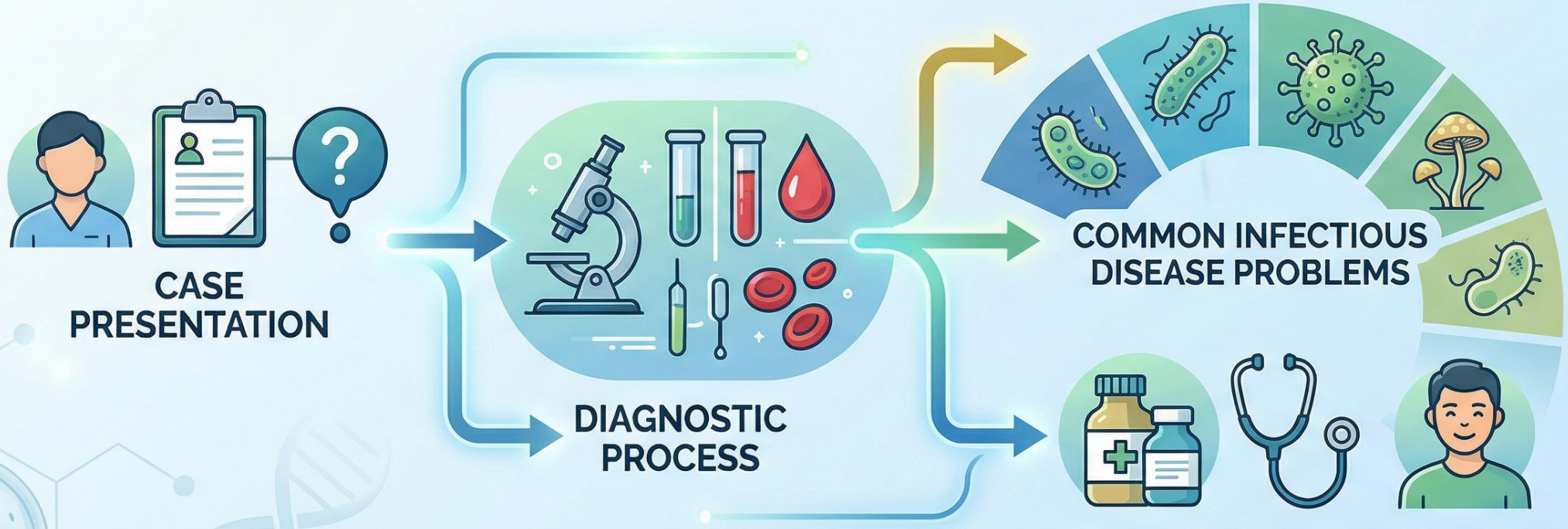
CASE APPROACH IN COMMON INFECTIOUS DISEASE PROBLEMS

FOR RESIDENT TEACHING | EXAM PREPARATION



APRIL 2026

Worawong Chueansuwan MD

Outline

- Common problem in ID long case exam. = **“Prolonged fever”** (fever > 4 wks.)
- Approach
  - Classical FUO
    - Common etiology TB, melioidosis, liver abscess
  - Infective endocarditis (NVE) (ESC 2023)
  - Immunocompromised : HIV related Ois, IFN gamma AutoAb

Clinical Presentation

- **Patient:** 25-year-old male, previously healthy.
- **Medical History:** No U/D, no regular medications, no herbal supplements.
- **Chief Complaint: Persistent high-grade fever (4 weeks), sore throat, and migratory joint pain.**
- **Physical Examination:**
  - Vital Signs: T 39.4°C, HR 120 bpm, BP 115/75 mmHg.
  - Skin: Evanescent, salmon-pink maculopapular rash during febrile peaks.
  - ENT: Pharyngeal erythema without exudates.
  - Lymph Nodes: Mildly tender cervical and axillary lymphadenopathy.
  - Abdomen: Significant hepatosplenomegaly.
  - MSK: Active arthritis of both wrists and right knee.
  - Other: Lungs clear, normal heart sounds.

Top 3 Differential Diagnosis by GEMINI

1. Adult-Onset Still's Disease (AOSD)
2. Lymphoma (e.g., HL, NHL)
3. Systemic Lupus Erythematosus (SLE)

Fever of unknown origin (FUO)

Petersdorf and Beeson (1961)

- Fever higher than 38.3°C (100.9°F) on several occasions, persisting **without diagnosis for at least 3 weeks** + ~~**at least 1 week's investigation in hospital**~~
- **Revised definition** : require investigation for **3 days of IPD or at least 3 OPD visits**

- **Revised into 4 distinct subclasses** due to changes in clinical practice
  1. Classic (median duration of fever was **40 - 44 days**)
  2. Nosocomial (health care associated)
  3. Neutropenic (immunodeficient)
  4. HIV-related

Hints

Cause of FUO (systematic reviews)

- Infection (38%)
- Neoplasm (12%)

} Age > 65

- Autoimmune (21%)
- Undiagnosed (23%)

} Age < 65

- Miscellaneous (7%)

Medicine (Baltimore) 1961;40:1–30
Curr Clin Top Infect Dis 1991;11:35–51
Am J Med Sci 1986;292:56–64

Etiology of Classic FUO (Infection)

- **Bacteria infection**
  - **Tuberculosis**
  - Typhoidal and **nontyphoidal salmonellosis (aortitis)**
  - **Infective endocarditis**
  - **Deep-seated infections** (abscesses and prostatitis)
- **Viral infection**
  - Mononucleosis-like infection (EBV, CMV, HHV-6, HHV-7)
- **Fungal infection**
  - Histoplasmosis
  - Talaromycosis
- **Zoonosis**
  - Rickettsioses
  - **Brucellosis**
  - Bartonellosis

N Engl J Med 2022;386:463-77.

Etiology of Classic FUO

- **Neoplasms**
  - **Lymphomas**
  - **Leukemias**
  - **Renal-cell carcinoma**
  - Hepatocellular carcinoma
  - **Metastatic cancers**
  - Atrial myxoma
- **Autoimmune disorders**
  - **Adult-onset Still disease**
  - Polymyalgia rheumatica
  - **Temporal arteritis**
  - **Systemic lupus erythematosus**
  - Inflammatory bowel disorders
- **Miscellaneous**
  - Drug-induced fever
  - Hepatitis
  - **Deep venous thrombosis**
  - Sarcoidosis
  - Addison's disease
  - Diseases of the thyroid gland
  - Central nervous system disorders
    - Intracranial hemorrhage and strokes

N Engl J Med 2022;386:463-77.

Approach : History

- **History taking should be attention to**
  - Recent travel, work environment
  - Exposure to pets and other animals
  - Recent contact with people exhibiting similar symptoms
  - Past medical history
  - List of the patient's medications (drug-induced fever)
- **Night sweats**
  - tuberculosis, autoimmune disorders, and hematologic malignancies
- **Weight loss**
  - malignancy, tuberculosis, HIV infection, or endocrine disorders

Hints
Review of systems

Approach : Physical examination (1)

- Auscultation of the heart is important to detect the presence of a **new murmur** associated with bacterial endocarditis
- **Relative bradycardia** (typhoid fever, rickettsioses and Q fever)
- **Hepatosplenomegaly** (infectious, malignancy and autoimmune disorders)
- Abdominal tenderness (IAIs, aortitis and lymphadenitis)
- **Palpable lymph nodes** (infectious or hematologic malignancy)
- **Oral lesions** such as ulceration (histoplasmosis, autoimmune or malignant)
- Inflammation or infection of the joints
- Rashes or **skin lesions** (SLE, sarcoidosis, HIV and CMV)

Abnormal physical findings were reported to diagnosis in 60% of FUO

Approach : Physical examination (2)

Site	Finding	Diagnosis
Head	Sinus tenderness	Sinusitis
Temporal artery	Nodules, **reduced pulsations**	**Temporal arteritis**
Oropharynx	Ulceration, toothache, **oral ulcer**	Disseminated **histoplasmosis**, periapical abscess
Fundi or conjunctivae	Choroid tubercle, petechiae, **Roth spot**	Disseminated TB/histoplasmosis, **endocarditis**
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	**Murmur**	**Infective or marantic endocarditis**
Abdomen	Enlarged iliac crest **lymph nodes**, splenomegaly, **hepatosplenomegaly**	**Lymphoma**, endocarditis, **disseminated** TB/histoplasmosis
Rectum	Perirectal fluctuance/tenderness, Prostatic tenderness/fluctuance	Abscess
Genitalia	Testicular nodule, Epididymal nodule	Periarteritis nodosa
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis
Skin and nails	Petechiae, **splinter hemorrhages**, subcutaneous nodules, clubbing	Vasculitis, **endocarditis**

Mandell, Douglas, and Bennett's, Principles and practice of Infectious disease, Ed 9th

Initial investigation

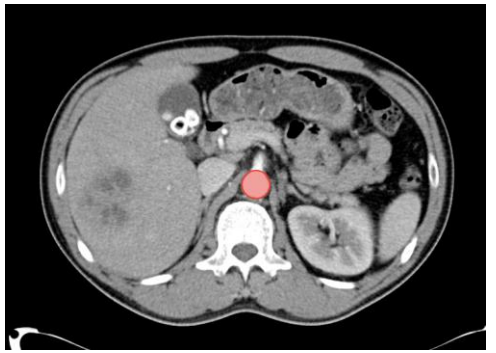
- Complete blood count with differential
- BUN/creatinine
- Liver function tests
- Erythrocyte sedimentation rate
- Urine and blood cultures
- Chest radiography
- Additional cultures obtained from affected areas

Further investigation

- **CT of the abdomen and pelvis (highest diagnostic yield)**
- **Serologic studies** : rule out collagen vascular diseases
- Nuclear imaging, bone marrow and liver biopsies, endoscopy, venous Doppler imaging, MRI, other invasive studies

Hints

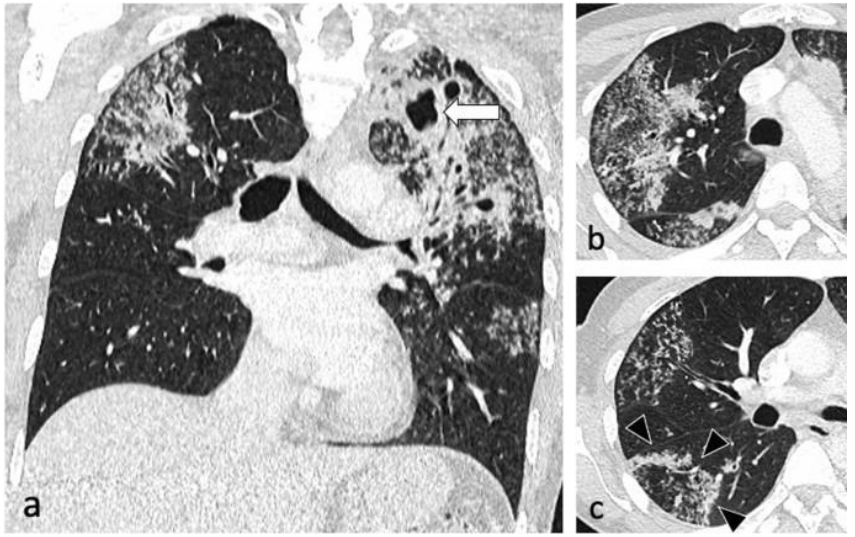
- Liver and spleen
- LN (necrosis)
- Bone (osteomyelitis)
- Psoas, paraspinal
- Aorta
- Prostate



Radiology. 1980 Aug;136(2):407-11
Arch Intern Med. 2003 Mar 10;163(5):545-51

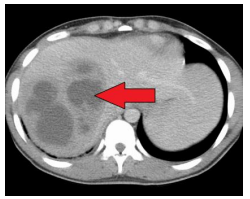
Imaging studies

- **Computed tomography** of abdomen, **ultrasound imaging** of gallbladder and hepatobiliary system have been used extensively to evaluate cases of FUO
- More than 3 CT or ultrasound were performed for each FUO patient evaluated
- **Diagnostic utility of imaging techniques in patients with FUO**
  - Plain-film chest radiography : 60%
  - Chest CT : 82%
  - Abdominal ultrasound : 86%
  - **Abdominal CT : 92%**

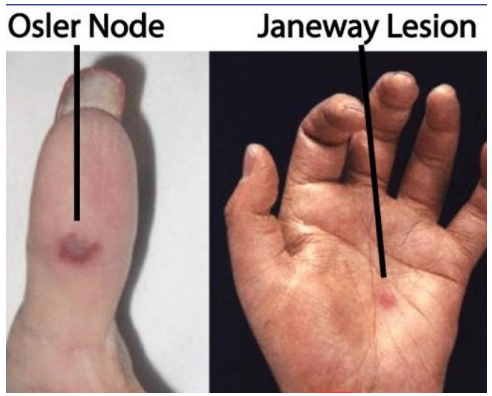
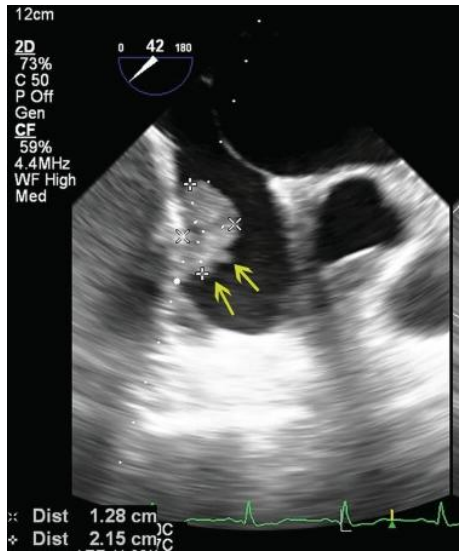


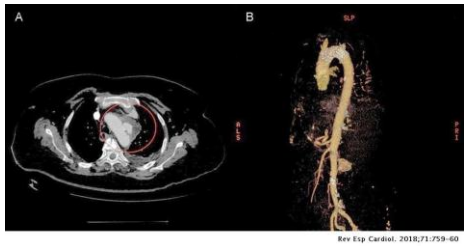
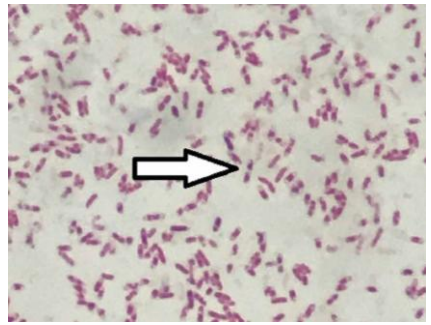
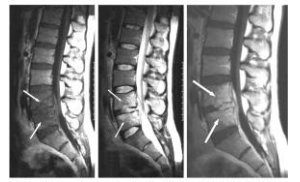
Medicine (Baltimore). 2007;86:26–38

Clinical clues

	History	Physical exam	1st Test	Other tests
Tuberculosis	• **fever**, chills, **weight loss**, **night sweats**; • **Prolonged cough (>2wk)** • **HIV infection (13%)**, or immunosuppression	• **Pulmonary**: tachypnea, **decreased breath sounds**, crackles, **dullness** to percussion; • **Extrapulmonary**: findings dependent upon site, **lymphadenopathy** common	• Smear AFB (Sn:55%) • **Culture (100%)** • Nucleic acid amplification tests (NAAT) **Xpert MTB/RIF Ultra** • **Sputum** (Sn:90%, Sp:96%) • **CSF**, LN, Synovial (97%) and pleural fluid (71%)	
Abdominal or pelvic abscess	• **recent abdominal or pelvic surgery**, childbirth; • **abdominal pain usually present;** lack of symptoms common in elderly	• guarding or rebound tenderness	• **CT abdomen and pelvis**: abdominal or pelvic abscess	
HIV (Acute HIV)	• **often asymptomatic**; fever, myalgia, diarrhea, fatigue, rashes; • **history of high-risk sexual activity** (multiple partners, unprotected, or male-male) • **intravenous drug use**	• diffuse lymphadenopathy	• 4th-generation HIV antibody/antigen test • **HIV RNA in very early (100,000-1,000,000 copies/mL)** **(false positive if <3,000)**	

Clinical clues

	History	Physical exam	1st Test	Other tests
Infective endocarditis	• **often insidious onset**; chills, malaise, weight loss, night sweats, arthralgia • **signs of HF** (shortness of breath, leg edema) • **signs of embolic** hemisensory/ motor deficit • **predisposing**; history of rheumatic fever, congenital heart disease, recent dental work, prosthetic valve, IDU, or prior SBE, **cardiac device**	• **new murmur, signs of congestive heart failure or peripheral emboli** (splinter hemorrhages, Osler nodes, Janeway lesions), Roth spots or retinal hemorrhages, focal neurologic deficit 	• **TTE: vegetation (63%)**, cardiac valve incompetence • Blood cultures: positive • Erythrocyte sedimentation rate: elevated 	• Chest x-ray: enlarged heart, edema, effusion, **prosthetic valve** • **TEE: vegetation(90-100%),** cardiac valve incompetence, intracardiac complication **(prosthetic valve)** • Cardiac CT : perivalvular • FDG-PET scan • CRP: elevated (diagnosis and monitoring disease progress)
Osteomyelitis	• general malaise, fever, pain over affected bone	• tenderness/redness/ swelling over affected area, drainage of pus through overlying skin	• **MRI:** decreased T1 signal, increased T2 signal represents marrow fat replaced by water due to edema, exudates, or ischemia.	• ESR: elevated • Blood cultures: positive • Needle aspiration: pus • Bone scan: focal uptake

	History	Physical exam	1st Test	Other tests
Nontyphoidal salmonellosis	• **fever**, **chills** • Intestinal ; abdominal pain, diarrhea, nausea, vomit (AGE) • Extraintestinal ; joint pain, bone pain	• guarding or rebound tenderness • tenderness/swelling over affected area	• Blood cultures: positive • **CTA whole aorta** 	• **Endovascular/vascular graft infection** • **Risk in age > 50** • Seeding atherosclerotic plaques or aneurysm
Melioidosis	• Risk factors: **diabetes**, **CKD**, thalassemia, **alcoholism, chronic lung** immunosuppressive therapy (1/3 no risk factor) • **fever**, **chills** • Productive cough • Skin lesions • joint pain, bone pain • suprapubic pain, dysuria, difficulty passing urine	• **pulmonary (50%)**: tachypnea, **consolidation**, crackles • **hepatosplenomegaly** (hepatosplenic abscess 20%) • skin : abscess • parotid (children) • prostate may be tender and boggy	• Blood cultures: positive • Gram stain of sputum or purulent drainage may demonstrate gram-negative bacilli. **("safety pin")** • **Serologic testing is not a reliable** method of diagnosis 	
Brucellosis	• animal contact or ingestion of **unpasteurized dairy**, • fever, sweats, malaise, **arthralgias (80%)**	• fever, lymphadenopathy, hepatosplenomegaly	• CBC : cytopenia (10-30%) • blood culture (15-70%) • Serologic test (ELISAs) • MRI :**SI joints (80%) and spinal joints (54%)**	• bone marrow culture: positive 

Drug associated fever

- Frequently overlooked because of lack of localizing signs and inappropriately well
- **Clinical presentation : eosinophilia (25%), relative bradycardia (10%), rash (5%)**
  - May occur at any point during course of drug therapy
    - Anti-neoplastic agents (median 0.5 days, mean 6 days) : may higher temperature than other agents
    - Antimicrobials agents (median 6 days, mean 7.8 days) : fever disappearing within 72 hours after stop
    - Central nervous system agents (median 16 days, mean 18.5 days) : serotonin syndrome, NMS
    - Cardiovascular agents (median 10 days, mean 44.7 days)
  - Degree of pyrexia can vary ranging from 37.2 to 42.8°C (the most common : 38.9 – 40 °C)

Mechanism
- Alterated thermoregulation
- Infusion related
- Pharmacologic action of drugs
- Hypersensitivity reaction
- Idiosyncratic reaction

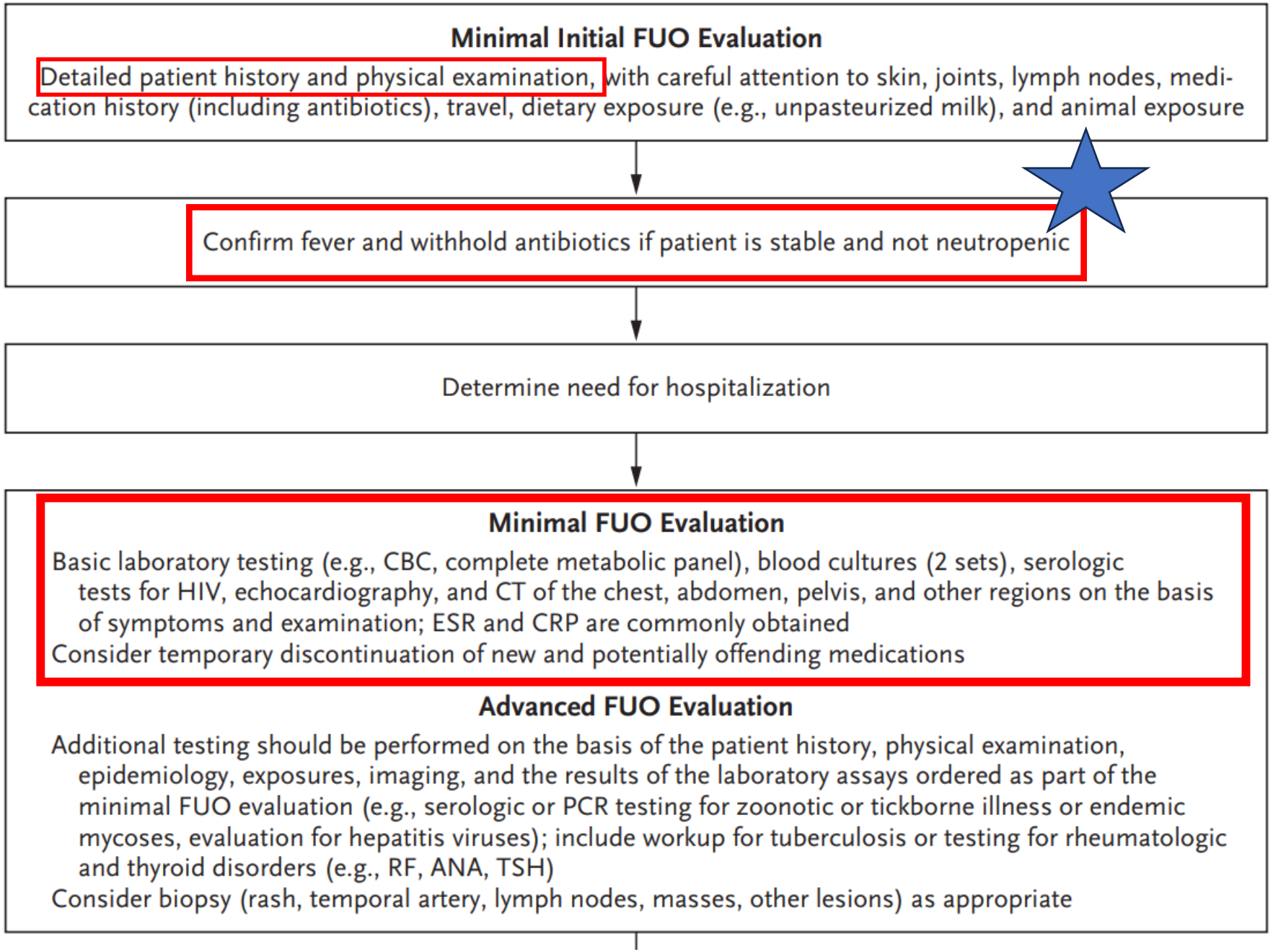
HarrisLF, HoldsambeckHK. Drug fever : surprisinglycommonand costly.Ala Med 1986;56:19–22
Johnson DH, Cunha BA. Drug fever. Infect Dis Clin NorthAm1996;10:85–91
Tabor PA. Drug-induced fever. Drug Intell Clin Pharm1986;20:413–20
Tisdale JE, Miller DA. Drug-induced diseases:prevention, detection, and management. Bethesda,MD: American Society of Health-SystemsPharmacists,2005

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Fever of Unknown Origin

Ghady Haidar, M.D., and Nina Singh, M.D.



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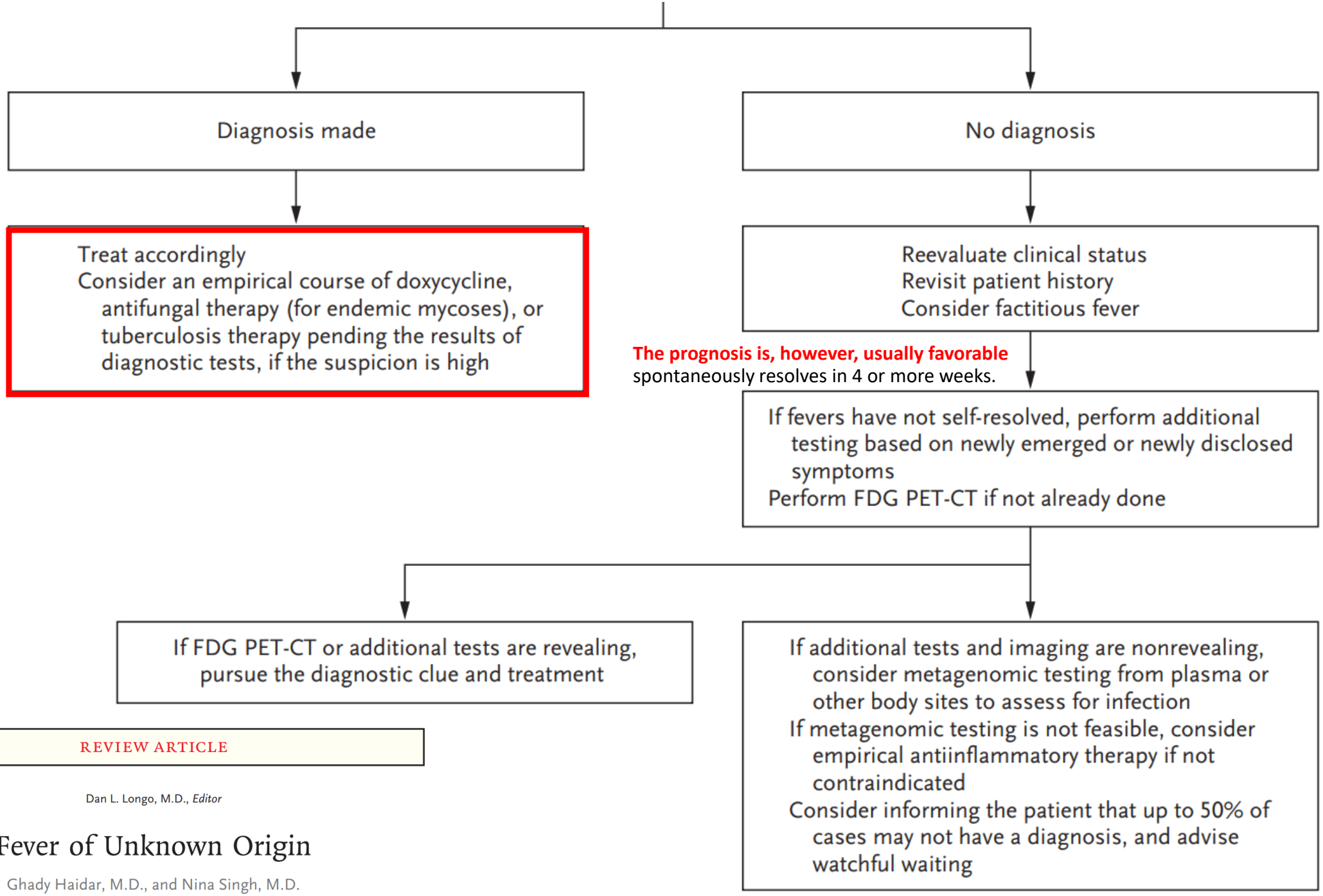

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N Engl J Med 2022;386:463-77.

Management

- **Negative workup**
  - About 20% of patients with documented FUO never have a confirmed diagnosis. **The prognosis is, however, usually favorable**; in most patients the fever usually spontaneously resolves in 4 or more weeks.
- **Empiric therapy and therapeutic trials**
  - For most cases of FUO, **treatment is withheld whenever possible** until a diagnosis can be made.
  - Except in **Seriously ill** (**neutropenia, severely immunocompromised**, rapidly deteriorating clinical status) that therapy cannot be withheld for further period of observation
  - Fevers secondary to malignancy or autoimmune disorders are more likely to **respond to a trial of NSAIDs** than infections

J Intern Med. 2003 Mar;253(3):263-75.

Patient Profile

- **Patient:** A 30-year-old female office worker from Bangkok.
- **Medical History:** SLE with Lupus Nephritis (Class IV) for 2 years. Currently on Prednisolone (20 mg/day) and MMF 2 g/day. Last flare was 6 months ago.
- **Chief Complaint: Persistent high-grade fever (3 weeks), dry cough, and 4 kg weight loss.**
- **Physical Exam:**
  - Vital Signs: T 38.8 C, HR 112 bpm, BP 100/60 mmHg, SpO2 94% on room air.
  - Skin: No active malar rash or discoid lesions. No livedo reticularis.
  - Lymph Nodes: Multiple, firm, non-tender cervical and axillary lymphadenopathy (1–2 cm).
  - Respiratory: Fine crackles heard bilaterally at both lung bases.
  - Abdomen: Significant hepatosplenomegaly (Liver 3 cm, Spleen 2 cm below costal margin).

Top 3 Differential Diagnosis by GEMINI

1. Disseminated Tuberculosis (TB)
2. Disseminated Talaromycosis
3. Disseminated CMV Infection

SLE : Risk factors

- **Recurrent episodes of infection (almost 50%)**
- Defects in clearance of immunocomplexes by the spleen, resulting in functional asplenia (5%)
- **Disease activity**
- **Lupus nephritis**
- **Immunosuppressive therapy**
- Invasive medical procedures
- Genetic alterations that predispose to SLE

- **Infections are a cause for hospitalization: up to 30% of patients with SLE**

Lupus 2012;21(4):449–51.
Best Pract Res Clin Rheumatol 2002;16(2):281–91.

ปัจจัยเสี่ยงในการติดเชื้อฉวยโอกาสในผู้ป่วย systemic lupus erythematosus

Risk factors
Disease activity (โดยเฉพาะในผู้ป่วยที่มี SLEDAI score มากกว่า 8 ในขณะเข้ารับการรักษาแรกรับ)
High anti-DNA titers
Low complement levels
Lupus nephritis
Leucopenia
Antiphospholipid antibodies
Prednisone-equivalent doses over 7.5–10 มก.ต่อวัน
Methylprednisolone high-dose pulses
Cyclophosphamide high-dose regimens

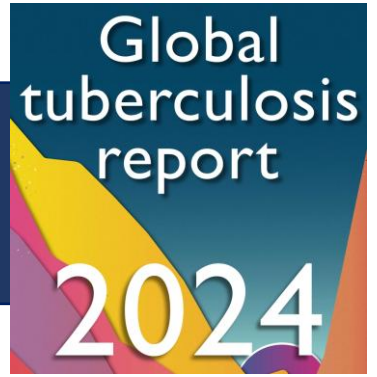
Infection in patients with SLE poses a real challenge to the physicians because the **distinction between infection and flare-up of disease can be difficult to distinguish or can coexist.**

Lupus. 2013 Oct;22(12):1286-94.

Bacterial infections	
Respiratory tract	*Streptococcus pneumoniae* *Mycobacterium tuberculosis*
Urinary tract	*Escherichia coli*, *Klebsiella* spp., *Pseudomonas* spp.
Skin and soft tissues	*Staphylococcus aureus*
Bacteremia/sepsis	*Escherichia coli*, *Staphylococcus aureus*, *Salmonella* spp
Viral infections	
Skin	Herpes zoster
Respiratory tract Gastrointestinal tract Central nervous system Lupus flare-like manifestations	Cytomegalovirus
Cervix	Human papillomavirus
Fungal infections	
Upper gastrointestinal tract Genitourinary tract	*Candida* spp.
Respiratory tract	*Pneumocystis jirovecii*
Central nervous system Respiratory tract	*Cryptococcus neoformans*

Lupus. 2013 Oct;22(12):1286-94.

Rate of TB Infection in Thailand (2024)



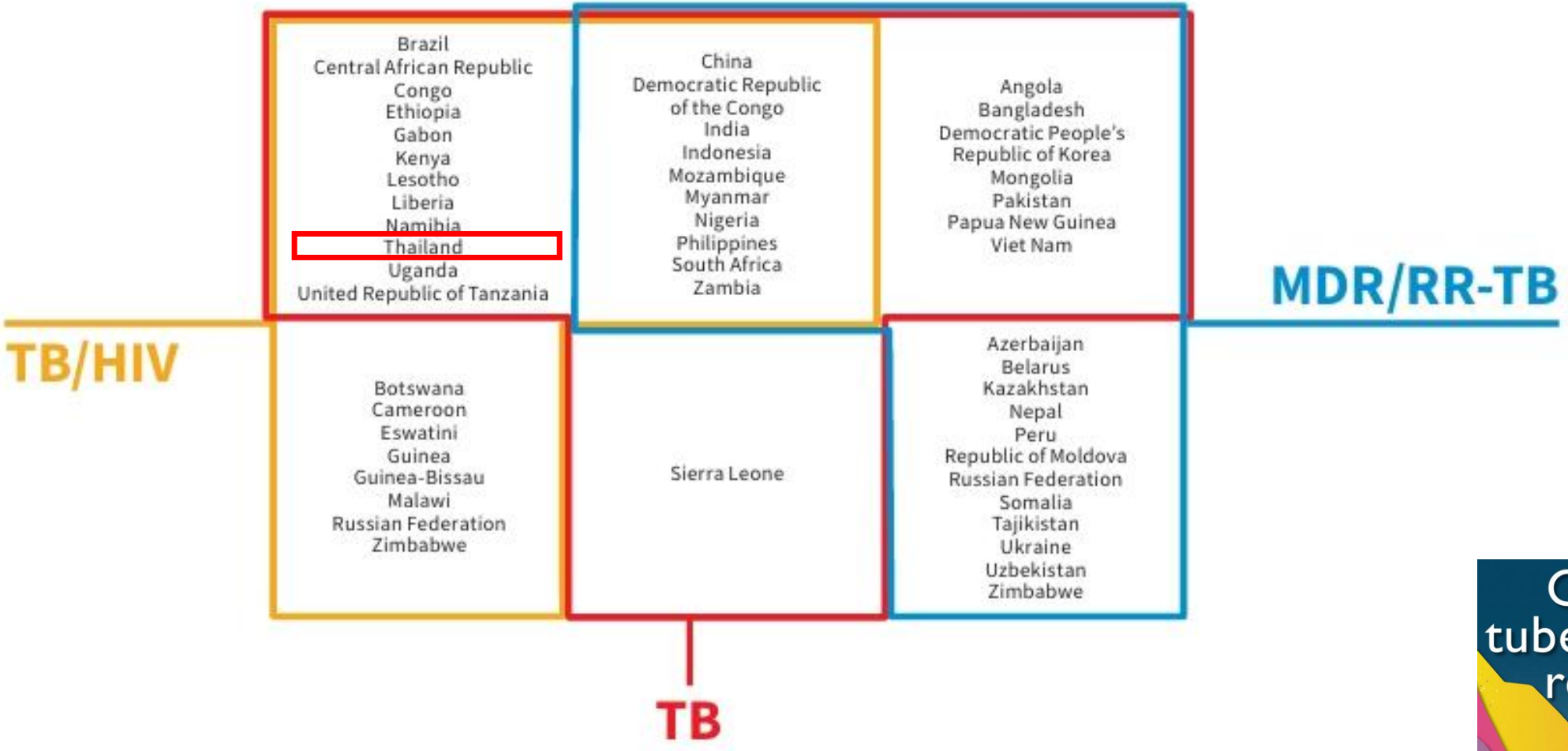
- In 2024, Thailand had an estimated tuberculosis incidence of 155 cases per 100,000 persons in the general population, (decreased from 143 in 2021).
  - TB mortality rate (including both TB-HIV co-infected and TB patients without HIV infection) was estimated to be **16 (13-19) per 100,000**
- WHO classifies Thailand as a high TB burden and TB/HIV burden country
- Decreased from 10.9% to 7.9% **of people with tuberculosis also had HIV.**
  - There were 10,000 cases of tuberculosis and 1,900 related deaths among the 500,000 people with HIV in the country.
  - 82% of people with TB/HIV were on ART, although it **reduces the risk of active TB by 65%.**
  - 0.4% of people with HIV received tuberculosis preventive therapy, which was like other countries in Asia and the Pacific.

Thailand Operational Plan

To End Tuberculosis, Phase 2 (2023 - 2027)

FIG. A3.1

The three global lists of high-burden countries for TB, HIV-associated TB and MDR/RR-TB being used by WHO in the period 2021–2025, and their areas of overlap



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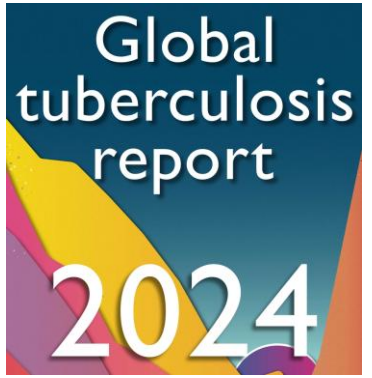


Screening test	No. of studies (no. of participants)	Sensitivity	No. of studies (no. of participants)	Specificity
WHO target product profile	NA	> 0.90	NA	> 0.70
Prolonged cough (≥ 2 weeks)	40 (6 737)	0.42	40 (1 284 181)	0.94
Any cough	21 (2 734)	0.51	21 (768 291)	0.88
Any TB symptom (cough, haemoptysis, fever, night sweats, weight loss)	28 (3 915)	0.71	28 (460 878)	0.64
Chest radiography (any abnormality)	22 (4 243)	0.94	22 (1 012 752)	0.89
Chest radiography (suggestive abnormality)	19 (2 152)	0.85	19 (464 818)	0.96
Molecular WHO-recommended rapid diagnostic test	5 (337)	0.69	5 (8 619)	0.99

NA: not applicable.

Table 1: Screening tools

Screening tool	Sensitivity*	Specificity*	Cost (USD)	Manufacturer	WHO recommendation
Symptom screening	77% (any TB symptom)	68% (any TB symptom)	N/A	N/A	People who screen positive for TB symptoms should be screened for HIV and receive CXR as a second screening test[11]
Chest X-ray (CXR)	90% (following positive symptom screen)	56% (following positive symptom screen)	$1 (digital CXR)[12]	Multiple	People with an abnormal CXR suggestive of TB should be given a TB diagnostic test[13]
CAD4TB	85–100%				
qXR	71%				

Common symptoms of pulmonary TB include current **coughing (> 2 weeks), night sweats, weight loss, fever,** and coughing up blood (called **hemoptysis**).

Screening use case		
CAD software	0.90–0.92	0.23–0.66
CXR with human reader	0.82–0.93	0.14–0.63

10. Among individuals aged 15 years and older in populations in which TB screening is recommended, computer-aided detection software programmes may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease *(new recommendation: conditional recommendation, low certainty of evidence).*

* Microbiological reference standard

Clinical manifestations and host

- Influenced by **degree of Immunodeficiency**
- **Severe immunocompromised**: rapid progression, sepsis syndrome and normal chest X-ray with positive sputum and culture

Clinical	immunocompetent	immunocompromised
TST/IGRA	Usually, positive	Usually, negative
Adenopathy	Unusual	Common
Pulmonary	Upper lobe	Lower and middle lobe
Cavitation	Often present (CD4>350)	Typical absent
Extrapulmonary	10-15% of cases	50% of cases (LN)

Am Rev Respir Dis 1992;146:53-6,
Am Rev Respir Dis 1993;148:1292-7

Microbiological confirmation of active TB disease

- **"See the bugs"** (smear) : 10,000 organisms/mL
  - detecting TB in only 50 percent of sputum samples with TB bacteria present.
- **"Grow the bugs"** (culture) : 10-100 organisms/mL
  - Liquid culture is the most sensitive and specific TB test, and as such it is the "gold standard" for TB diagnosis. Confirmatory results can take about two to six weeks.
- **"Multiply the bugs"** (molecular) : 100-1000 organisms/mL
  - Rapid molecular tests are highly sensitive and specific for detecting and microbiologically confirming TB and can produce results in less than two hours.
  - Recommended by the **WHO as the initial TB diagnostic test**

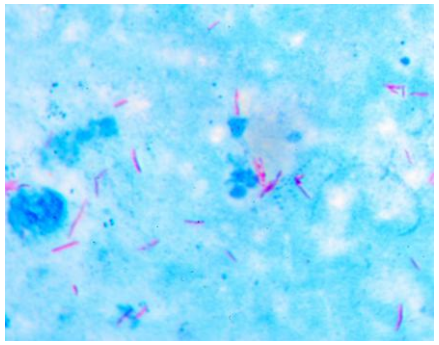
Cannot distinguish dead or viable organism

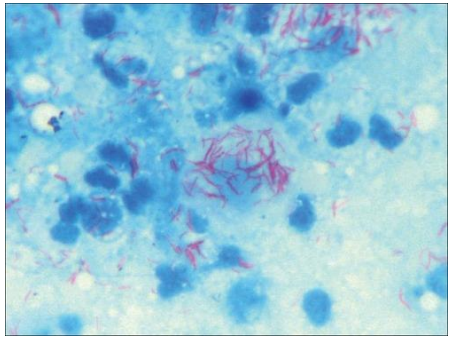
WHO recommendation since 2013 for the use of rapid molecular tests as the initial TB test for all

World Health Organization. Approaches to improve sputum smear microscopy for tuberculosis diagnosis: expert group meeting report. Geneva: World Health Organization; 2009

Microscopic exam : Acid-Fast Stain

- Acid-Fast Stain
- **Staining of mycolic acid**
- Positive in:
  - Any *Mycobacterium* spp.
    - *M. leprae*
    - *M. tuberculosis*
    - Non-tuberculous Mycobacteria
  - *Legionella* spp.* esp. *L. micdadei*
  - *Rhodococcus* spp. (cocci)





- **Modified Acid-Fast Stain**
- **Any acid-fast positive organisms**
  - ***Nocardia* (filamentous branching)**
  - *Gordonia* (bacilli)
  - *Tsukamurella* (bacilli)

2-days VS 3-day AFB

Select studies of sensitivity gained by serial AFB smears.

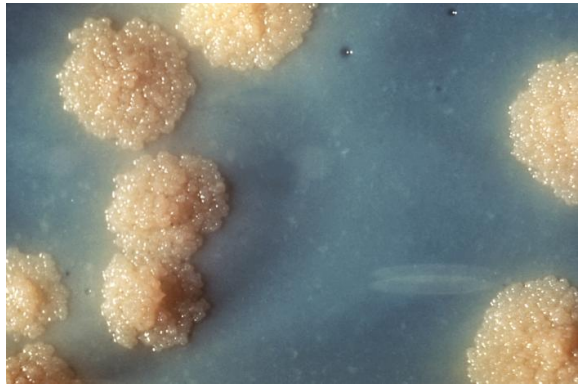
Study	# positive smears	% of total positives detected by:		
		1st smear	2nd smear	3rd smear
Ipuge et al. [25]	11,650	83.4	12.2	4.4
Nelson et al. [26]	53	77.4	15.1	7.5
Walker et al. [27]	166	77.1	15.0	7.9
Mathew et al. [28]	19	89.4	5.3	5.3
Wilmer et al. [29]	64	89.1	7.8	3.1
Khogali et al. [30]	60	93	5	2
Rehman et al. [31]	1164	77.0	16.3	6.7
Hassan et al. [32]	719	96.4	3.6	0

*Rogers BH, et al. N Engl J Med. 1979;301(18):959–961.
Bentz JS, et al. Diagn Cytopathol. 2000;22(1):45-8.

Culture : most sensitive and specific test (liquid)

Solid media (~4-6 wks.)

- Löwenstein–Jensen media (LJ media)
- Malachite green added to inhibit other bacteria
- Need 6 weeks to confirm negative

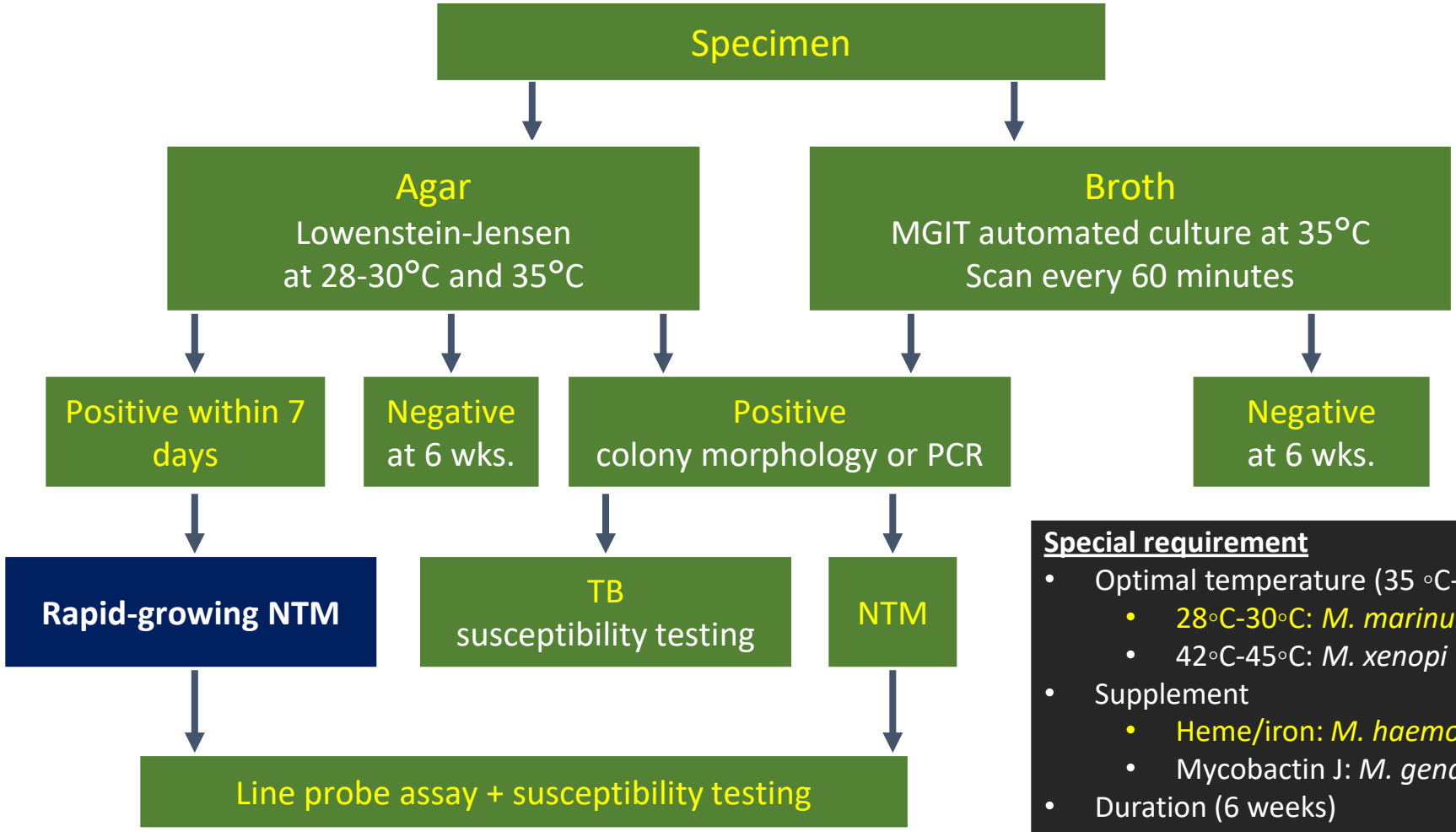


Liquid media (broth) (~2 wks.)

- Middlebrook 7H9: Mycobacteria Growth Indicator Tube (MGIT)
- Faster detection
- Cannot differentiate rapid growing *Mycobacteria* from others

Caulfield AJ, et al. J Clin Tuberc Other Mycobact Dis 2016;4:33-43.

Mycobacteria – current culture method



Special requirement

- Optimal temperature (35 ◦C-37 ◦C)
  - 28◦C-30◦C: *M. marinum*, *M. haemophilum*, RGM
  - 42◦C-45◦C: *M. xenopi*
- Supplement
  - Heme/iron: *M. haemophilum*
  - Mycobactin J: *M. genavense*
- Duration (6 weeks)
  - 10 to 12 weeks: *M. ulceran, M. genavense, M. malmoense*

Summary of TB Diagnostic Tests

Test Method	Target Detection	Target Population / Samples	Key Features & Clinical Utility
Xpert MTB/RIF	MTB complex and rpoB gene (Rifampicin resistance)	Sputum and Extrapulmonary samples (CSF, lymph nodes, etc.)	Recommended as the **initial test for TB and Rifampicin resistance.**
Xpert MTB/RIF Ultra	MTB and Rifampicin resistance **(Enhanced sensitivity)**	Sputum and **Extrapulmonary (e.g., ~71% sensitivity in pleural fluid)**	**More sensitive** but less specific than the standard version; can **detect very small concentrations** (10-100 organisms/mL). Requires storage ≤30°C.
Urine LAM	Lipoarabinomannan (LAM) - a component of the TB cell wall	PLWHA (People Living With HIV/AIDS), **especially those with CD4 < 100**	A rapid point-of-care test; the **only TB test shown to reduce mortality** in advanced HIV cases.
Line Probe Assays (LPA)	Genetic mutations for 1st and 2nd line drug resistance	Sputum or culture isolates	Used for rapid **Drug Susceptibility Testing (DST).** Provides results within one day for Rifampicin, Isoniazid, Fluoroquinolones, and second-line injectables.
Truenat (MTB/RIF)	MTB and Rifampicin resistance	Sputum	A portable, rapid molecular test recommended as an initial diagnostic tool, **similar to Xpert.**

Key Takeaways from the Data

- **Extrapulmonary TB (EPTB):** For patients with signs of EPTB, **WHO recommends Xpert Ultra as the initial test** for samples like cerebrospinal fluid (CSF), lymph node aspirates, and biopsies due to its high sensitivity.

- **Xpert Ultra vs. Standard:** **The Ultra version is better for "paucibacillary" cases** (where few bacteria are present), but its high sensitivity may lead to lower specificity (potential for false positives in patients with a history of treated TB).

- **HIV Co-infection:** **Urine LAM** is a critical tool for PLWHA with disseminated infection, as it uses an easily obtainable sample (urine) to provide a quick diagnosis that saves lives.

- **Drug Resistance:** **LPA is the gold standard for rapid screening** of both first-line (Rifampicin/Isoniazid) and second-line drug resistance, allowing for much faster treatment adjustments than traditional liquid cultures.

Rapid diagnostics for tuberculosis detection. Geneva: World Health Organization; 2021.
Expert Rev Anti Infect Ther. 2012 Jun;10(6):631-5.
Trans R Soc Trop Med Hyg. 2016 Mar;110(3):180-5.

Treatment monitoring

1.3 Treatment monitoring

Table 7: Tests for treatment monitoring

Test for treatment monitoring	Sensitivity*	Specificity*	Cost (USD)	Manufacturer	WHO recommendation
Smear microscopy	50% (sputum)	98%[110] (sputum)	$0.26 to $10.50[111]	Multiple	The WHO recommends the use of smear microscopy and culture, rather than smear microscopy alone, for monitoring TB treatment[112]
BACTEC MGIT liquid culture	100%	100%	$16.88[113]	BD	
Solid culture	100%	100%	$12.35[114]	Multiple	

* Microbiological reference standard (MRS)

World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2014. https://apps.who.int/iris/bitstream/handle/10665/130918/9789241548809_eng.pdf.

HOW to Treat TB

ตารางที่ 5.3 ระยะเวลาการรักษาวัณโรคในผู้ติดเชื้อเอชไอวี

ระยะเวลาการรักษาวัณโรค	
กรณีทั่วไป	▪ รักษา 6 เดือน ▪ รักษาผู้ป่วยวัณโรคนอกปอดเช่นเดียวกับวัณโรคปอด
▪ กรณีที่มีการตอบสนองช้า ▪ มีโพรงฝีขนาดใหญ่ในปอด ▪ ตรวจย้อมเสมหะยังพบเชื้อ และผลเพาะเชื้อวัณโรคในเดือนที่ 2 หรือ 3 หลังการรักษายังให้ผลบวก โดยผลทดสอบความไวไม่พบเชื้อดื้อยา	รักษา 9 เดือน
วัณโรคกระดูกและข้อ/วัณโรคระบบประสาท	รักษา 12 เดือน

- พิจารณาการให้สเตียรอยด์ กรณีที่เป็นวัณโรคระบบประสาท (CNS) โดยให้ prednisolone 1 มก./กก./วัน เป็นเวลา 3 สัปดาห์ และค่อยลดขนาดยาจนหยุดยาได้ภายในระยะเวลา 3 สัปดาห์

แนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวี ประเทศไทย ปี 2564/2565

Common TB Pitfalls: High-Yield Facts for Long Case Exams

Topic	Common Resident Pitfalls	Clinical Pearl / Evidence-Based Fact
Atypical Presentation	Expecting upper lobe cavitation in all patients.	In severely **immunocompromised patients, cavitation is typically absent**, and lesions often involve the **lower or middle lobes**. A normal CXR can occur even with positive cultures.
Initial Diagnostic Choice	Ordering only a sputum smear as the first-line investigation.	**Xpert MTB/RIF (or Ultra) is the WHO-recommended initial test** for both pulmonary and extrapulmonary TB.
Treatment Monitoring	Using only smear microscopy to track patient response.	Effective monitoring requires **both smear and culture;** liquid culture is the gold standard for diagnosis and monitoring.
Adjunctive Therapy	Neglecting steroids in cases with CNS involvement.	For **TB Meningitis**, **adjunctive Prednisolone (1 mg/kg/day) for 3 weeks** followed by a 3-week taper is essential.

Clinical Presentation

- **Patient:** A 55-year-old male farmer from Ubon Ratchathani, Thailand.
- **Medical History:** Poorly controlled Type 2 Diabetes (HbA1C 11.2%), heavy smoker, and treated for Pulmonary TB 10 years ago.
- **Chief Complaint: High-grade fever (4 weeks), night sweats, chronic productive cough, and a 6 kg weight loss.**
- **Physical Exam:** T 38.9°C, HR 110 bpm, BP 100/60 mmHg.
  - Respiratory: Crackles at the Right Upper Lobe (RUL).
  - Abdomen: Mildly tender hepatomegaly.
  - GU: Digital Rectal Exam (DRE) reveals a boggy, tender prostate.

Top 3 Differential Diagnosis by GEMINI

1. Disseminated Melioidosis
2. Reactivation Tuberculosis (TB)
3. Disseminated Histoplasmosis

Melioidosis
Epidemiology and Risk Factors

Category	Key High-Yield Facts
Pathogen	***Burkholderia pseudomallei*** (Aerobic, Oxidase+, GNB).
Thai Burden	Estimated 2,000–3,000 cases reported annually in Thailand.
Transmission	Inoculation (soil/water), Inhalation (during heavy rain/storms), or Ingestion.
Risk Factors	**Diabetes Mellitus (60%, most common)**, CKD, Thalassemia, Alcoholism, Chronic Lung Disease, malignancy, and immunosuppression
Important Note	Approximately **1/3 of patients** may have no identifiable risk factors.

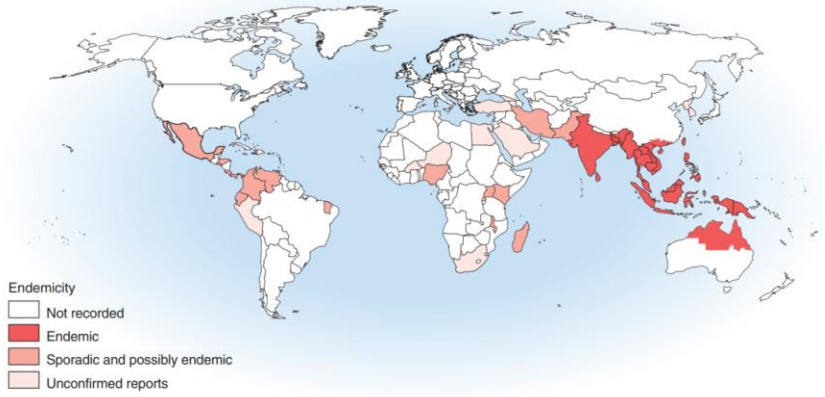
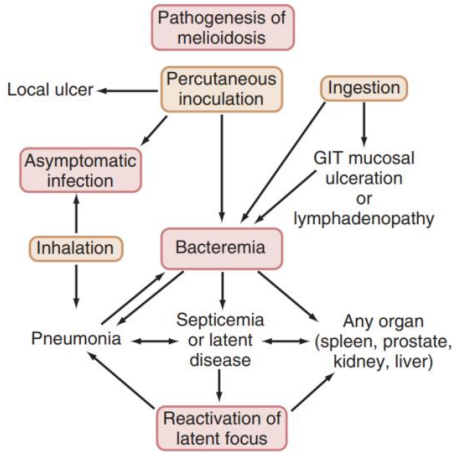


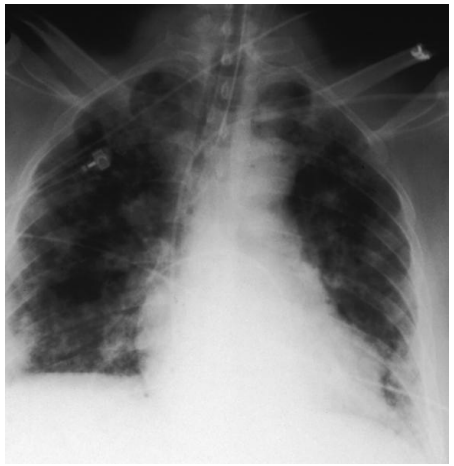
FIG. 221.1 Known global distribution of melioidosis.

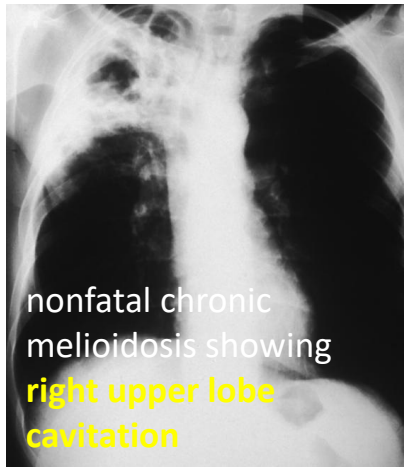
Nat Microbiol.2016;1:15008.
Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 10th ed. Philadelphia, PA: Elsevier; 2024.

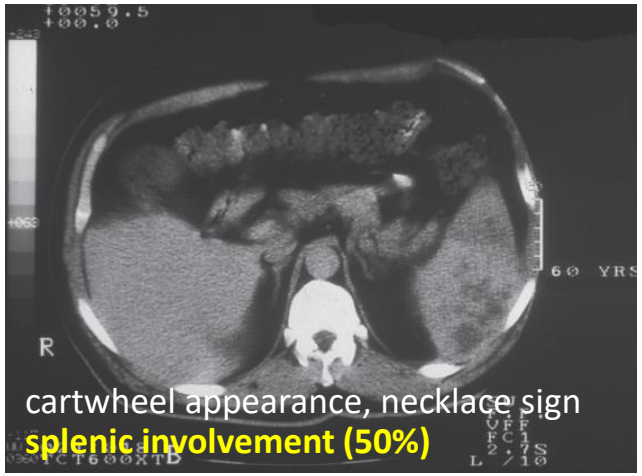
Clinical Manifestations (The "Great Mimicker")

System	Common Presentations
Pulmonary (50%)	**Acute pneumonia** with high fever, productive cough, tachypnea, and consolidation. **Chronic pneumonia (10%)(TB mimic)**
Visceral Abscess	**Hepatosplenic abscess (20%)**—often described as **"Swiss cheese"** appearance on imaging.
Genitourinary	**Prostate abscess** (tender and boggy on rectal exam) and suprapubic pain.
Specific Sites	Parotid abscess (common in children) and localized skin abscesses.
Disseminated	Septicemia with multi-organ failure and disseminated skin nodules.



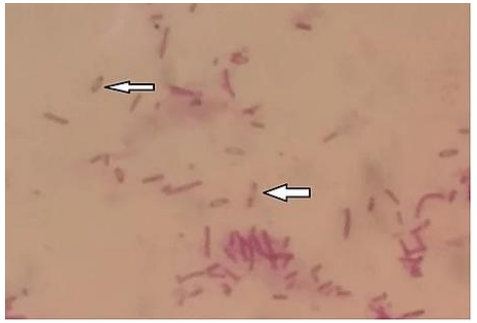






Diagnostic Workup

Test	Utility & Key Findings
Gram Stain	Shows **Gram-negative bacilli** with classic **"Safety pin"** bipolar staining appearance.
Culture	**Gold Standard.** Order blood, sputum, urine, and pus/aspirate cultures (notify lab to use Ashdown's agar).
Serology (IHA)	**Not a reliable method for diagnosis** in endemic areas like Thailand due to **high background titers.**
Imaging	**Ultrasound or CT abdomen** is essential to look for visceral abscesses (liver, spleen, prostate).



Management: Intensive and Eradication Phases

Treatment Phase	Preferred Regimen (Adult Dosage)	Duration
1. Intensive Phase	**Ceftazidime 2 g IV q 6–8h (First-line)** or Meropenem 1 g IV q 8h (for severe sepsis).	**10–14 days** (Extend to 4–8 weeks for deep abscesses or osteomyelitis).
2. Eradication Phase	**Trimethoprim-Sulfamethoxazole (TMP-SMX)** high dose; Amoxicillin-Clavulanate (Second-line).	**12–20 weeks** (3–5 months) is mandatory to prevent relapse.

Surgical Intervention: Prompt drainage of large abscesses (prostate, liver, soft tissue) is essential for successful therapy

พิจารณาให้การรักษาด้วยการรักษาด้วยยามากกว่า 2 ชนิดในบางกรณีเท่านั้น เช่น **การติดเชื้อในกระดูก การติดเชื้อในระบบประสาทส่วนกลาง และการติดเชื้อบริเวณต่อมลูกหมาก** เช่น Chloramphenicol ร่วมกับ doxycycline และ trimethoprim/sulfamethoxazole (TMP/SMX)หรือ cefoperazone/sulbactam

Resident Pitfalls and "Long Case" Pearls

Pitfall Topic	Resident Mistake	Correct Clinical Judgment
Abdominal Imaging	Failing to look for visceral abscesses in septic patients.	**US or CT Abdomen** is mandatory for all Melioidosis cases to rule out hepatosplenic or prostatic abscesses.
Drug Selection	Using Aminoglycosides or Third-gen Cephalosporins (Ceftriaxone).	*B. pseudomallei* is intrinsically resistant to many standard antibiotics. **Use Ceftazidime or Carbapenems only.**
Duration of Rx	Stopping treatment too early (e.g., 2–4 weeks).	**Short courses lead to high relapse rates.** Total treatment must reach 12–20 weeks.
Prostate Exam	**Overlooking the prostate** as a source of persistent fever.	Perform a Digital Rectal Exam (DRE); a tender, boggy prostate suggests an abscess requiring drainage.

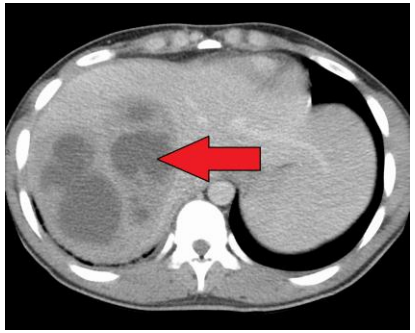
Pyogenic vs. Amebic Liver Abscess

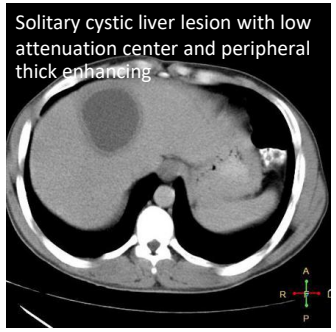
Feature	Pyogenic Liver Abscess (PLA)	Amebic Liver Abscess (ALA)
Epidemiology	Older adults, DM, Biliary disease, Post-procedure.	**Young-middle aged males** (10:1 ratio), Travel history, MSM.
Microbiology	**Western:** Polymicrobial (*E. coli*, *Klebsiella*, Anaerobes). **Asia: Monomicrobial (*K. pneumoniae*).**	*Entamoeba histolytica* (Protozoa).
Source	Biliary (50-60%), Portal (Appendicitis), Cryptogenic.	Fecal-oral; translocation from colon to portal vein.
Imaging	Often **multiple**, involvement of **both lobes common.**	Typically solitary, localized to the **Right Lobe.**
Diagnosis	Blood/Pus culture (Aspiration is gold standard).	Serology (Ab) + Imaging; PCR of pus if available.
Aspirate	Purulent, foul-smelling (if anaerobes present).	"Anchovy paste" appearance (non-foul smelling).

AASLD Liver Fellow Network. Hepatic Abscesses: Where Hepatology meets Infectious Disease [Internet]. Alexandria (VA): American Association for the Study of Liver Diseases; [cited 2024 May 21]. Available from: https://www.aasld.org/liver-fellow-network/core-series/clinical-pearls/hepatic-abscesses-where-hepatology-meets

Management and Source Control

Component	Clinical Approach
Empiric Abx	**PLA: Ceftriaxone + Metronidazole** (covers Gram-negatives and Anaerobes). **ALA: Metronidazole** or Tinidazole followed by a luminal agent (e.g., Paromomycin).
Drainage (PCD)	**Standard for PLA > 5 cm** or if symptoms persist > 48-72h on Abx. Reduces pressure and prevents rupture.
Needle Aspirate	Indicated for smaller abscesses (< 5 cm) or to obtain culture when blood cultures are negative.
Surgical Drain	Reserved for: Rupture, complex multi-loculated abscesses, or failed percutaneous drainage.
Duration	**4–6 weeks total. Usually 2–3 weeks IV**, transitioning to oral based on clinical response and CRP trend.





AASLD Liver Fellow Network. Hepatic Abscesses: Where Hepatology meets Infectious Disease [Internet]. Alexandria (VA): American Association for the Study of Liver Diseases; [cited 2024 May 21]. Available from: https://www.aasld.org/liver-fellow-network/core-series/clinical-pearls/hepatic-abscesses-where-hepatology-meets

High-Yield Clinical Pearls for Internists

Clinical Scenario	The "Internist's" Action / Pearl
Klebsiella pneumoniae (KLA)	**Hypervirulent Syndrome:** Can cause metastatic infection (Endophthalmitis, Meningitis). If the patient has blurry vision, **urgent Ophthalmology consult** is mandatory.
The CRC Connection	**PLA + *K. pneumoniae* or *S. anginosus* group**: Strongly associated with occult Colorectal Cancer (CRC). **Screening Colonoscopy** is required once the acute infection resolves.
Biliary Source	If the source is biliary, **ERCP** may be necessary to relieve obstruction (stones/stricture) to achieve complete resolution.
Imaging Lag	**Do not rely** on US/CT to monitor early response. **Radiographic resolution can take months**, even after clinical cure. Monitor via fever, WBC, and CRP.
Metronidazole in ALA	Remember: Metronidazole kills the trophozoites in the liver but not the cysts in the gut. Always follow with a **luminal amebicide** to prevent recurrence.

AASLD Liver Fellow Network. Hepatic Abscesses: Where Hepatology meets Infectious Disease [Internet]. Alexandria (VA): American Association for the Study of Liver Diseases; [cited 2024 May 21]. Available from: https://www.aasld.org/liver-fellow-network/core-series/clinical-pearls/hepatic-abscesses-where-hepatology-meets

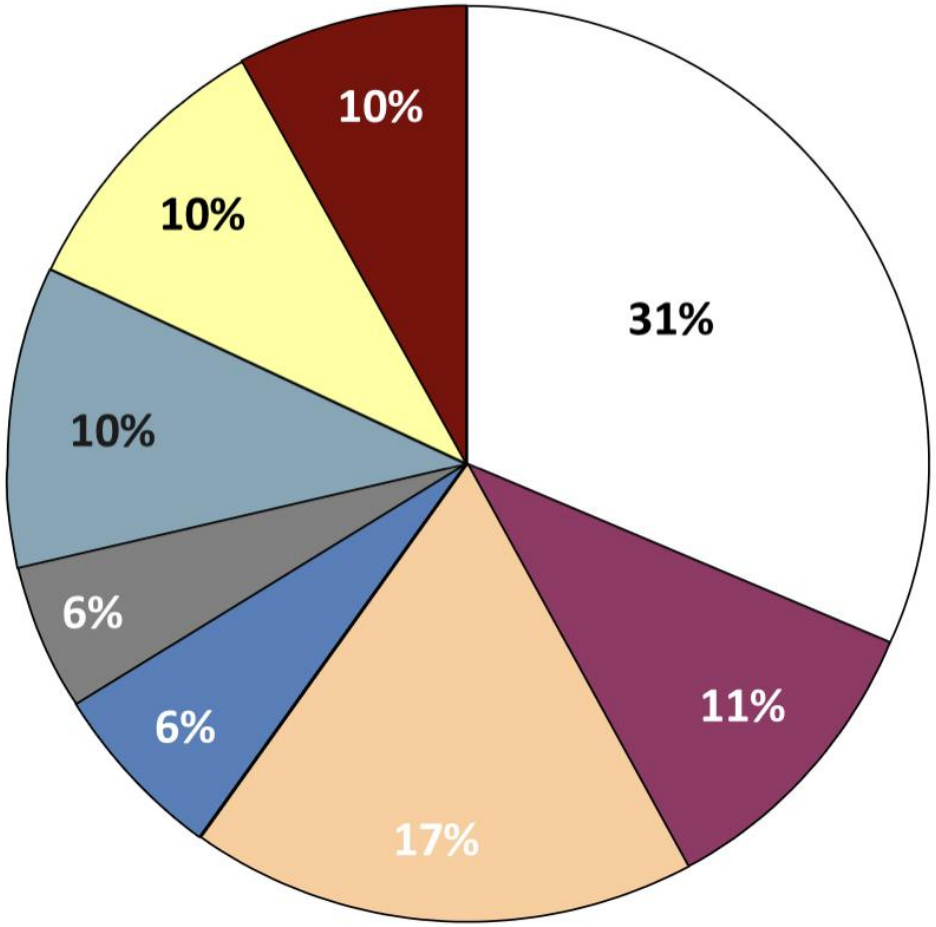
Patent Profile

- **Patient:** A 50-year-old female school teacher from rural Thailand.
- **Medical History:** Chronic Rheumatic Heart Disease (Known Mitral Regurgitation); no regular follow-up for 5 years. Dental extraction 6 weeks ago without antibiotic prophylaxis.
- **Chief Complaint: Low-grade fever (4 weeks), generalized weakness, and sudden-onset left-arm weakness (12 hours).**
- **Physical Exam:**
  - Vital Signs: T 38.2 C, HR 98 bpm, BP 110/60 mmHg.
  - HEENT: Fundoscopic exam reveals Roth spots.
  - Cardiac: Grade 4/6 holosystolic murmur at the apex radiating to the axilla.
  - Peripheral: Small, tender, purple-pink nodules on the finger pads (Osler Nodes).
  - Neurological: Left-sided hemiparesis (Power Grade 2/5).

Top 3 Differential Diagnosis by GEMINI

1. Infective Endocarditis (IE)
2. Atrial Myxoma
3. Non-Bacterial Thrombotic Endocarditis (NBTE)

Microbiology of Definite endocarditis in ICE*
(2,781 patients)



S. aureus **+/- predisposing heart valve**
CoNS
Viridans group streptococci
Streptococcus bovis
Other Streptococci
Enterococci
Other
Culture negative

Hints (Thailand)
- GBS
- *S. suis*
- *Salmonella*

*ICE: International Collaboration of Endocarditis

Murdoch et al. Arch Intern Med. 2009;169(5):463-473.

Clinical manifestations

- Acute (BT 39.4°–40°C)
  - **β-Hemolytic streptococci**, ***S. aureus***, and pneumococci
  - *Staphylococcus lugdunensis* or enterococci (occasionally)
- Subacute (low grade fever)
  - **viridans streptococci**, **enterococci**, CoNS, and the HACEK group
  - *S. aureus* (occasionally)
- Indolent
  - **CNIE** ; *Bartonella* species, *T. whipplei*, *C. burnetii*, or *M. chimaera*

Immune complex deposition : GN
Peripheral signs

Hints
- *S. aureus* IE
- SAB > IE (10%) need echo.
- metastatic infections (10–15%)

TABLE 128-2 Clinical and Laboratory Features of Infective Endocarditis

FEATURE	FREQUENCY, %
Fever	80–90
Chills and sweats	40–75
Anorexia, weight loss, malaise	25–50
Myalgias, arthralgias	15–30
Back pain	7–15
Heart murmur	80–85
New/worsened regurgitant murmur	20–50
Arterial emboli	20–50
Splenomegaly	15–50
Clubbing	10–20
Neurologic manifestations	20–40
Peripheral manifestations (Osler's nodes, subungual hemorrhages, Janeway lesions, Roth's spots)	2–15
Petechiae	10–40
Laboratory manifestations	
Anemia	70–90
Leukocytosis	20–30
Microscopic hematuria	30–50
Elevated erythrocyte sedimentation rate	60–90
Elevated C-reactive protein level	>90
Rheumatoid factor	50
Circulating immune complexes	65–100
Decreased serum complement	5–40

Epidemiological clue

Epidemiological feature	Common microorganism
IDU	*S. aureus*, CONS, β-Hemolytic streptococci, Fungi, Aerobic Gram-negative bacilli (*Pseudomonas aeruginosa*) and Polymicrobial
Indwelling cardiovascular medical devices	*S. aureus*, CONS, Fungi, Aerobic Gram-negative bacilli and *Corynebacterium* sp
Poor dental health, dental procedures	VGS, Nutritionally variant streptococci, *Abiotrophia defectiva*, *Granulicatella* sp, *Gemella* sp and HACEK organisms
Alcoholism, cirrhosis	*Bartonella* sp, *Aeromonas* sp, *Listeria* sp, *S. pneumoniae* and β-Hemolytic streptococci
Early (≤1 y) prosthetic valve placement	Coagulase-negative staphylococci, *S. aureus*, Aerobic Gram-negative bacilli, Fungi, *Corynebacterium* sp, *Legionella* sp
Dog or cat exposure	*Bartonella* sp, *Pasteurella* sp, *Capnocytophaga* sp
Contact with contaminated milk or infected farm animals	*Brucella* sp, *Coxiella burnetii*, *Erysipelothrix* sp
AIDS	*Salmonella* sp
Gastrointestinal lesions	*S. gallolyticus*, *Enterococcus* sp, *Clostridium septicum*

Circulation. 2015 Oct 13;132(15):1435-86.

Indication for echocardiographic in bacteremia

- **Incidence of IE**
  - *E. faecalis* (12–17%)
  - *S. aureus* (8-14%)
  - non-β-hemolytic streptococci (7%)

- *S. aureus* bacteremia is associated with a **high prevalence of IE** and a resultant **high risk for mortality (25%)**, echocardiographic evaluation

TABLE 128-4 Features Guiding the Need for Echocardiographic Assessment in Patients with Selected Monomicrobial Bacteremia

BLOOD CULTURE ISOLATE		
S. AUREUS[a]	*E. FAECALIS*[b]	NON-β-HEMOLYTIC STREPTOCOCCI[c]
Intracardiac device	Symptoms ≥7 days	Symptoms ≥7 days
Prior endocarditis	Emboli	Greater than two positive cultures
Injection drug use	Greater than two positive cultures	One species: *S. gallolyticus*, *S. sanguinis*, *S. mutans* (not *S. anginosus*)
Cerebral/peripheral emboli	Unknown origin (no focus)	
Meningitis	Heart murmur	Heart murmur or valve disease
Preexisting valve disease	Valve disease (including prior endocarditis)	Community acquired
Persistent bacteremia (≥72 hours)		
Vertebral osteomyelitis		
Community acquisition		
Non-nosocomial health care associated		
Indeterminate or positive TTE		

Source: [a]S Tubiana et al: J Infect 72:544, 2016 and A Showler et al: JACC Cardiovasc Imaging 8:924, 2015. [b]A Berge et al: Infection 47:45, 2019. [c]T Sunnerhagen et al: Clin Infect Dis 66:693, 2018.

Clin Infect Dis 66:693, 2018

Characteristics with lower risk of IE in SAB

- Absence of permanent intracardiac device
- Sterile F/U blood cultures within 4 days
- No hemodialysis dependence
- Nosocomial acquisition
- Absence of secondary foci of infection
- No clinical signs of infective endocarditis

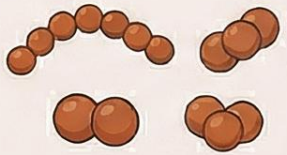
JAMA. 2014;312:1330-41

STREPTOCOCCAL AND RELATED SPECIES GRADIENT: Virulence & Colonization

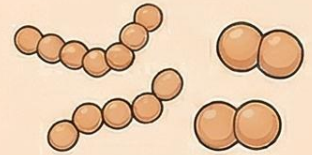
HIGH POTENTIAL

LOW POTENTIAL

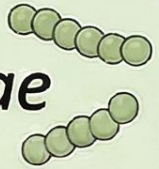
sanguinis, mutans, *bovis** , *Abiotrophia*



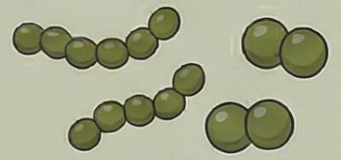
*mitis** , *Granulicatella*, *Aerococcus urinae*



anginosus, salivarius, *S. dysgalactiae*, *S. agalactiae*



S. pyogenes, *S. pneumoniae*



*Might differ for some species

Top Causes of Culture-Negative IE (CNIE)

- When **blood cultures are negative at 48–72 hours**, residents should immediately consider these factors:

Cause	Frequency / Importance	Clinical Logic
Prior Antibiotics	**33–50% of cases**	The most common cause of "apparent" CNIE; even a single dose can suppress growth.
Fastidious Organisms	Highly significant	Organisms that grow slowly or require specific media (e.g., HACEK group, **Nutritionally Variant Streptococci**.) .
Uncultivable Organisms	Diagnostic challenge	Organisms that cannot be grown on standard agar (e.g., *Coxiella burnetii*, *Bartonella* spp., *Tropheryma whipplei*).
Non-Infectious Causes	"Mimickers"	Non-bacterial thrombotic endocarditis (NBTE/Marantic), SLE (Libman-Sacks), or Behçet's disease.

Diagnostic Logic for Specific Pathogens

Pathogen	Epidemiological Clues	Diagnostic Strategy
HACEK Group	**Poor dental health, dental procedures**	**Extended culture** (up to 14 days); usually grows in 3.4 days with modern systems .
Coxiella burnetii	Contact with **infected farm animals or contaminated milk**	Major Criterion: **Single positive culture or Phase I IgG titer > 1:800.**
Bartonella spp.	**Body lice (homelessness), cat/dog exposure**	**Serology** or PCR from blood/valve tissue; often associated with large vegetations.
Brucella spp.	**Unpasteurized dairy, farm animal contact**	**Extended culture or serology** (ELISA/Agglutination) .
T. whipplei	Chronic diarrhea, arthralgia, weight loss	PCR or histology **(PAS-positive macrophages)** from valve tissue.

"Exam Tip"

Always check for **Relative Bradycardia**. If a patient has FUO, a heart murmur, and relative bradycardia, consider zoonotic causes like **Q fever** (*C. burnetii*) or **Brucellosis**

Table 10 **Definitions of the 2023 European Society of Cardiology modified diagnostic criteria of infective endocarditis**

Major criteria

(i) Blood cultures positive for IE

(a) Typical microorganisms consistent with IE from two separate blood cultures:
Oral streptococci, *Streptococcus gallolyticus* (formerly *S. bovis*), HACEK group, *S. aureus*, *E. faecalis*

(b) Microorganisms consistent with IE from continuously positive blood cultures:
- ≥2 positive blood cultures of blood samples drawn >12 h apart.
- All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart).

(c) Single positive blood culture for *C. burnetii* or phase I IgG antibody titre >1:800.

(ii) Imaging positive for IE:

Valvular, perivalvular/periprosthetic and foreign material anatomic and metabolic lesions characteristic of IE detected by any of the following imaging techniques:
- Echocardiography (TTE and TOE).
- Cardiac CT.
- [18F]-FDG-PET/CT(A).
- WBC SPECT/CT.

Minor criteria

(i) Predisposing conditions (i.e. predisposing heart condition at high or intermediate risk of IE or PWIDs)[a]

(ii) Fever defined as temperature >38°C

(iii) Embolic vascular dissemination (including those asymptomatic detected by imaging only):
- Major systemic and pulmonary emboli/infarcts and abscesses.
- Haematogenous osteoarticular septic complications (i.e. spondylodiscitis).
- Mycotic aneurysms.
- Intracranial ischaemic/haemorrhagic lesions.
- Conjunctival haemorrhages.
- Janeway's lesions.

(IV) Immunological phenomena:
- Glomerulonephritis.
- Osler nodes and Roth spots.
- Rheumatoid factor.

(V) Microbiological evidence:
- Positive blood culture but does not meet a major criterion as noted above.
- Serological evidence of active infection with organism consistent with IE.

IE Classification (at admission and during follow-up)

Definite:
- 2 major criteria.
- 1 major criterion and at least 3 minor criteria.
- 5 minor criteria.

Possible:
- 1 major criterion and 1 or 2 minor criteria.
- 3–4 minor criteria.

Rejected:
- Does not meet criteria for definite or possible at admission with or without a firm alternative diagnosis.

Hints
- *E. faecalis*

Empirical antimicrobial therapy for suspected infection should be avoided unless the patient's clinical condition (eg, sepsis) warrants it (Class III; Level of Evidence C).

Circulation. 2015 Oct 13;132(15):1435-86.

ESC European Society of Cardiology
European Heart Journal (2023) **44**, 3948–4042
https://doi.org/10.1093/eurheartj/ehad193

TABLE 128-5 Antibiotic Treatment for Infective Endocarditis Caused by Common Organisms[a]

ORGANISM(S)	DRUG (DOSE, DURATION)	COMMENTS
Streptococci		**For PVE 6-week regimens are preferred.**
Penicillin-susceptible streptococci, *S. gallolyticus* (MIC ≤0.12 µg/mL[b])	• Penicillin G (2–3 mU IV q4h for 4 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable.
	• Ceftriaxone (2 g daily as a single dose for 4 weeks)	Can use ceftriaxone in patients with non-immediate penicillin allergy.
	• Vancomycin[c] (15 mg/kg IV q12h for 4 weeks)	Use vancomycin for patients with immediate (urticarial) or severe penicillin allergy. Obtain allergy consultation for further evaluation including role of β-lactam desensitization.
	• Penicillin G (2–3 mU IV q4h) *or* ceftriaxone (2 g IV daily) for 2 weeks ***plus*** Gentamicin[d] (3 mg/kg daily IV or IM, as a single dose[e] or divided into equal doses q8h for 2 weeks)	Avoid 2-week regimen when risk of aminoglycoside toxicity is increased and in prosthetic-valve or complicated endocarditis. Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable.
Relatively penicillin-resistant streptococci, *S. gallolyticus* (MIC >0.12 µg/mL and <0.5 µg/mL[f])	• Penicillin G (4 mU IV q4h) *or* ceftriaxone (2 g IV daily) for 4 weeks ***plus*** Gentamicin[d] (3 mg/kg daily IV or IM, as a single dose[e] or divided into equal doses q8h for 2 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable. Penicillin alone at this dose for 6 weeks or with gentamicin during the initial 2 weeks is preferred for PVE caused by streptococci with penicillin MICs of ≤0.12 µg/mL.
	• Vancomycin[c] as noted above for 6 weeks	Use vancomycin for patients with immediate (urticarial) or severe penicillin allergy. Obtain allergy consultation for further evaluation including role of β-lactam desensitization. Ceftriaxone alone or with gentamicin can be used in patients with non-immediate β-lactam allergy.
Moderately penicillin-resistant streptococci (MIC, ≥0.5 µg/mL and <8 µg/mL[g]); *Granulicatella*, *Abiotrophia*, or *Gemella* spp.	• Penicillin G (4–5 mU IV q4h) *or* ceftriaxone (2 g IV daily) for 6 weeks ***plus*** Gentamicin[d] (3 mg/kg daily IV or IM as a single dose[e] *or* divided into equal doses q8h for 6 weeks)	Preferred for PVE caused by streptococci with penicillin MICs of >0.12 µg/mL. Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable.
	• Vancomycin[c] as noted above for 6 weeks	Regimen is preferred by some.

Need MIC for penicillin

Enterococci[h]		**For PVE 6-week regimens are preferred.**
	• Penicillin G (4–5 mU IV q4h) *plus* gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks	Can treat NVE for 4 weeks if symptoms last <3 months. Treat NVE with >3 months of symptoms for 6 weeks. Can abbreviate gentamicin course in some patients (see text).
	• Ampicillin (2 g IV q4h) *plus* gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks	Can use IV amoxicillin in lieu of ampicillin (same dose). Can abbreviate gentamicin course in some patients (see text).
	• Vancomycin[c] (15 mg/kg IV q12h) *plus* gentamicin[d] (1 mg/kg IV q8h), both for 6 weeks	Use vancomycin plus gentamicin only for penicillin-allergic patients (preferable to desensitize to penicillin if immediate (urticarial) allergy; consult allergy) and for isolates resistant to penicillin/ampicillin.
	• Ampicillin (2 g IV q4h) *plus* ceftriaxone (2 g IV q12h), both for 6 weeks	Use for *E. faecalis* isolates with or without high-level resistance to gentamicin or for patients at high risk for aminoglycoside nephrotoxicity (creatinine clearance rate <50 mL/min; see text).
Staphylococci (*S. aureus* and coagulase-negative)		
MSSA infecting native valves (no foreign devices) including complicated right-sided and left-sided endocarditis.	• Nafcillin, oxacillin, *or* flucloxacillin (2 g IV q4h for 6 weeks)	Addition of gentamicin is not recommended. For uncomplicated right-sided endocarditis a 2-week course may be effective (see text).
	• Cefazolin (2 g IV q8h for 6 weeks)	Can use cefazolin regimen for patients with non-immediate penicillin allergy; see text regarding cefazolin vs antistaphylococcal penicillin as primary therapy. Addition of gentamicin not recommended.
	• Vancomycin[c] (15 mg/kg IV q12h for 6 weeks)	Only use vancomycin for patients with immediate (urticarial) or severe penicillin allergy until allergy consultation can be obtained for β-lactam desensitization evaluation; addition of gentamicin not recommended.
MRSA infecting native valves (no foreign devices)	• Vancomycin[c] (15 mg/kg IV q8–12h) or daptomycin (8–10 mg/kg daily) for 6 weeks	No role for routine use of rifampin (see text). For daptomycin treatment, see text.
MSSA infecting prosthetic valves	• Nafcillin, oxacillin, *or* flucloxacillin (2 g IV q4h for 6–8 weeks) ***plus*** Gentamicin[d] (1 mg/kg IM or IV q8h for 2 weeks) ***plus*** • Rifampin[i] (300 mg PO q8h for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility and await blood culture clearance before initiating rifampin (see text); if patient is highly allergic to penicillin, use regimen for MRSA and obtain allergy consultation; if β-lactam allergy is of the minor non-immediate type, cefazolin can be substituted for oxacillin, nafcillin, or flucloxacillin.
MRSA infecting prosthetic valves	• Vancomycin[c] (15 mg/kg IV q12h for 6–8 weeks) ***plus*** Gentamicin[d] (1 mg/kg IM or IV q8h for 2 weeks) ***plus*** • Rifampin[i] (300 mg PO q8h for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility and await blood culture clearance before initiating rifampin (see text). Daptomycin (8–10 mg/kg daily) could be considered as an alternative to vancomycin but data are limited.

Recommendations for antibiotic regimens for initial empirical treatment of infective endocarditis (before pathogen identification) (1)

Recommendations		Class	Level
In patients with community-acquired NVE or late PVE (≥12 months post-surgery), ampicillin in combination with ceftriaxone or with (flu)cloxacillin and gentamicin should be considered using the following doses:		IIa	C
Adult antibiotic dosage and route			
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. or i.m. in 2 doses		
(Flu)cloxacillin	12 g/day i.v. in 4–6 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Ceftriaxone	100 mg/kg i.v. or i.m. in 1 dose		
(Flu)cloxacillin	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		

2023 ESC Guidelines for the management of endocarditis
(European Heart Journal; 2023 – doi: 10.1093/eurheartj/ehad193)

Antimicrobial therapy: principles and methods

The treatment of IE relies on the combination of prolonged antimicrobial therapy and - in about half patients - surgical eradication of the infected tissues.

Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of PVE should last longer (at least 6 weeks) than that of native valve endocarditis (NVE) (2–6 weeks).

In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.

The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity.

Main complications of left-sided valve IE and their management

Surgical treatment is used in approximately half of patients with IE because of severe complications.

Early consultation with a cardiac surgeon is recommended in order to determine the best therapeutic approach. Identification of patients requiring early surgery is frequently difficult and is an important scope of the 'Heart Team'.

In some cases, surgery needs to be performed on an emergency basis (within 24 h), urgent basis (within a few days, <7 days), irrespective of the duration of antibiotic treatment. In other cases, surgery can be postponed to allow 1 or 2 weeks of antibiotic treatment under careful clinical and echocardiographic observation before an elective surgical procedure is performed.

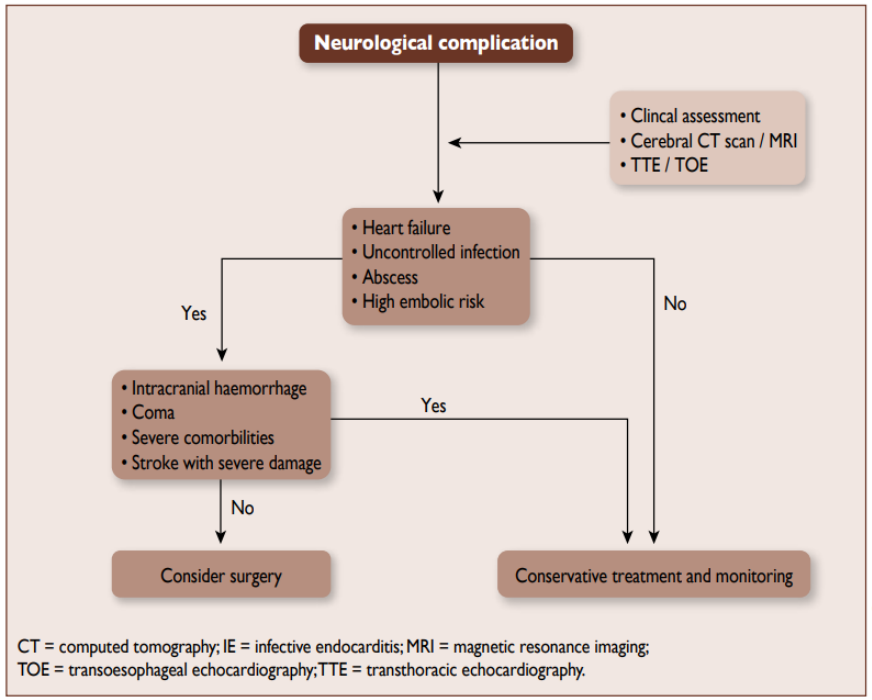
The three main indications for early surgery in IE are its 3 main complications, i.e. HF, uncontrolled infection, and prevention of embolic events.

Neurological complications

Symptomatic neurological events develop in 15–30% of all patients with IE and additional silent events are frequent. Stroke (ischaemic and haemorrhagic) is associated with excess mortality. Rapid diagnosis and initiation of appropriate antibiotics are of major importance to prevent a first or recurrent neurological complication.

After a first neurological event, if cerebral haemorrhage has been excluded by cranial CT and neurological damage is not severe (i.e. coma), surgery indicated for HF, uncontrolled infection, abscess, or persistent high embolic risk should not be delayed and can be performed with a low neurological risk (3–6%) and good probability of complete neurological recovery. Conversely, in cases with intracranial haemorrhage, neurological prognosis is worse and surgery should generally be postponed for at least 1 month.

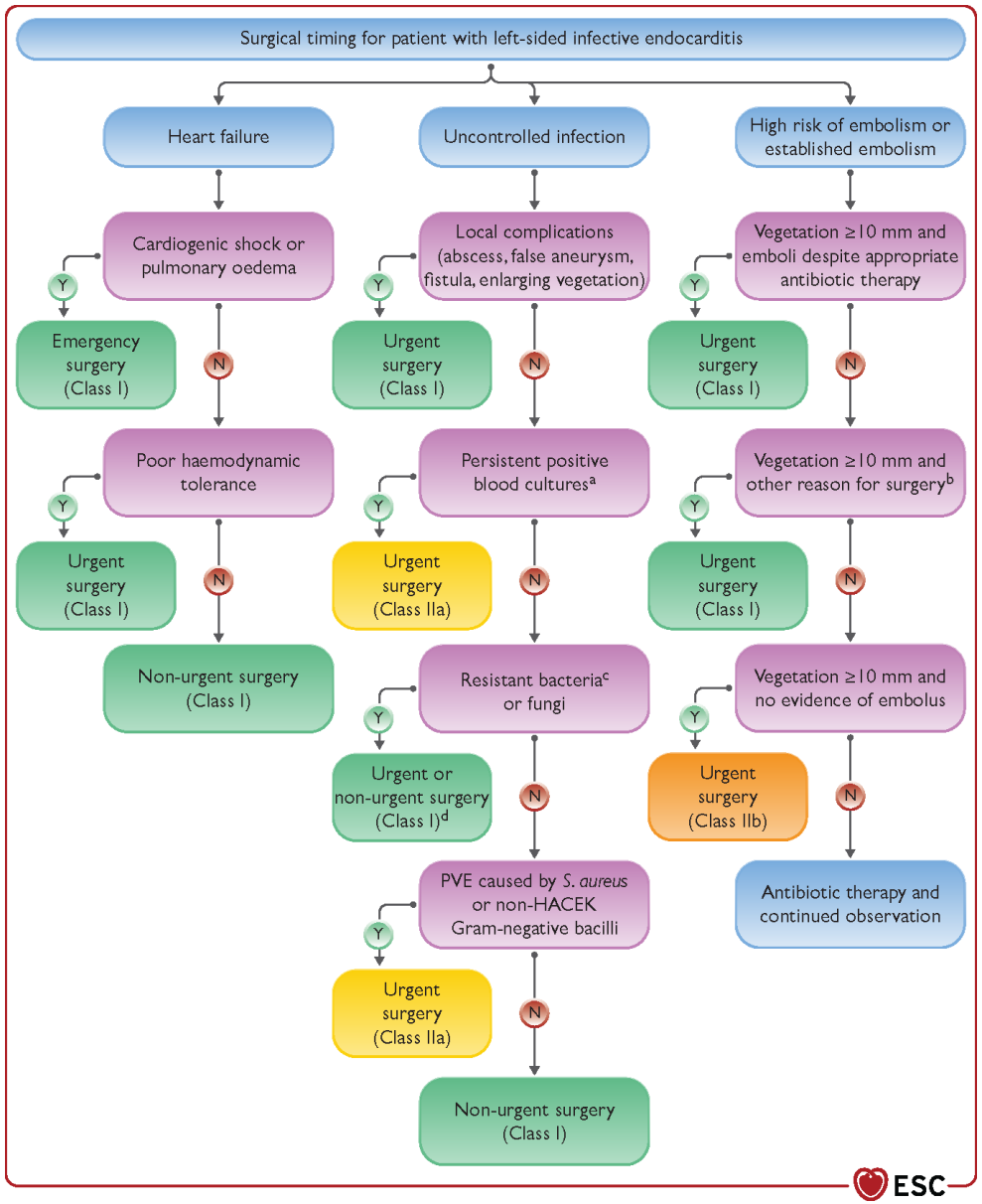
Therapeutic strategy for patients with IE and neurological complications



CT = computed tomography; IE = infective endocarditis; MRI = magnetic resonance imaging; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

Figure 10

Proposed surgical timing for infective endocarditis



2023 ESC Guidelines for the management of endocarditis
(European Heart Journal; 2023 – doi: 10.1093/eurheartj/ehad193)

Surgical Timing for Left-Sided Infective Endocarditis (IE)

Indication	Timing	Clinical Scenarios & Classification
Heart Failure	**Emergency** (< 24h)	**Cardiogenic shock or refractory pulmonary edema** due to severe regurgitation or fistula (Class I) .
	Urgent (< 7 days)	Persistent symptoms of heart failure or echocardiographic signs of poor hemodynamic tolerance (Class I) .
Uncontrolled Infection	Urgent (< 7 days)	**Locally invasive infection:** Abscess, false aneurysm, fistula, or enlarging vegetation (Class I) .
	Urgent (< 7 days)	**Persistent positive blood cultures** despite appropriate antibiotic therapy (Class I) .
	Urgent / Non-urgent	Infection caused by **fungi or highly resistant bacteria** (Class I) .
	Urgent (< 7 days)	**PVE (Prosthetic Valve Endocarditis)** caused by *S. aureus* or non-HACEK Gram-negative bacilli (Class IIa) .
Prevention of Embolism	Urgent (< 7 days)	Vegetation ≥10 mm with evidence of one or more embolic events despite appropriate antibiotics (Class I) .
	Urgent (< 7 days)	Vegetation ≥10 mm associated with other surgical indications (e.g., heart failure) (Class I) .
	Urgent (< 7 days)	**Isolated large vegetation (> 10 mm)** without evidence of embolism (Class IIb) .

Special Consideration: Neurological Complications

- **Ischemic Stroke / TIA: Surgery is not delayed** if heart failure, uncontrolled infection, or high embolic risk is present, provided coma is absent and neurological damage is not severe (Class I).

- **Intracranial Hemorrhage:** Surgery should generally be **postponed for at least 1 month.**

Antibiotic prophylaxis for IE (Dental procedures)

TABLE 128-9 High-Risk Cardiac Lesions for Which Endocarditis Prophylaxis is Advised Before Dental Procedures

Prosthetic heart valves or material
Left ventricular assist devices or implantable heart
Prior endocarditis
Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits
Completely repaired congenital heart defects during the 6 months after repair
Repaired congenital heart disease with residual defects adjacent to prosthetic material
Surgical or transcatheter pulmonary artery valve or conduit placement
Valvulopathy developing after cardiac transplantation[a]

[a]Not a target population for prophylaxis according to recommendations of the European Society for Cardiology.

Source: Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (W Wilson et al: Circulation 116:1736, 2007; W Wilson et al: Circulation 143:e963, 2021; and G Habib et al: Eur Heart J 30:2369, 2009).

TABLE 128-8 Antibiotic Regimens for Prophylaxis of Endocarditis in Adults with High-Risk Cardiac Lesions[a,b]

A. Standard oral regimen
Amoxicillin: 2 g PO 1 h before procedure
B. Inability to take oral medication
Ampicillin: 2 g IV or IM within 1 h before procedure
C. Penicillin allergy
1. Clarithromycin or azithromycin: 500 mg PO 1 h before procedure
2. Cephalexin[c]: 2 g PO 1 h before procedure
3. Doxycycline: 100 mg PO 1 h before procedure
D. Penicillin allergy, inability to take oral medication
Cefazolin[c] or ceftriaxone[c]: 1 g IV or IM 30 min before procedure

[a]Dosing for children: for amoxicillin, ampicillin, cephalexin, or cefadroxil, use 50 mg/kg PO; cefazolin, 25 mg/kg IV; clindamycin, 20 mg/kg PO or 25 mg/kg IV; clarithromycin, 15 mg/kg PO; and vancomycin, 20 mg/kg IV. [b]For high-risk lesions, see Table 128-9. Prophylaxis is not advised for other lesions. [c]Do not use cephalosporins in patients with immediate hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin.

Source: Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (W Wilson et al: Circulation 116:1736, 2007; W Wilson et al: Circulation 143:e963, 2021; and G Habib et al: Eur Heart J 30:2369, 2009).

Hints

- Expanded high risk > LVAD, implantable prosthetic heart
- Elimination clindamycin (CDI)
- Add Doxycycline (allergy to pen.)

Infective Endocarditis (IE) Resident Pitfalls & Pearls

Topic	Common Pitfall	The "Nerd Cool" Clinical Pearl
Antibiotic Timing	Starting empiric antibiotics immediately for every fever.	**Avoid empiric therapy unless the patient is in sepsis**; wait for cultures to increase diagnostic yield.
S. aureus (SAB)	Thinking SAB is "just a skin contaminant."	***S. aureus* bacteremia carries a high risk of IE (10%);** all cases require echocardiographic evaluation .
Negative Cultures	Assuming a negative culture rules out IE.	**Prior antimicrobial therapy is the top reason (33–50%)** for culture-negative IE (CNIE) . Consider fastidious organisms like the HACEK group or ***Bartonella.***
Imaging Selection	Relying only on TTE when a prosthetic valve is present.	**TEE has much higher sensitivity (90–100%) than TTE (63%),** especially for prosthetic valves or intracardiac complications.
Dental Prophylaxis	Giving clindamycin to all penicillin-allergic patients.	Clindamycin is eliminated from prophylaxis due to CDI risk; use **Clarithromycin/Azithromycin or Doxycycline** instead .

Patient Profile

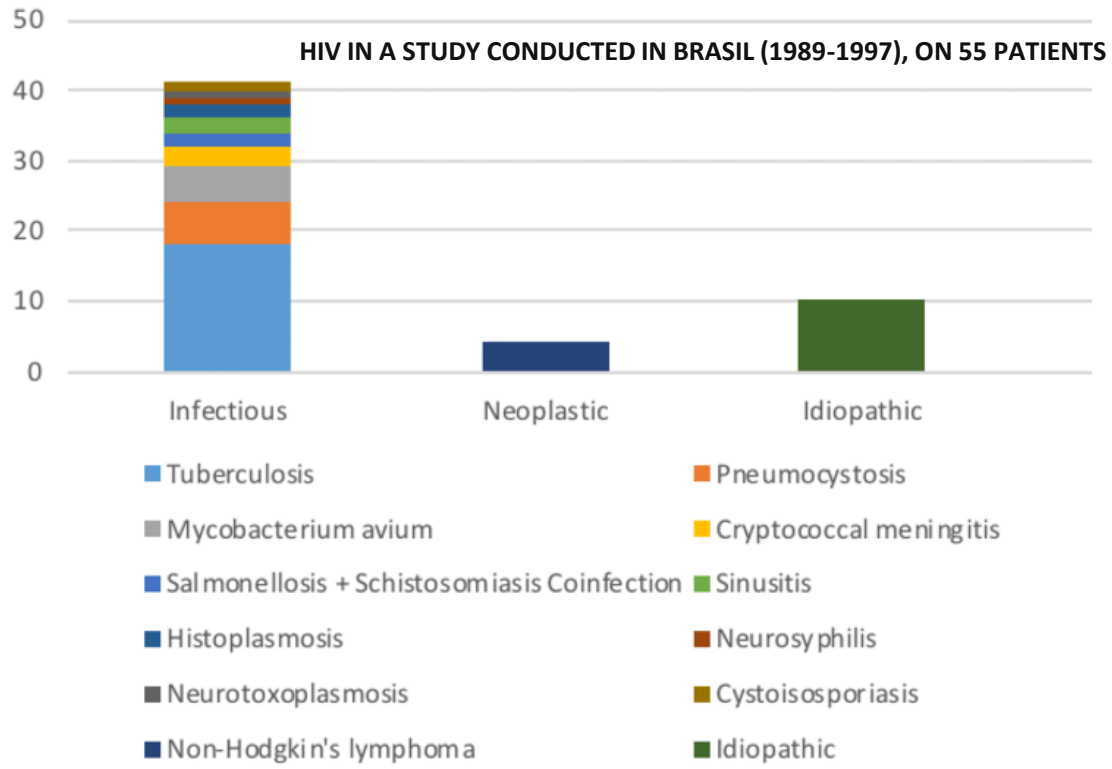
- **Patient:** A 40-year-old male from Northern Thailand.
- **Medical History:** Known HIV infection for 8 years; defaulted ART for 2 years. Previously on TDF/3TC/EFV.
- **Chief Complaint: Prolonged fever (1 month), significant weight loss (8 kg), and progressive blurred vision in the left eye (1 week).**
- **Physical Exam:**
  - Vital Signs: T 38.5C, HR 105 bpm, BP 100/60 mmHg.
  - HEENT: Fundoscopic exam (Left eye) shows extensive retinal hemorrhages and "pizza pie" exudates along the vascular arcades.
  - Skin: Multiple small, umbilicated papules (molluscum-like) on the face and trunk.
  - Abdomen: Significant hepatosplenomegaly (Liver 4 cm, Spleen 3 cm below costal margin).
  - Lymph Nodes: Generalized small, firm, non-tender lymphadenopathy.

Top 3 Differential Diagnosis by GEMINI

1. (Co-infection)
2. Disseminated Talaromycosis + CMV Retinitis
3. Disseminated Cryptococcosis + CMV Retinitis

HIV related FUO : Etiology

- Most cases of FUO in HIV-infected patients are the result of **opportunistic infections**
- Etiology
  - Infection (88%) - OIs
  - Neoplasm (8%) - NHL
  - Miscellaneous (4%)



Eur J Intern Med 2009;20: 474–7

Opportunistic infections (OIs)

Bacteria
- *Salmonella*
- Rhodococcosis

Fungus
- *Cryptococcus*
- *Histoplasma*
- *Talaromyces*
- PCP
- *Microsporidium*

Mycobacterium
- TB
- MAC

Virus
- CMV
- JC virus
- HHV-8

Parasites
- *Toxoplasma*
- *Cryptosporidium*
- *Cyclospora*
- *Cystoisospora*

CD4 cell count (cells/mm³)

CD4 cell count

<50	• MAC, CMV, PCNSL, *Cryptosporidium*
<100	• *Toxoplasma*, PML, *Talaromyces*, *Histoplasma*
<200	• *Cryptococcus*, PCP
Any	• SY, TB, bacterial infection

Clinical Hints for Diagnosis
- Oral candidiasis
- Oral hairy leukoplakia
- Pruritic papular eruption

Important OIs in immunocompromised patients

- **CNS presentation**
  - Mass or Mass-like
    - Toxoplasmosis, TB, Cryptococcoma and PCNSL
  - Chronic meningitis
    - TB, Cryptococcal
- **Pulmonary presentation**
  - Chronic cough
    - *Nocardia spp.*
    - *Rhodococcus equi*
    - Mycobacteria (TB, NTM)
    - **Fungi (Yeast and dimorphic fungi)**
  - Dyspnea on exertion
    - PCP, CMV
- **GI presentation**
  - Chronic diarrhea
    - Mycobacteria (TB and MAC)
    - **Fungi (Yeast and dimorphic)**
      - *C. neoformans*
      - ***H. capsulatum***
    - CMV
    - Protozoa (no systemic S/S)
    - Lymphoma
- **Disseminated presentation**
  - Prolonged fever

For each disease:

- Clinical Manifestations
- Diagnosis
- Treatment Recommendations
- Monitoring and Adverse Events
- Management of Treatment Failure

OIs Screening

- CXR (all cases)
- If **CD4 <100 cells/mm^3**
  - Serum cryptococcal Ag (CrAg)
  - Indirect ophthalmoscope for CMV

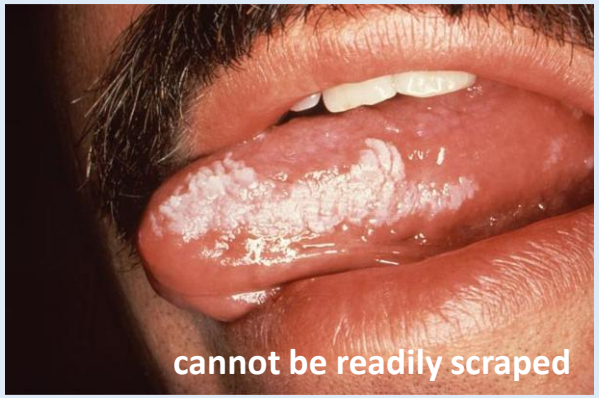
Serum CrAg screening
– High risk case (CD4 <100 cells/mm^3) **AND**
– High prevalent area i.e., South Africa and Asia
Antifungal primary prophylaxis
– Lack of survival benefit
– No routine recommendation

Serum CrAg detection **before symptomatic** meninigitis develop **median 22 d** (5-234 d)

แนวทาง
การตรวจวินิจฉัย รักษา และป้องกัน
การติดเชื้อเอชไอวี ประเทศไทย ปี 2564/2565
Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2021/2022

Markers of immunosuppression

Oral candidiasis

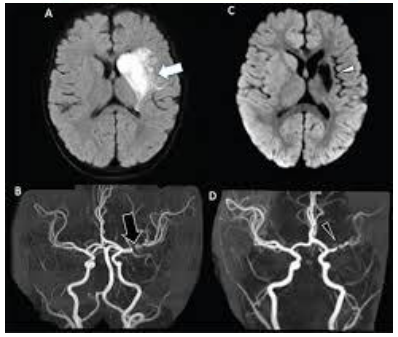


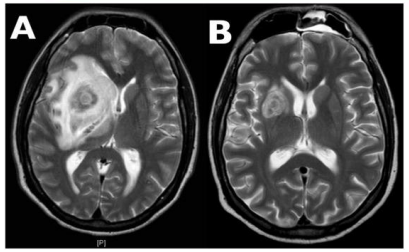
Oral hairy leukoplakia

N Engl J Med. 1987;316:61–66.

Clues : imaging characteristics

White Matter Disease	Stroke/Vascular Findings	Meningeal Enhancement	Mass Lesions	Brainstem	Bilateral Temporal
CMV, EBV, VZV, JCV	*A. fumigatus*, Crypto, Mucor, VZV	Bacterial, Fungal, Autoimmune, Neoplastic	*N. asteroides*, TB, Crypto, Toxo, Lymphoma	*L. monocytogenes*, VZV, JCV, West Nile	HSV, HHV 6, Paraneoplastic

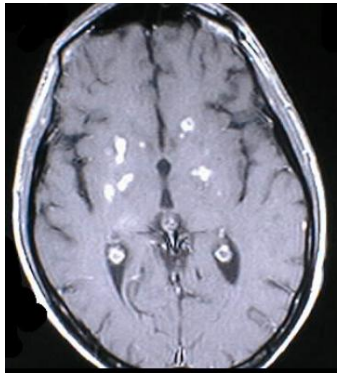




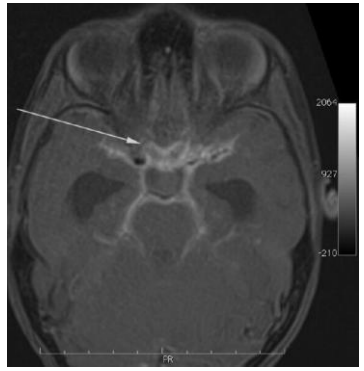
Thakur KT, Wilson MR. Continuum 2018;24

Chronic meningitis

Cryptococcal meningitis	TB meningitis
• Fever, headache (frontal) • Visual disturbance (IICP) • Hearing loss • Stiff neck • CN neuropathy (CN6) • Seizure (uncommon) • Other site : Pulmonary	• Fever, headache (occipital) • Altered mental status • CN neuropathy (basal arachnoiditis) • Stroke like (vasculitis) • Hydrocephalus (Late) • Other site of TB (Pulmonary, LN, Disseminated)
Imaging	**Imaging**
• Gelatinous pseudocysts (T2 hyperintensity)	• Basal meningeal enhancement (50%)
• Leptomeningeal enhancement	• Hydrocephalus
• Hydrocephalus	• Vasculitis or infarction



perivascular spaces in the basal ganglia (gelatinous pseudocysts- do not enhance)



enhancing basal exudates in the perichiasmal region

Meningitis : CSF Findings

CSF profile	Cryptococcal meningitis	TB meningitis	Aseptic meningitis (HIV, PML, CMV, Syphilis)
Opening pressure	Very high (≥25 cm H_2O in 60% to 80%)	High (Late) or normal	Normal
Protein	Slightly ↑ or normal	Slightly ↑ to very high	Slightly ↑ or normal
Cell count	Slightly ↑ or normal or no WBC (low CD4, Poor prog)	↑↑(lymphocytes predominate) (Early PMN**)	Slightly ↑ or normal (PMN : CMV radiculitis)
Microscopy	India ink stain (60-80%)	+/-	
Serology and Culture	55% of H/C 95% of CSF culture CrAg Sn,Sp 99%	+/- (17%) Xpert MTB/RIF 85% *Int J Tuberc Lung Dis. 2015 Oct; 19(10): 1209–1215.*	

AIDSinfo

Cryptococcosis

Meningoencephalitis is most frequent manifestation

- Clinical features: headache, fever, stiffness of neck, cranial nerve palsies & papilledema
- Neck stiffness, photophobia, or other **classic meningeal signs** and symptoms in **25-35% of cases**

After "CNS and lung" infection,

- Next most involved organs Include skin, prostate, and bone

Cutaneous manifestations

- Occur in **10%-15% of cases**
- Papules, pustules, nodules, ulcers, or draining sinuses
- Cellulitis with necrotizing vasculitis is reported in patients who undergo organ transplantation
- **Umbilicated papules in patients with AIDS**

Hints : DDX

1. Viral infection : Molluscum contagiosum
2. Fungal infection
    1. *Cryptococcus neoformans*
    2. *Histoplasma capsulatum*
    3. *Talaromyces marneffei*

Management of ICP

Management of ICP

- Check pressure after initial normal pressure
- Keep pressure < 20 mmH_2O
- Daily lumbar puncture keep pressure < 20 mmH2O or ½ of initial pressure
- **Persistent ICP**, consult for lumbar drain or shunting

Figure 1 Attachment and placement of temporary external lumbar drainage

Manosuthi, et al. Int J of STD & AIDS 2008; 19: 268–271.

Treatment of Cryptococcosis (AIDS)

B. การรักษา (Treatment)

Induction phase: อย่างน้อย 2 สัปดาห์แรก หรือจนกว่าผู้ป่วยจะมีอาการดีขึ้น

ยาหลัก คือ

- Amphotericin B 1.0 มก./กก./วัน ทางหลอดเลือดดำร่วมกับ flucytosine 100 มก./กก./วัน ชนิดกิน แบ่งให้ วันละ 4 ครั้งเป็นเวลา 1 สัปดาห์ ตามด้วย fluconazole 1200 มก./วัน ชนิดกิน นาน 1 สัปดาห์
- Amphotericin B 0.7-1.0 มก./กก./วัน ทางหลอดเลือดดำร่วมกับ fluconazole 800-1200 มก./วัน ชนิดกิน เป็นเวลา 2 สัปดาห์

สำหรับการติดเชื้อที่เยื่อหุ้มสมอง หรือในรายที่มีอาการติดเชื้อรุนแรง หรือมีการติดเชื้อแบบแพร่กระจาย

ยาทางเลือก คือ

- Flucytosine 100 มก./กก./วัน ชนิดกิน แบ่งให้วันละ 4 ครั้ง ร่วมกับ fluconazole 1,200 มก./วัน ชนิดกิน เป็นเวลา 2 สัปดาห์
- Amphotericin B 1.0 มก./กก./วัน ทางหลอดเลือดดำ ในกรณีที่ไม่สามารถใช้ fluconazole ได้

Consolidation phase: 8-10 สัปดาห์

ยาหลัก คือ

- Fluconazole 400-800 มก./วัน กินวันละครั้ง

ยาทางเลือก คือ

- Itraconazole 400 มก. แบ่งกินวันละ 2 ครั้ง

แนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวี ประเทศไทย ปี 2564/2565

World Health Organization

27 June 2022 | Guideline

In a prespecified superiority analysis, **mortality risk was significantly lower in the liposomal amphotericin B group** compared with the control group

Fewer participants experienced grade 3 or 4 adverse events (Renal, anemia)

Induction therapy (2022 recommendations)

A single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (1200 mg/daily for adults; 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) should be used as the preferred induction regimen for treating people with cryptococcal meningitis.

Strong recommendation; moderate-certainty evidence for adults and low-certainty evidence for children

Alternative induction regimens

If liposomal amphotericin B is not available:
A seven-day course of amphotericin B deoxycholate (1 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) followed by seven days of fluconazole (1200 mg daily for adults and 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).

Strong recommendation; moderate-certainty evidence for adults and low-certainty evidence for children and adolescents

Treatment of Cryptococcosis

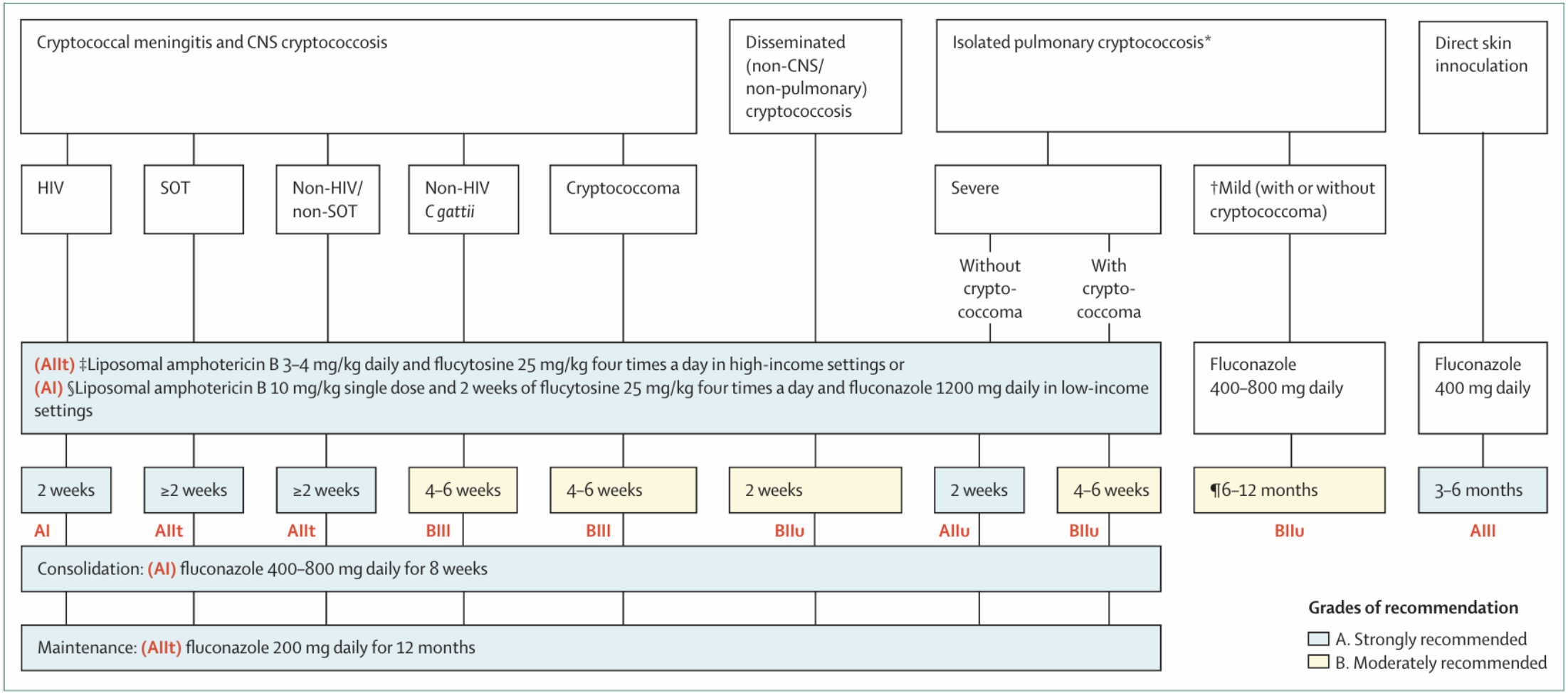


Figure 1: **Recommended first-line antifungal therapy by cryptococcosis syndrome**
Grading of recommendation and level of evidence in bolded red letters. Recommendation grading by shading: blue (strongly recommended; A) and yellow (moderately recommend; B). SOT=solid organ transplantation. *C gattii=Cryptococcal gattii*. w=weeks. *Isolated *Cryptococcal neoformans* or *Cryptococcal gattii* pulmonary cryptococcosis, mild is defined as asymptomatic or mildly symptomatic patients or with a solitary small nodule (<2 cm); whereas severe is defined as multiple lesions, large lesions (≥2 cm), lobar consolidation, cavitation, multi-lobar involvement, or hypoxaemic. †If the presence of *Cryptococcus* spp in respiratory specimens is deemed to be airway colonisation after careful evaluation and no treatment is elected, regular follow-up is recommended, especially in the setting of future immunosuppression. ‡Strongly preferred in cryptococcal meningitis and CNS cryptococcosis in SOT and non-HIV non-SOT patient populations, disseminated cryptococcosis, and severe pulmonary cryptococcosis. ‡Has not been directly compared against §. §Has only been trialled in people with cryptococcal meningitis and there are no supporting data of its use in SOT or non-HIV non-SOT patients or in other cryptococcosis syndromes. ¶Can consider a shorter duration (eg, 3 months) in immunocompetent individuals with mild isolated pulmonary cryptococcosis.

The Lancet Infectious Diseases. 2024 Aug 1;24(8):e495-512.

CMV disease (CNS)

Ventriculoencephalitis

- More acute course
- Focal neurologic signs, CN palsy, nystagmus
- Rapid progression to death
- MRI/CT: periventricular enhancement

Polyradiculopathy

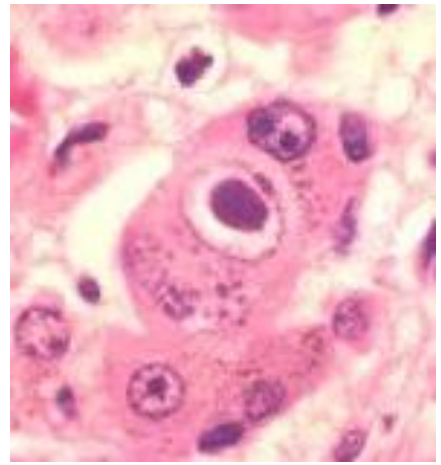
- Progressive lower extremity weakness (~GBS),pain, spasticity, areflexia, urinary retention & hypoesthesia
- CSF finding: PMN pleocytosis and low glucose level

Diagnosis

- **CSF PCR for CMV or VL**
- Pathology

Treatment early with GCV and foscarnet

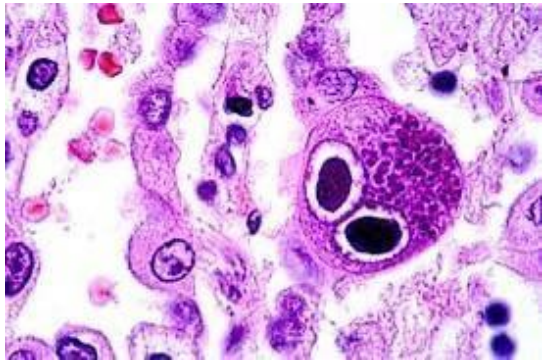
- No clinical trials, but found some poor respond with GCV alone



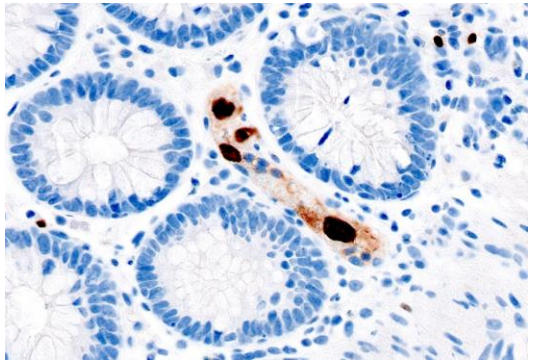
"owl eye" morphology

Diagnostic Performance of Investigations for CMV GI Disease

Investigation Method	Sensitivity (Sn)	Specificity (Sp)	Key Clinical Insights / Highlights
Plasma CMV PCR (at ≥ 1,000 copies/mL)	~50% – 85%	~60% – 90%	**20–50% of patients with proven GI** disease are **PCR negative in blood.**
Endoscopy (Gross Lesions)	90%	Low (~30%)	Sensitive for finding **ulcers/erosions** but lacks specificity (mimics MMF or GvHD).
H&E Histology (Owl's Eye)	~10% – 50%	>95%	**Highly specific but poor sensitivity.** Often misses early or low-level viral replication.
Tissue IHC (Gold Standard)	~75% – 93%	>95%	Clinician's suspicion is key. Picks up **4.1% additional cases when H&E is negative**, but symptoms persist.
Tissue CMV PCR	~95% – 100%	~40% – 60%	High Sn but low Sp; cannot reliably distinguish between **"Latent virus" and "Active disease."**



Basophilic nuclear and cytoplasmic inclusions



CMV infected cells in a single vessel

Am J Clin Pathol, 2014
Am J Surg Pathol, 2017
Hum Pathol, 2017
CID 2013

HIV-related respiratory disease

Table 3.1 Possible causes of severe HIV-related respiratory disease

Bacteria	Fungi	Parasites	Viruses	Non-infectious
Streptococcus pneumoniae	*Pneumocystis jirovecii*	*Toxoplasma gondii*	Cytomegalovirus	**Kaposi's sarcoma**
Haemophilus influenzae	*Cryptococcus neoformans*	*Strongyloides stercoralis*	Adenovirus	**Lymphoma: Hodgkin and non-Hodgkin**
Staphylococcus aureus	*Histoplasma capsulatum*		Influenza A virus	**Lung cancer**
Pseudomonas aeruginosa	*Penicillium marneffei*			**Emphysema**
Escherichia coli	*Aspergillus* spp			**Immune reconstitution inflammatory syndrome**
Mycobacterium tuberculosis	*Coccidioides immitis*			**Pulmonary hypertension**
Mycobacterium avium-intracellulare complex	*Blastomycetes dermatitidis*			**Lymphoid interstitial pneumonitis**
Mycobacterium kansasii				**Non-specific interstitial pneumonitis**
				Sarcoid
				Pulmonary thrombo-embolic disease

Hints : TMS/SMX prophylaxis
- PCP (reduced mortality)
- Toxoplasmosis
- Nocardiosis
- Bacterial infection (*Salmonella, Listeria, S. aureus*)

CD4 > 200
- *M. tuberculosis*

CD4 = 50-200 (usually <100)
- *P. jerovecii*, *C. neoformans*, dimorphic fungi, *Nocardia* spp., *M. kansasii*, *R. equi*, KS (HHV-8)

CD4 < 50
- *M. avium complex*, cytomegalovirus

HIV Medicine (2011), 12 (Suppl. 2), 25–42

Common radiological appearances of pulmonary infections in HIV patients

Chest radiograph or CT abnormality	Acute or subacute onset (<1-4 weeks symptoms)	Chronic onset (>4 weeks symptoms)
Focal consolidation 	• Any organism, but especially pyogenic bacteria • Legionellosis	• Mycobacteriosis • Nocardiosis • Fungi (aspergillosis, endemic fungal infections, cryptococcosis)
Diffuse interstitial infiltrate 	• *Pneumocystis jirovecii* • Bacteria, especially *Haemophilus influenzae* (influenza, CMV)	• Mycobacteriosis • Fungal pneumonia, especially cryptococcal • Toxoplasmosis • CMV
Nodules 	• Tuberculosis • Fungi (cryptococosis, aspergillosis) • Bacteria	• Nocardiosis • Fungi
Adenopathy 	• Tuberculosis	• Mycobacteriosis • Endemic fungal infections
Cavitary infiltrate 	• Tuberculosis • *Staphylococcus aureus* (IDU) • Fungi • Anaerobes • *Pseudomonas aeruginosa* • Legionellosis	• Mycobacteriosis • Nocardiosis • Fungi • *Rhodococcus equi*
Pleural effusion 	• Pyogenic bacteria • Fungi • Tuberculosis	• Fungi • Nocardiosis
Pneumothorax 	• *Pneumocystis jirovecii*	

Key & Abbreviations
CT: computed tomography, **CMV**: cytomegalovirus: **IDU**: intravenous drug users. Patients with acute, subacute or chronic onset have <1 week, 1–4 weeks or >4 weeks of symptoms, respectively.

om *Eur Respir J. 2012;39(3):730-45*

Rhodococcosis

- Intracellular small Gram-positive cocci or bacilli
- weakly AFB pos, mAFB pos
- Zoonosis
- CD4 <100 cells/mm3
- Necrotizing granulomatous reaction

Clinical spectrums: common to relapse

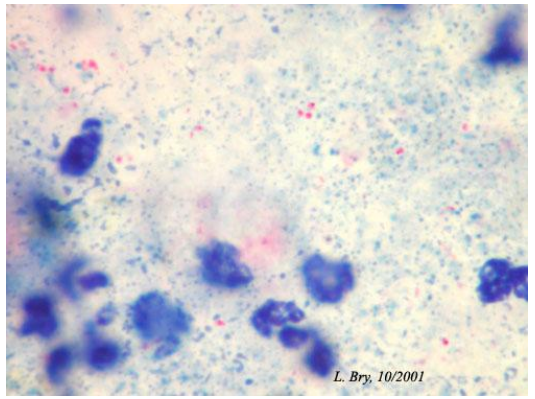
- Pulmonary (80%)
  - Subacute pneumonia (H/C pos 50%)
  - **CXR: TB-like disease; cavity** (single or multiple, thick wall, air-fluid level), nodules, infiltration, effusion (UL)
  - **Complications:** lung abscess, empyema, pneumothorax, mediastinitis
- Extrapulmonary (20%)
  - Disseminated disease to pulmonary disease: **brain or internal organ abscess** (late phase)
  - Localized disease : direct inoculum

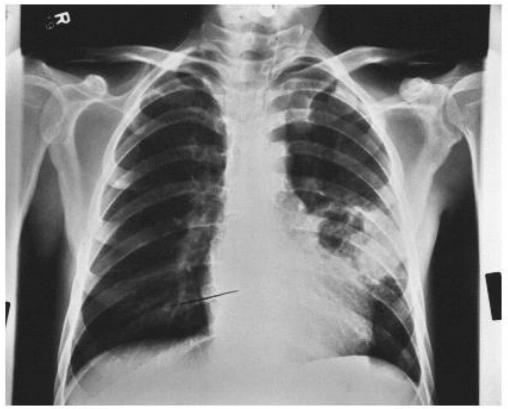
Immunocompromised, serious infection: at least 2 from the following

1. Carbapenems: Imipenem 500 mg iv q 6 hrs. or vancomycin 1 g iv q 12 hrs.
2. 1 of the drug listed under primary regimen
   - Rifampicin, FQs, aminoglycoside, linezolid or macrolide

Duration of treatment

- Intensive phase
  - 2-3 wks., 8 wks. for brain abscess
- Maintenance
  - ≥6 months, until C/S negative and resolved clinical





Nocardiosis

- Aerobe Actinomycetes, short chain mycolic acid
- Nocardia appear as gram-positive, beaded, weakly acid-fast, branching rods.
- **Localized disease**
  - Subacute or indolent infection with suppuration
  - Productive or nonproductive cough, dyspnea, hemoptysis, and fever,
  - CXR: mass-like with cavity ± effusion
  - CNS
  - SSTIs: Mycetoma, nodular lymphangitis
- **Disseminated disease**
- **Therapy and Follow-Up**
  - Trimethoprim-sulfamethoxazole (TMP-SMX) is the mainstay of treatment

Combination antimicrobial therapy
- At least two agents is recommended for immunocompromised hosts, those with more than one site of infection and severe pulmonary involvement or isolated CNS disease.

Recommended regimens
- Include amikacin and imipenem or meropenem, or amikacin and TMP-SMX.

FIG. 253.4 **Brain abscess.** Magnetic resonance image showing *Nocardia* brain abscess.

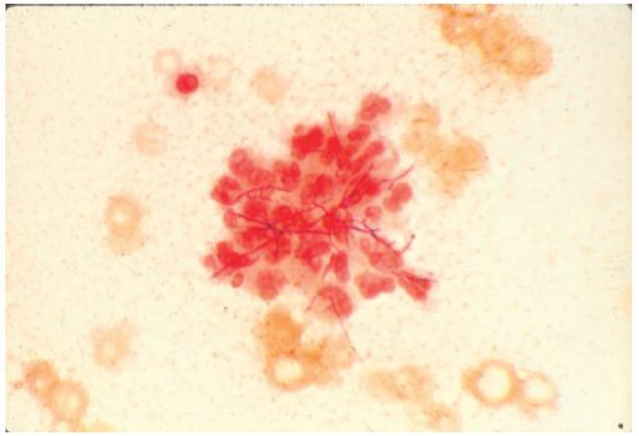
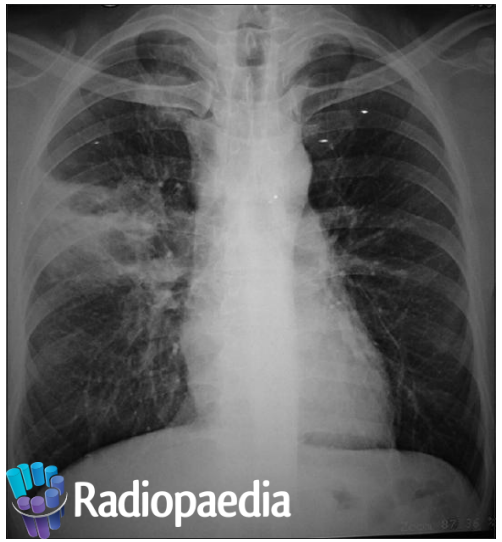


FIG. 253.1 **Pulmonary nocardiosis.** Photomicrograph of direct Gram-stained smear from a patient with pulmonary nocardiosis, showing typical branching rods.

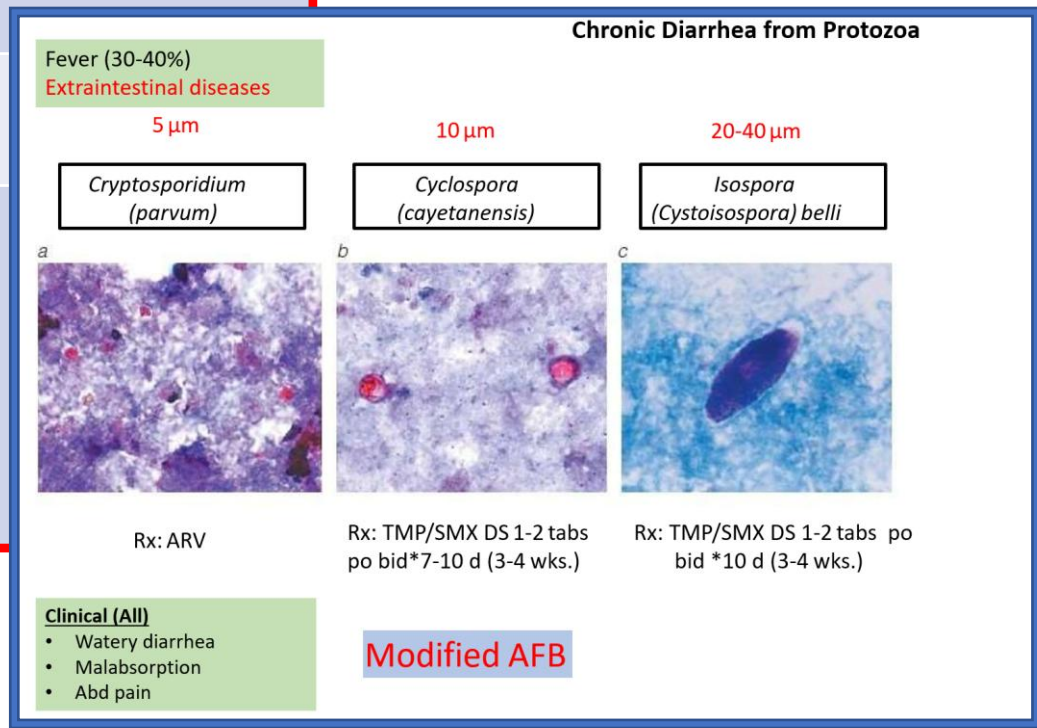


1. lobar or multilobar consolidation
   - abscess formation cavitation in 30%
2. solitary lung masses and/or nodules
3. reticulonodular infiltrates [9]
4. mediastinal or hilar lymphadenopathy is **not** a feature of nocardiosis

Nonspecific : pleural thickening , pleural effusion

Diarrhea in HIV-infected patients

Acute	Chronic (> 4wks)	
Bacteria • *Salmonella* (NTS) • *Shigella* • *Campylobacter* • *C.difficile*	**Mycobacteria** • TB • MAC	**Fungus** • *Histoplama* • *Talaromyces* • *Microsporidia*
Enteric viruses • Adenovirus	**Virus** • CMV	
	Parasites • *Cryptosporidium* • *Cyclospora cayatanensis* • *Giardia lamblia* • *Cystoisospora belli*	



Intraluminal lesion in HIV-infected patients

Common lesion : Terminal ileum

OIs	Malignancy
Virus: CMV colitis	Solid malignancy: CA colon
Mycobacterium: TB, MAC	Hematologic malignancy: lymphoma
Parasites: *Cryptosporidium*	HIV-associated: KS
Fungus • *Histoplama* • *Talaromyces*	

Disseminated presentation

- **Prolonged fever (unrecognized fever)**
- **Constitutional symptoms (BW before illness)**
- Lymphadenopathy (localized or generalized)
- Hepatosplenomegaly
- Skin lesion or mucosal lesion
- Hematologic abnormalities (anemia or cytopenia)
- Elevated alkaline phosphatase

Histoplasmosis and Talaromycosis

- **Cellular immunity**
- **Dimorphic fungi**
  - Yeast at 37°C
  - Mold at 25- 30°C
- Talaromycosis
  - *Talaromyces marneffei*
- Histoplasmosis
  - *Histoplasma capsulatum*

- **Most common - Disseminated infection**
- Prolonged fever, weight loss, skin lesions, hepatosplenomegaly, lymphadenopathy, pancytopenia
- **Oral lesions: histoplasmosis** (50% of chronic PDH)
- Adrenal gland lesions: histoplasmosis
- **Skin lesions: talaromycosis (80%)**

- Histoplasmosis, acquired through **inhalation** of mycelial fragments and microconidia, is most often self-limiting but can cause potentially lethal infection in patients with **preexisting condition**
- **Reservoir of *H. capsulatum* (soil)**

Spectrum of *Histoplasma capsulatum*–Induced disease (5-10%)

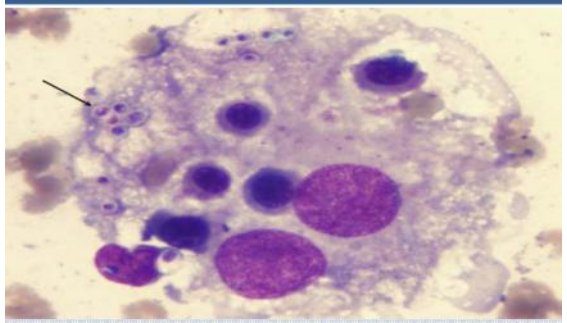
Manifestations	Acute Pulmonary Disease	Chronic Cavitary Pulmonary Disease	Progressive Disseminated Disease (PDD)
Clinical Presentation	Often asymptomatic or influenza-like illness.	Fever, productive cough, chest pain. **Cavitary lesions in upper lobes (90%).**	Fever, weight loss, **hepatosplenomegaly, hematologic disturbances.**
Immunologic			
Positive Skin Test	>90%	70%-90%	30%-55%
Lymphocyte Transformation	+++	+ to +++	±
Antibody to H. *capsulatum*	25%-85%	75%-95%	70%-90%
Antigenuria	20%	40%	60%-90%
Pathologic			
Positive Culture (Lungs)	<25%	5%-70%	50%-70%
Histology	Caseating and noncaseating granulomas; few yeasts; giant cells.	Noncaseating granulomas, interstitial fibrosis, necrosis; few to moderate yeasts.	**Diffuse macrophage proliferation**; abundant yeasts; few giant cells.

The major risk factors manifestation of histoplasmosis **age older than 54 years and immunosuppression.** **GI (70%), adrenal (10%), CNS (5-20%) and skin (10%)**

Diagnosis

- **Fungal culture (Gold standard)**
  - growth 3-6 weeks **(< 7 days**, 90%)
  - 10-15% (acute), 60% (cavity)
  - **BM/Blood 50% (AIDS)**
- Antigen detection (urine, blood, BAL)
  - **90% acute PDH**
  - 40% cavity
  - monitor **relapse**
- **Serology**
  - retrospective diagnosis
  - **negative up to 50% of immunosuppressed**
- **Histochemical identification**
  - **GMS**
  - PBS 40% (acute PDH)
- Molecular diagnosis (PCR?)

Histoplasmosis

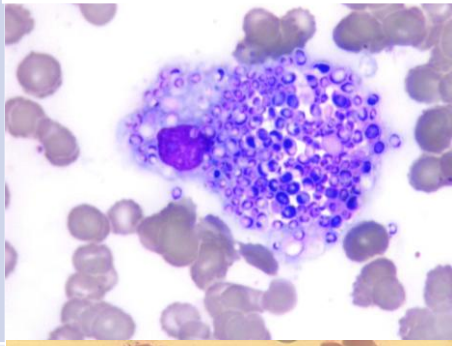
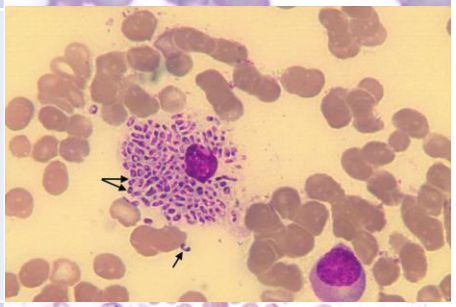
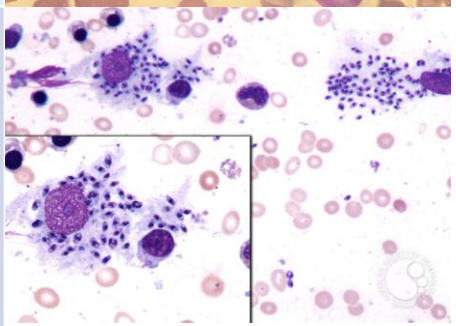
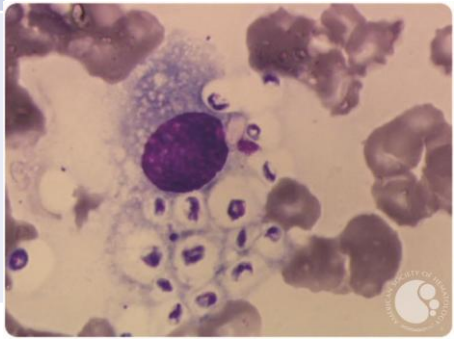


Intracellular or extracellular, monomorphous small round to oval yeast cells

Small (2–5 µm) narrow **budding yeasts** of *H. capsulatum*

Serum LDH levels higher than 600 IU/mL are highly likely to have disseminated histoplasmosis.
Elevated serum ferritin levels are strongly suggestive of histoplasmosis.

Clin Microbiol Rev. 2007;20:115–132.

Pathogen	Microscopic Morphology	Key Lab / Investigation	Microscopic
Histoplasma capsulatum	**Intracellular** or extracellular, **monomorphous** small round/oval yeast (2-5 µm) with **narrow-base budding.**	• Serum LDH > 600 IU/mL and elevated Ferritin (highly suggestive). • **Fungal culture is the gold standard (3-6 weeks).** • Antigen detection (Urine/Blood) has 90% sensitivity in acute disease.	
Talaromyces marneffei	**Intracellular** or extracellular small round/oval yeast; **unique sausage/elongated forms** with a **central transverse septum.**	• **Wright's stain of skin scrapings** or **Bone Marrow (BM)** for rapid ID. • **Fungal culture is the gold standard;** often grows in < 7 days (90%) in disseminated cases.	
Leishmania amastigotes	**Intracellular amastigotes** within macrophages; must identify both a **nucleus** and a **bar-shaped kinetoplast.**	• Splenic aspiration (highest sensitivity at 96%) or **BM aspiration (70% sensitivity).** • PCR and specialized culture (Novy-McNeal-Nicolle media) are gold standards.	
Cryptococcus neoformans	**Extracellular**, large round **encapsulated yeast cells**; varying sizes with **narrow-neck budding.**	• India ink stain (60-80% Sn). • **Serum/CSF CrAg (Antigen)** is the top choice with 99% Sn and Sp. • CSF opening pressure is often very high (≥ 25 cm H2O).	

Treatment Summary:
Disseminated Histoplasmosis and Talaromycosis

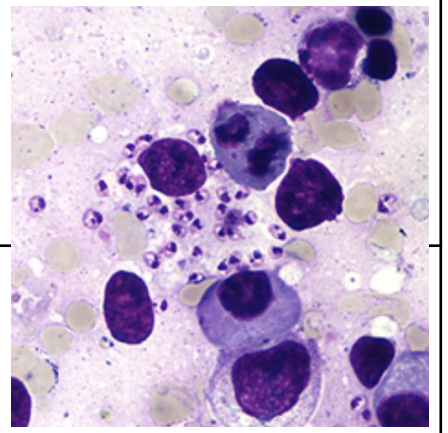
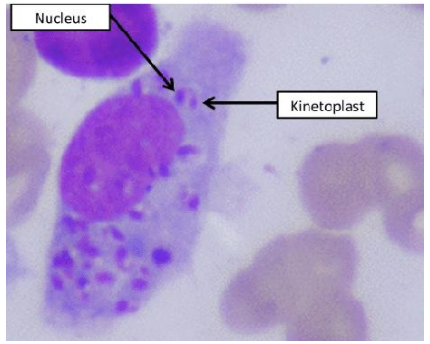
Treatment Phase	Preferred Regimen (Drug & Dosage)	Duration / Criteria
Induction Phase	**Amphotericin B (0.6–0.7 mg/kg/day)** intravenous	**7–14 days;** clinical and lab improvement usually seen within 1–2 weeks
Consolidation Phase	**Itraconazole:** Loading dose of 600 mg/day for 3 days, **followed by 400 mg/day**	**10–12 weeks**
Maintenance Phase (Secondary Prophylaxis)	**Itraconazole 200 mg/day**	**At least 6 months** ; must also have sustained CD4/viral suppression
Mild to Moderate Disease	**Itraconazole 400 mg/day** (if no hemodynamic instability or severe illness)	As per clinical response and consolidation guidelines

CD4 Response

Talaromycosis: CD4 >100 cells/mm³ for at least 6 months.
Histoplasmosis: CD4 >150 cells/mm³ for at least 6 months.

Critical Clinical Pearls

- **Pregnancy Warning: Itraconazole is strictly contraindicated during pregnancy.**
- **Optimizing Absorption:**
  - Capsules: Must be taken **with food.**
  - Oral Solution: Must be taken **while fasting**; this increases absorption by 50%.
- **Therapeutic Drug Monitoring (TDM):** Aim to maintain Itraconazole serum levels >1 mg/L for efficacy.
- **Primary Prophylaxis:** Consider Itraconazole 200 mg/day for HIV patients with **CD4 < 150 cells/µL living in high-prevalence areas**

	History	Physical exam	1st Test	Other tests
Leishmaniasis (visceral disease)	• Associated with recent travel to areas endemic for sand flies • **HIV increased risk for VL**	• Hepato**splenomegaly**, lymphadenopathy, • hyperpigmentation of face, hand, foot, • abdominal skin (kala azar)	• bone marrow or spleen aspirations (sn 70 and 96) • Culture (Novy-McNeal-Nicolle media) • **PCR** • Serologic tests : not recommended	**Treatment VL** • **Preferred L-Amb**  nucleus and kinetoplast in each amastigote. 

Histoplasmosis	• Exposure to **bat excreta** in houses, or **caves** in region surrounding the Ohio and Mississippi River valleys of the United States or regions of Central and South America, Africa, Asia, Australia	• pulmonary (70%) pneumonia, pulmonary cavities
		• weight loss (60%)
		• hepatomegaly (60%)
		• splenomegaly (40%)
		• lymphadenopathy (40%)
		• Skin lesion (10%)
		• mucosal involvement (50%)
			• **Fungal culture (Gold standard)**
			• Antigen detection (urine, blood, BAL)
			• Serology
			  • **negative up to 50% of immunosuppressed**
			• Histochemical identification
			  • **GMS**
			• Molecular diagnosis (PCR?)	

Mycobacterium avium complex (MAC)

- Acquired by inhalation or ingestion
- Colonize natural water sources, pools, and hot tubs
- Disseminated infection in HIV-infected patients
  - Common sites: liver, Gi, spleen, and BM

- **MAC entry into bloodstream** leads to elevated TNF-α and IL-6:
  (1) **High fever**, night sweats, and BW loss
  (2) **Severe anemia**
  (3) **GI :** abdominal pain, diarrhea, intraabdominal LN, hepatosplenomegaly

- Marked elevation of serum ALP (5%)
- Hemoculture for mycobacteria : **positive (90%)**

Mycobacterial infection

Tuberculosis	*M. avium* complex
Any CD4	CD4 < 50
CD4 > 350 pulmonary diseases Disseminated infections pulmonary involvement (81.8%)	Disseminated infections pulmonary involvement (40%)
Extrapulmonary (CNS, **LN(68.2%)**, pleura, pericardium)	**Spleen (46.7%)**, lymph node, liver, GI, **bone marrow (WBC<4,000, ~100%)**
Sepsis syndrome	Anemia, elevated ALP
Atypical CXR (81.8%)	Positive hemoculture (90%)

Hsieh SM, et al. AIDS. 1998;12:1301–7.

Treatment of MAC (AIDS)

B. การรักษา (Treatment)

- Clarithromycin 500 มก. กินวันละ 2 ครั้ง หรือ azithromycin 500 มก. กินวันละครั้ง ร่วมกับ ethambutol 15 มก./กก./วัน

ในกรณีที่อาการรุนแรงหรือมี CD4 <50 cells/mm3 ควรใช้ยาอื่นร่วมด้วยอีก 1-2 ชนิด ได้แก่ ยากลุ่ม quinolones (levofloxacin 500 มก. วันละครั้ง หรือ moxifloxacin 400 มก. วันละครั้ง) หรือ amikacin 10-15 มก./กก. ทางหลอดเลือดดำวันละครั้งในกรณีที่มีการรักษาไม่ได้ผล คือ หลังการรักษา 4-8 สัปดาห์ แล้วผลเพาะเชื้อจากเลือดยังคงให้ผลบวก ให้ส่งเพาะเชื้อตรวจหาความไวต่อยา ให้เพิ่มยาใหม่อย่างน้อยอีก 2 ชนิด เข้าไปในสูตรยาเดิมที่ใช้รักษาอยู่

Disseminated disease (AIDS) **12 months after culture conversion**, secondary prophylaxis till CD4 >100/µL for 6 months

Hints : favor azithromycin

- Pregnancy
- Less drug-drug interactions
- Less side effects
- better adherence and outcomes (NTM-PD)

Differential Diagnosis: Disseminated Infections in FUO (HIV)

Pathogen	Immunity / Risk Factors	Clinical Clues (PDCs)	Diagnostic Highlights
Tuberculosis (TB)	Any CD4 count; HIV increases risk (13%)	Fever, weight loss, night sweats; **Prolonged cough (>2 wks); Lymphadenopathy (68.2%)**	**Xpert MTB/RIF Ultra** is the recommended initial test for pulmonary/extrapulmonary TB; Liquid culture is the gold standard
Leishmaniasis (Visceral)	**Southern Thailand** travel; Sand fly exposure; HIV increases risk	**Massive splenomegaly;** Hyperpigmentation of face/hands (Kala-azar); Cytopenia	**BM or splenic aspiration**; **Amastigotes** showing both a nucleus and a **kinetoplast**
Talaromycosis (Penicilliosis)	CD4 < 100 cells/mm³	**Umbilicated papules (80%);** Hepatosplenomegaly; Lymphadenopathy	Wright's stain from skin lesion or BM; **Intracellular/extracellular sausage-shaped yeast with a central septum**
Histoplasmosis	CD4 < 100-150 cells/mm³; **Exposure to bat/bird droppings**	**Oral ulcers (50%);** Adrenal gland involvement; **High LDH (>600 IU/mL)** and ferritin	Antigen detection (Urine/Blood/BAL); **Small round/oval yeast with narrow-base budding**
MAC infection	CD4 < 50 cells/mm³ +3	High fever and night sweats; **Severe anemia;** Marked **elevation of ALP**	**Hemoculture for Mycobacteria (90% positive);** Lymph node/Liver/BM involvement

Patient Profile

- Patient: A 55-year-old female, a housewife from Central Thailand.
- Medical History: Previously healthy, no underlying diseases. **HIV ELISA is negative.**
- **Chief Complaint: Chronic low-grade fever (2 months), generalized "painful" skin nodules, and enlarging neck lumps.**
- Physical Exam:
  - Vital Signs: T 38.3C, HR 92 bpm, BP 120/70 mmHg.
  - Lymph Nodes: Massive generalized lymphadenopathy; cervical, supraclavicular, and axillary nodes (3–5 cm), matted and firm.
  - Skin: Multiple erythematous plaques and pustular skin lesions (Sweet-like syndrome) on the trunk and extremities.
  - Musculoskeletal: Point tenderness over the sternum and right pretibial area.
  - Abdomen: Mild hepatosplenomegaly.

Top 3 Differential Diagnosis by GEMINI

1. Disseminated NTM Infection with Anti-IFN-γ Autoantibody
2. Lymphoma (e.g., HL, NHL)
3. Disseminated Tuberculosis (TB)

Disease Overview and Pathogenesis

Parameter	Description
Definition	An acquired immunodeficiency syndrome in previously healthy adults, also known as "**Adult-onset immunodeficiency" or "AIDS-like syndrome."**
Primary Driver	Presence of high-titer **neutralizing autoantibodies** targeting Interferon-gamma (IFN-γ).
Molecular Mechanism	Autoantibodies block IFN-γ from binding to its receptors **(IFNGR1/IFNGR2).**
Signaling Block	**Inhibits the JAK-STAT1 pathway**, specifically preventing STAT1 phosphorylation (pSTAT1).
Downstream Effect	Reduced production of **IL-12 and TNF-α**, leading to **impaired intracellular killing by macrophages.**

Clin Infect Dis. 2020;71(1):53-62.
Front Immunol. 2021;12:788368.
Sci Rep. 2020;10:8968.
Exp Biol Med (Maywood). 2021;246(7):790-795.

Epidemiology and Clinical Presentation

Feature	Key Findings
Demographics	Primarily affects **Southeast Asian adults (median age ~45-50 years).**
Genetic Predisposition	Strong association with HLA alleles: **HLA-DRB1*16:02 and HLA-DQB1*05:02.**
Common Sites	**Lymph nodes (most common)**, followed by bone, skin, lungs, and central nervous system (CNS).
Sweet Syndrome	A reactive skin disease **highly prevalent in patients with this syndrome (up to 38% in Thai cohorts).**
US vs. Thai Cohort	US patients are predominantly female (91%) compared to Thai patients (64%).

Acute Febrile Neutrophilic Dermatosis
Tender, erythematous/violaceous plaques or nodules.
"Juicy" or succulent appearance.
Pseudovesiculation

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Microbiological Spectrum

Category	Thai Cohort	US Cohort (SE Asian Descent)
Dominant NTM	***Mycobacterium abscessus*** (Rapid-growing mycobacteria).	***Mycobacterium avium complex* (MAC)** (Slow-growing mycobacteria).
Fungal Infections	***Talaromyces marneffei*** (common), Histoplasmosis, Cryptococcosis.	Significantly less common than in Thailand.
Other Bacteria	**Non-typhoidal Salmonella (19-36%)**, *Burkholderia pseudomallei*.	Rare; MAC remains the primary focus.
Viral Pathogens	Herpes Zoster (VZV) reactivation (21%).	Less frequent viral reactivation.

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Diagnostic Evaluation

Test Type	Description and Performance
Indirect ELISA	High sensitivity but **low specificity** due to non-specific IgG binding; may give false positives.
Inhibitory ELISA	**Superior specificity** and 100% Positive Predictive Value (PPV) for NTM infection.
Inhibitory Titer	**A titer ≥ 5,000** is a reliable marker to distinguish active from inactive NTM infection.
Functional Assay	pSTAT1 flow cytometry confirms the autoantibody's ability to neutralize IFN-γ biological activity.
QuantiFERON-TB	Can be repurposed for screening; "Indeterminate" results may suggest neutralizing antibodies.

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Management and Clinical Outcomes

Strategy / Drug	Therapeutic Response and Clinical Impact
Antimicrobials	Base treatment; however, infections **can be refractory and chronic** despite aggressive antibiotics.
Rituximab (Anti-CD20)	**B-cell depletion** leads to reduced autoantibody titers and **restores IFN-γ signaling.** Associated with clinical remission in progressive NTM.
Cyclophosphamide	**Effectively lowers antibody titers and leads to clinical improvement.** Some reports suggest faster remission and lower relapse rates compared to rituximab.
Daratumumab (Anti-CD38)	Targets plasma cells; can suppress antibody levels and improve outcomes in **rituximab-refractory cases.**
Secondary Prophylaxis	**Indefinite prophylaxis** (e.g., daily Azithromycin) may be used to prevent new infections.
Long-term Outcome	**Autoantibody titers tend to decrease over time**, but the clinical course remains chronic with risks of persistent infection and death.

Medians to infection clearance are long (**3–5 years**); titers may stay stable without immunomodulation.

Summary of NTM Treatment Regimens

Mycobacterial Species	Treatment Phase	Recommended Drug Regimen	Key Notes
Mycobacterium avium complex (MAC)	**Standard**	**Macrolide-based (3 drugs):** Clarithromycin or Azithromycin + Ethambutol + Rifampicin or Rifabutin.	If macrolide-resistant, use alternatives like Clofazimine, Moxifloxacin, or Linezolid.
	Severe Case	**Add Amikacin (IV)** for the first 2–4 weeks.	Monitor renal function if using Amikacin.
Mycobacterium abscessus	**Initial (2–4 weeks)**	**IV (at least 2):** Amikacin + Imipenem (or Cefoxitin or Tigecycline) . **Oral (1–3):** Azithromycin, Clofazimine, or Linezolid.	Total 3 drugs for susceptible strains; at least 4 drugs for resistant/inducible strains.
	Continuation	**Oral (2–3 drugs):** Azithromycin, Clofazimine, and/or Linezolid.	Duration of IV therapy may be extended to 4 weeks for resistant strains.
Mycobacterium fortuitum	**Initial (1–2 months)**	**3–4 drugs:** Based on susceptibility (Amikacin, Imipenem, Quinolones, Doxycycline, or TMP-SMX).	Often susceptible to more drugs than *M. abscessus.*
	Continuation	**Reduce to 2–3 drugs** once clinical improvement is noted.	Surgical drainage may be required for deep abscesses.

คำแนะนำการรักษาการติดเชื้อมัยโคแบคทีเรียที่ไม่ใช่วัณโรค ***สมาคมโรคติดเชื้อแห่งประเทศไทย***

Table 3
Treatment regimens for selected NTM species in transplant recipients.

Organism	Recommended regimen	Alternative/second line drugs	Duration	Other
SGM				
M. avium complex	AZM 250–500 mg/d +RFB 300 mg/d + EMB 15 m/k/d±AMK IV	RIF, CLR, AMK, MXF	12 mos of negative sputum cultures (for pulmonary dse)	
M. kansasii	RFB 300 mg, EMB15m/k/d, INH 5/m/k/d + Pyridoxine 50 mg/d If with RIF resistance-3 drug regimen based on in-vitro susceptibilities	AZM, MXF, SXT, STR	12 mos of negative sputum cultures (for pulmonary dse)	
M. marinum	Two active agents, usually AZM + EMB	RIF/RFB,CLR, EMB, DOX	3–4 mos	Uniformly resistant to INH/PZA
RGM				
M. abscessus	Must be based on in-vitro susceptibility data: AZM 250 mg/d plus IV (AMK, FOX, IPM)	LZD, TGC Linezolid, tigecycline	4–6 mos	Uniformly resistant to anti-TB drugs
M. chelonae	Must be based on in-vitro susceptibility data: AZM plus (1) other agent (TOB, LZD, IPM)	AMK, DOX, CIP	4–6 mos	
M. fortuitum	At least 2 active agents with in vitro activity	AMK, CIP, SXT, FOX, IPM, AZM, DOX	12 mos of negative sputum cultures (for pulmonary dse) 4-6 mos for SSTI or bone-joint	Inducible resistance to MAC
Fastidious NTM				
M. haemophilum	No standardized susceptibility data	AMK, AZM, CIP, RIF, RFB,	Not determined	Uniformly resistant to EMB
M. genavense	AZM + at least one other active agent	AMK, RFB/RIF, CIP, AZM, STR	Not determined	EMB with limited activity
M. gordonae	Must be based on in-vitro susceptibility data	EMB, RFB, AZM, LZD, CIP	Not determined	Most frequently isolated contaminant

AZM – Azithromycin, RFB – Rifabutin, AMK – Amikacin, CLR- Clarithromycin, MXF – Moxifloxacin, SXT – Trimethoprim-sulfmethoxazole, STR – Streptomycin, FOX – Cefoxitin, IPM – imipenem, LZD – Linezolid, TGC – tigecycline, DOX – Doxycycline, CIP – ciprofloxacin, MAC – macrolides, PZA – Pyrazinamide.

Category	Recommendations
Treatment Duration	Patients should receive antimicrobial therapy for **at least 2–4 years**. Studies in Thailand and the US indicate that infection clearance typically takes **approximately 3 years.**
Criteria for Stopping Treatment	Treatment may be considered for **cessation if the patient meets all the following:** • Significant clinical improvement. • No palpable superficial lymph nodes. • Resolution of previous imaging abnormalities. • No repeat isolation of the pathogen from any site. • Total treatment duration of at least 2–4 years.
Clinical & Lab Monitoring	• **Clinical Symptoms:** Monitor for fever, weight loss, and new or worsening lymphadenopathy. • **Laboratory Tests:** Regular checks of CBC, CRP, and ESR to identify potential relapses. • **Antibody Titers:** Monitor anti-IFN-Y autoantibody levels at least **once a year** to help plan long-term care or the introduction of immunosuppressants.
Safety & Side Effect Monitoring	• **Renal & Liver Function: Monitor LFTs** and renal function, especially for drugs like Amikacin, Clarithromycin, and Ethambutol. • **Auditory & Visual: Conduct hearing tests** for Amikacin/Streptomycin use and eye exams every 6 months for Ethambutol. • **Cardiac:** Periodic EKG monitoring for drugs that cause **QT prolongation** (e.g., Macrolides, Clofazimine, Quinolones).

Management of Relapse or Refractory Cases	• Consider adjunctive immunosuppressive therapy (e.g., Rituximab, Cyclophosphamide, Bortezomib) if the patient:
	  • Experiences ≥2 relapses or worsening symptoms despite treatment.
	  • Requires ≥3 courses of IV antibiotics within one year.

TAKE-HOME MESSAGES: ID LONG CASE PEARLS

1. Diagnostic Logic and FUO
   - **Abdominal CT** has the highest diagnostic yield (92%).
   - Initial TB Choice: **Xpert MTB/RIF Ultra**
2. Tropical ID: Melioidosis and Liver Abscess
   - Melioidosis "Must-Dos": Mandatory DRE (for prostate abscess) and **Abdominal CT/US (for visceral abscesses)** in all cases.
   - Treatment Duration: Melioidosis requires 12–20 weeks of total therapy to prevent relapse.
   - ***K. pneumoniae* Abscess (KLA):** Check vision (Endophthalmitis) and perform screening colonoscopy for occult Colorectal Cancer (CRC).
3. IE and Adult-Onset Immunodeficiency
   - *S. aureus* Bacteremia : Carries a 10% risk of IE; **all cases require echocardiography.**
   - **TEE over TTE:** TEE has 90–100% sensitivity, especially for prosthetic valves or perivalvular complications.
   - **Anti-IFN-gamma AutoAb: Suspect in healthy SE Asian adults with disseminated NTM, OIs, or Sweet syndrome.**
4. HIV and Opportunistic Infections (OIs)
   - **MAC Infection:** Occurs at CD4 < 50; look for high fever, severe anemia, and high ALP.
   - **Talaromycosis:** Look for umbilicated papules and sausage-shaped yeast with a central septum.
   - **Cryptococcus:** Manage ICP by daily LP to keep pressure < 20 cmH2O.

"Board Tip: Never start empiric antibiotics in a stable FUO case—wait for the cultures to find the real bug! "

GOOD LUCK IN YOUR EXAMS!

(BEING A NERD
IS ACTUALLY COOL
WHEN YOU'RE MY AGE)