA):* Can be done from smear-positive samples or culture isolate to detect genetic mutations conferring resistance.
  - First line [isoniazid (H) and rifampicin (R)]
  - Second line (fluoroquinolones and aminoglycosides)

Turnaround time of LPA is up to 72 hours, NAAT ~2 hours.

- Different sequencing methods used in drug-resistant TB include the following:
  - Sanger's sequencing
  - Pyrosequencing
  - Whole-genome sequencing
  - Targeted next-generation sequencing

- **Meliodosis:**[10] It is caused by soil saprophyte, *Burkholderia pseudomallei*, endemic in most of India and Southeast Asia, and is highly endemic in Thailand, Malaysia, Singapore, and Northern Australia. Patients usually present with chronic pneumonia mimicking TB, localized skin abscesses or ulcers, fulminant septic shock with abscesses in multiple internal organs or may remain asymptomatic.
  - *Culture:* Positive culture of *B. pseudomallei* gives a definitive diagnosis. These are oxidase-positive aerobic bacilli and maybe many times misidentified by commercial methods as *Pseudomonas* spp. or other *Burkholderia cepacia* MALDI ToF MS does not identify it, VITEK 2 should be used.
  - *ELISA:* Detects antibodies against *B. pseudomallei* and is useful as a supportive diagnosis.
  - *PCR:* DNA detection by PCR can help in early diagnosis; however, it is not available widely.
  - *Active melioidosis detect lateral flow assay:* It is a lateral flow-based immunoassay that can detect capsular polysaccharides of *B. pseudomallei* from different samples like whole blood, pus, sputum, urine, etc. It can be used as a point-of-care test in resource-limited setting. It demonstrates a sensitivity of 85.71% with a specificity of 93.62%.[11]
- **Tropical rickettsial infections:**[10] In South and Southeast Asia, scrub typhus (Orientia tsutsugamushi) and murine typhus (Rickettsia typhi) are highly endemic and are often mistaken for typhoid.
  - Scrub typhus
    - ELISA detecting Orientia-specific IgM and IgG antibodies has improved diagnostic accuracy
    - *PCR:* They form the central pillar in the diagnosis of scrub typhus.
    - *Weil–Felix:* OX-K agglutination test based on the cross reactivity of antiOrientia antibodies to *Proteus mirabilis*, specifically the OX-K (Kingsbury) strain. However, it is unreliable and not routinely used.
  - Spotted fevers, epidemic typhus, and endemic typhus
    - Immunohistochemistry of skin biopsies aid in diagnosis
    - Diagnosis is mainly based on serology and PCR.
      - Convalescent-phase serum showing seroconversion or a four-fold rise in titer helps to establish a diagnosis
      - Blood, skin biopsies, swabs from eschar base help in molecular detection.
    - Immunofluorescence may also be used.
    - *Weil–Felix:* Agglutination reaction based on cross reactivity. *P. vulgaris* OX2 and OX19 antigens react with antibodies to the spotted fever group; while *P. vulgaris* OX19 antigen reacts with antibodies to typhus-group.

- **Brucellosis**[10,12]
  - *Culture:* Isolation of brucella from blood, bone marrow, or tissue samples remain the mainstay in diagnosis of Brucellosis.
  - *Serology:* Standard agglutination test, with a titer of at least 1:160 helps in the diagnosis. The rose-bengal card agglutination test is a useful screening tool. These tests detect IgM which may be positive even in the first week. IgG assays are positive from second week.
  - *PCR:* It is positive in symptomatic patients with negative serology. It can come positive as early as 10 days after inoculation, especially during outbreaks or relapses.

- **Tetanus**[10]
  - Diagnosis of tetanus is mainly dependent on history and clinical examination findings.
  - *Microscopy: Clostridium tetani* is a spore-bearing Gram-positive to Gram variable bacillus.
  - *Culture:* They are strict anaerobes and very difficult to grow. Also, a positive culture does not indicate whether it contains toxin-producing plasmid.
  - Strychnine poisoning, is the differential diagnosis. Hence toxicological studies of serum and urine should be performed to rule out this poisoning.

Viral Infections

- **Dengue**[13]
  - *NAATs:* Reverse transcriptase-polymerase chain reaction (RT-PCR) on whole blood or serum is the preferred method of laboratory diagnosis in ≤7 days from symptom onset.
  - *NS1 antigen:* Enzyme immunoassay to detect dengue virus NS1 antigen in serum is routinely used for diagnosis in the first 5 days.

- *IgM ELISA:* IgM antibodies usually appear ≥4 days after fever onset and can be detected by IgM Antibody capture ELISA (most useful after 1 week of fever onset). However, interpreting results may be difficult at times as people infected or vaccinated against other cross-reactive flaviviruses (Zika, West Nile, yellow fever, and Japanese encephalitis viruses) may yield false-positive serologic dengue diagnostic test results.
- For patients presenting between 5 days to 7 days of fever onset, combination of rRT-PCR or NS1and IgM should be used.
- *RDTs:* Immunochromatographic lateral flow assays detecting NS1 and IgM antibodies are available as point-of-care tests. However, these need to be confirmed with ELISA.
- *Plaque reduction neutralization tests:* These are quantitative assays that measure virus-specific neutralizing antibody titers and can resolve cross-reactivity issues.
- *IgG ELISA:* Neutralizing antibodies develop after IgM antibodies and consist primarily of IgG antibodies and may last life long and hence not useful as a diagnostic test.

- **Japanese encephalitis**[14]
  - *Antibody detection:* Hemagglutination inhibition test, compliment fixation test, ELISA for IgG (four-fold difference in paired sera), and IgM (MAC) antibodies. IgM ELISA is the preferred diagnostic modality for samples collected 3 to 5 days after onset of infection. JE IgM can be detected even in CSF for confirmatory diagnosis.
  - *Antigen detection:* Immunofluorescence and immunoperoxidase can be used.
  - *RT-PCR:* It is a confirmatory test.

- **Crimean–Congo hemorrhagic fever (CCHF):** Early diagnosis of CCHF is essential for appropriate patient management as well as preventing potential transmission to healthcare workers caring for the patient.
  - History and epidemiological data play a key role in early diagnosis of CCHF.
  - *Viral detection assays*
    - RT-PCR from blood is the most widely used test for diagnosis in the first 10 – 12 days after symptom onset. The detection of a viral load of $>1 \times 10^9$ copies/ml by quantitative RT-PCR is an indicator of poor prognosis.[15]
    - Viral antigen detection by ELISA has good sensitivity in the first 5 days of illness. However, the sensitivity decreases with detectable anti-Crimean-Congo hemorrhagic fever virus (CCHFV) antibodies.
    - Immunohistochemical staining can also show evidence of viral antigen in formalin-fixed tissues.
  - *Serological testing*
    - *ELISA:* Detects IgM and IgG antibodies. This is most likely to be useful after the first week of illness as IgM antibodies are usually detectable 7 – 9 days after symptom onset with a sensitivity of 87.8% and specificity of 98.9%. The sensitivity and specificity of IgG ELISA are 80.4% and 100%, respectively.[16]
    - Indirect immunofluorescence assays also used for antibody detection is usually for research purpose.

- **Hantavirus**[10]
  - *RT-PCR:* Can be done on blood and tissues for rapid diagnosis.
  - *ELISA for antibodies:* Virtually all hantavirus patients have both IgM and IgG ELISA antibodies positive when they present clinically. The presence of specific IgM provides evidence of a recent infection but has lower specificity than a rise in IgG titers in acute and convalescent serum specimens.
  - Immunohistochemical staining of tissue can also help in diagnosis.

- **Ebola hemorrhagic fever:** It is seen in sub-Saharan Africa. Combination of symptoms suggestive of Ebola and history of a possible exposure within 21 days before the onset of symptoms is important is for suspecting a case of Ebola.
  - They usually have mild lymphopenia and thrombocytopenia, and elevated hepatic transaminases, with AST>ALT.
  - *PCR:* It is the most common modality of early diagnosis. However, the viral load reaches detectable levels usually after 3 days of symptom onset. If specimens collected earlier are negative, repeat testing with fresh specimen to be tested after 48 hours.[17]
  - *ELISA for antibodies:* It is used for confirmation of exposure or infection.
  - Laboratory confirmed cases are to be notified immediately for rapid contact tracing.

- **Rabies**[11,18]
  - Immunohistochemical staining for rabies antigen from a skin biopsy taken from nape of the neck, corneal smears are usually used for diagnosis.
  - Reverse-transcription heminested PCR test on skin biopsy specimens showed ≥98% sensitivity and 100% specificity.
  - Neutralizing antibodies against rabies virus in CSF or serum is diagnostic in unimmunized patients, though it lacks sensitivity.

Parasitic Infections

- **Malaria**
  - Thick film more sensitive and thin film to help diagnose parasitemia. Thin film is used to speciate.
  - RDTs[19] are immunochromatographic tests for detection of malarial antigens.
    - *Histidine rich protein-2 is specific for* Plasmodium falciparum*:* sensitivity of 95% and specificity of 95.2%. However, it may remain positive for 1 – 5 weeks after effective therapy; hence not useful for detecting treatment failure
    - *Plasmodium* lactate dehydrogenase: pan specific or *Plasmodium vivax* specific
    - *Aldolase:* Pan specific for *Plasmodium species*
    - Most of the RDTs can detect as low as 200 parasites/μL. However, the sensitivity increases with higher parasitic load
    - These are less sensitive for *P. malaria* and *P. ovale*
  - *NAAT:* PCR and loop-mediated isothermal amplification are highly sensitive. However, these are not routinely available and also not recommended for routine diagnosis in endemic areas as they may have persistent low-level parasitemia.

- **Leishmaniasis**[20]
  - *Specimens*
    - *Visceral leishmaniasis:* Bone marrow aspiration is the most preferred. Other specimens that can be used include liver, enlarged lymph nodes, and whole blood (buffy coat) are other potential sources of tissue specimens
    - *Cutaneous leishmaniasis:* Full-thickness skin biopsy from an active appearing skin lesion that has been cleansed (cellular debris and eschar/exudates removed)

  - *Mucosal leishmaniasis:* Biopsies from mucosal areas that have macroscopic abnormalities are recommended for specimen collection
- Multiple testing modalities to be used simultaneously like visualization of the characteristic amastigote in smears or tissue (histopathology), parasite isolation by *in vitro* culture in Novy–MacNeal–Nicolle media; PCR and DNA sequencing for species identification
- *Serological tests (antileishmanial antibodies):* rK39-based immunochromatographic test can be done along with other diagnostic assays for visceral leishmaniasis but not recommended for cutaneous leishmaniasis
- Leishmanin skin test is a delayed-type of hypersensitivity reaction

- **Trypanosomiasis**
  - Human African trypanosomiasis (sleeping sickness) occurs in sub-Saharan Africa, transmitted by the vector, the tsetse fly.
    - *Microscopy:* Detection of trypanosomes in lymph node aspirates, chancre fluid, blood, bone marrow, or CSF (late stages). A wet film for the motile trypanosomes, and a Giemsa stained fixed blood smear (thin or thick) should be examined. Concentration techniques like centrifugation followed by an examination of the buffy coat; mini anion-exchange/centrifugation; and the quantitative buffy coat technique for blood samples and examination of sediment after centrifugation of other samples like CSF improve the detection capacity by microscopy.
    - *Antibody detection:* Reliable serological tests available only for *T brucei gambiense* infection, which detects specific antibodies. The card agglutination test for trypanosomiasis (CATT) has been used as a screening tool by mobile teams and has helped the control of *T brucei gambiense* disease.[21] CATT can be done with blood from a finger prick, serum, or plasma, which is then scored visually for agglutination reaction after 5 minutes. Newer rapid diagnostic kits are also available. However, in areas with low prevelance of disease, CATT and other RDTs have very poor specificity. Antibody detection is of limited use for *T. b. rhodesiense*, as they present with high levels of parasitemia. ELISAs are useful tools for largescale surveys, postelimination monitoring, and animal reservoir studies due to their high sensitivity and specificity.
    - *Molecular detection: T brucei gambiense*-specific and *T brucei rhodesiense*-specific PCR assays exist but have poor sensitivity as they target single-copy genes.
  - *American trypanosomiasis (Chagas disease):* It is caused by Trypanosoma cruzi in South America.[10]
    - Acute disease is diagnosed by detecting trypomastigotes in blood or CSF. They can be seen as motile trypomastigotes in wet film (buffy coat of blood) or can be seen in Giemsa stained smears. Tissue smear stained with H/E may show the amastigote forms. In highly suspected cases who are negative on microscopic examination, PCR can be tried if available.
    - Chronic disease diagnosis is mainly done by detecting specific IgG antibodies. Serological tests like ELISA, indirect hemagglutination, chemiluminescence, and indirect immunofluorescence can be used.

- **Schistosomiasis:**[22] Adult worms of *S. mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum* are found in the mesenteric venous plexus of infected hosts and eggs are shed in feces; *S. haematobium* adult worms reside in the urinary bladder venous plexus and eggs are shed in terminal urine.
  - *Microscopy*
    - Detection of Schistosoma eggs in stool (*S. mansoni*, *S. japonicum* or other species) or urine (*S. haematobium*) is the usual method for diagnosis. Three samples collected on different days and concentration techniques for stool samples and centrifuging the urine and examining the sediment improves the chances of detection of eggs on microscopy. Hematuria may give a clue towards *S. haematobium* infection. Terminal urine should be collected between 10 am to 2 pm.
    - When stool or urine examinations are negative, eggs may be demonstrated by tissue biopsy (rectal biopsy for all species and biopsy of the bladder for *S. haematobium*).
  - *Serological diagnosis*
    - *ELISA:* FAST-ELISA for antibody detection may be useful to indicate schistosome infection in patients in whom eggs of Schistosomes are not detected in stool or urine but have traveled in schistosomiasis endemic areas. However, the sensitivity and specificity of these tests are variable. These are usually positive at least 6 to 8 weeks after likely infection.
    - *Immunoblot:* Species-specific immunoblot assays may be used for diagnosis based on travel history.

Conclusion

Early diagnosis has an impact on patient management. Our diagnostic armamentarium is increasing and we are moving from complex time-consuming tests to rapid diagnostics. However, we need more reliable point-of-care tests for prompt diagnosis and management of tropical infections.

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