Case approach in common infectious disease problems

Nov 2024

Outline

- Common problem in ID long case exam. = **“Prolonged fever”** (fever > 4 wks.)
- Approach
  - Classical FUO
    - Common etiology
  - Infective endocarditis (NVE) (ESC 2023)
  - HIV related OIs

Case

A 65-year-old retired government employee was admitted to our hospital with history of high-grade swinging temperature up to 39°C. She had had a sore throat, which lasted for a few days accompanied by rigors, and myalgia. Her general practitioner prescribed amoxicillin/clavulanic acid. **The symptoms were persistent over four weeks.**

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.

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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.

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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

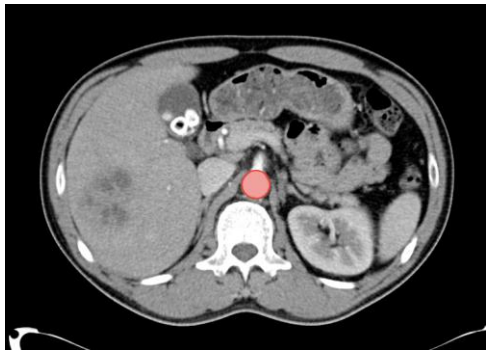
Initial investigation

- 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

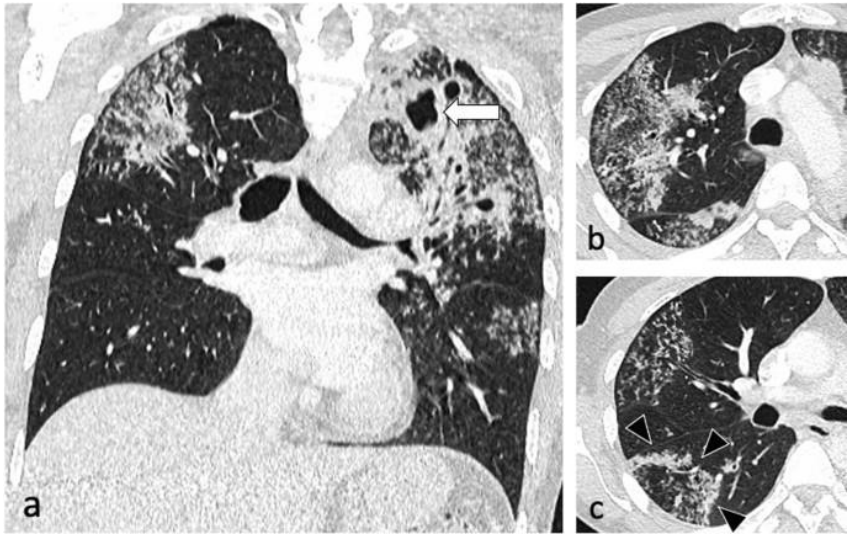
- Liver and spleen
- LN (necrosis)
- Bone (OM)
- Psoas, paraspinal
- Aorta
- Prostate



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

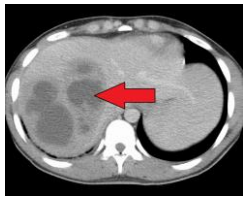
Imaging studies

- **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%**

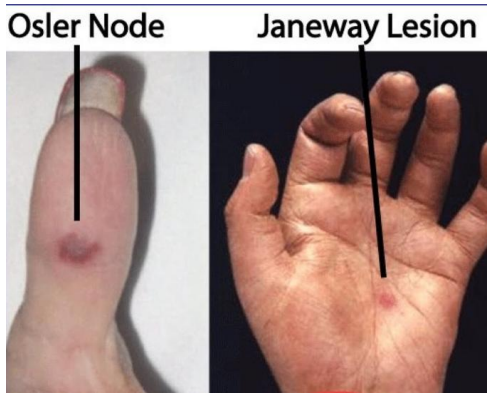
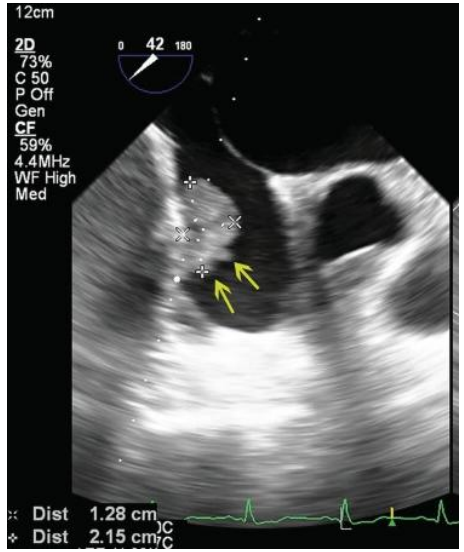


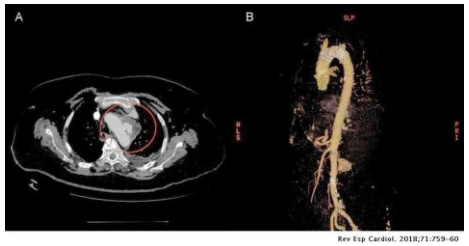
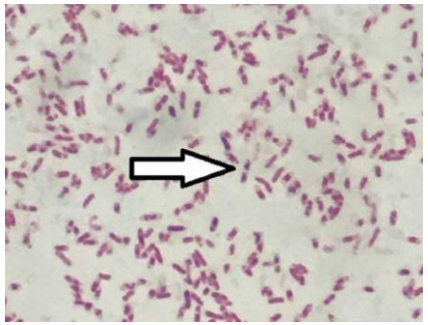
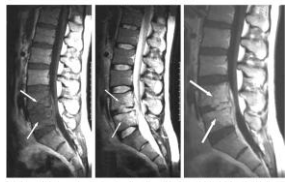
Medicine (Baltimore). 2007;86:26–38

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

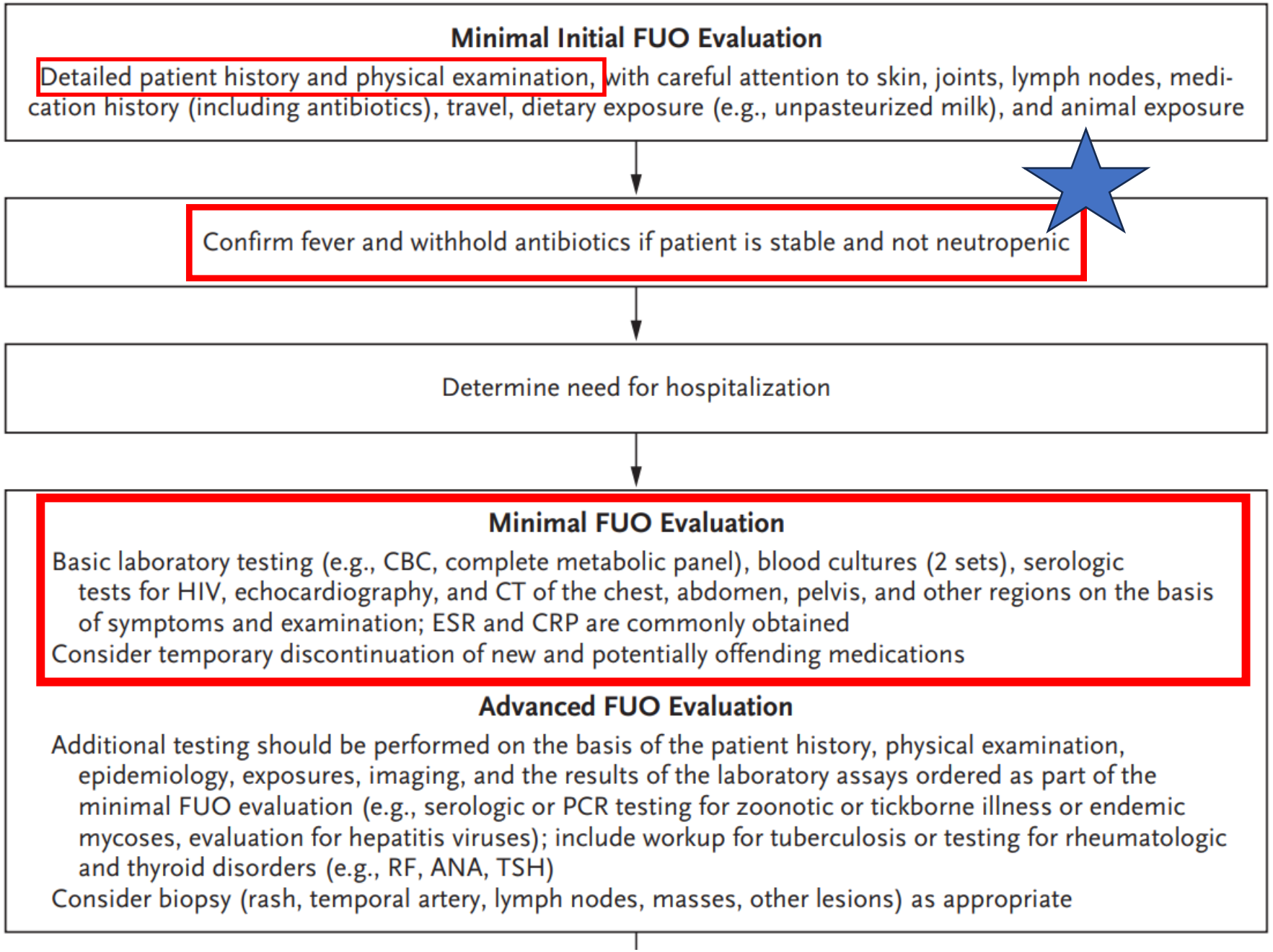
HarrisLF, HoldsambeckHK. Drug fever : surprisinglycommonand costly.Ala Med 1986;56:19–22
Johnson DH, Cunha BA. Drug fever. Infect Dis Clin NorthAm1996;10:85–91
Tabor PA. Drug-induced fever. Drug Intell Clin Pharm1986;20:413–20
Tisdale JE, Miller DA. Drug-induced diseases:prevention, detection, and management.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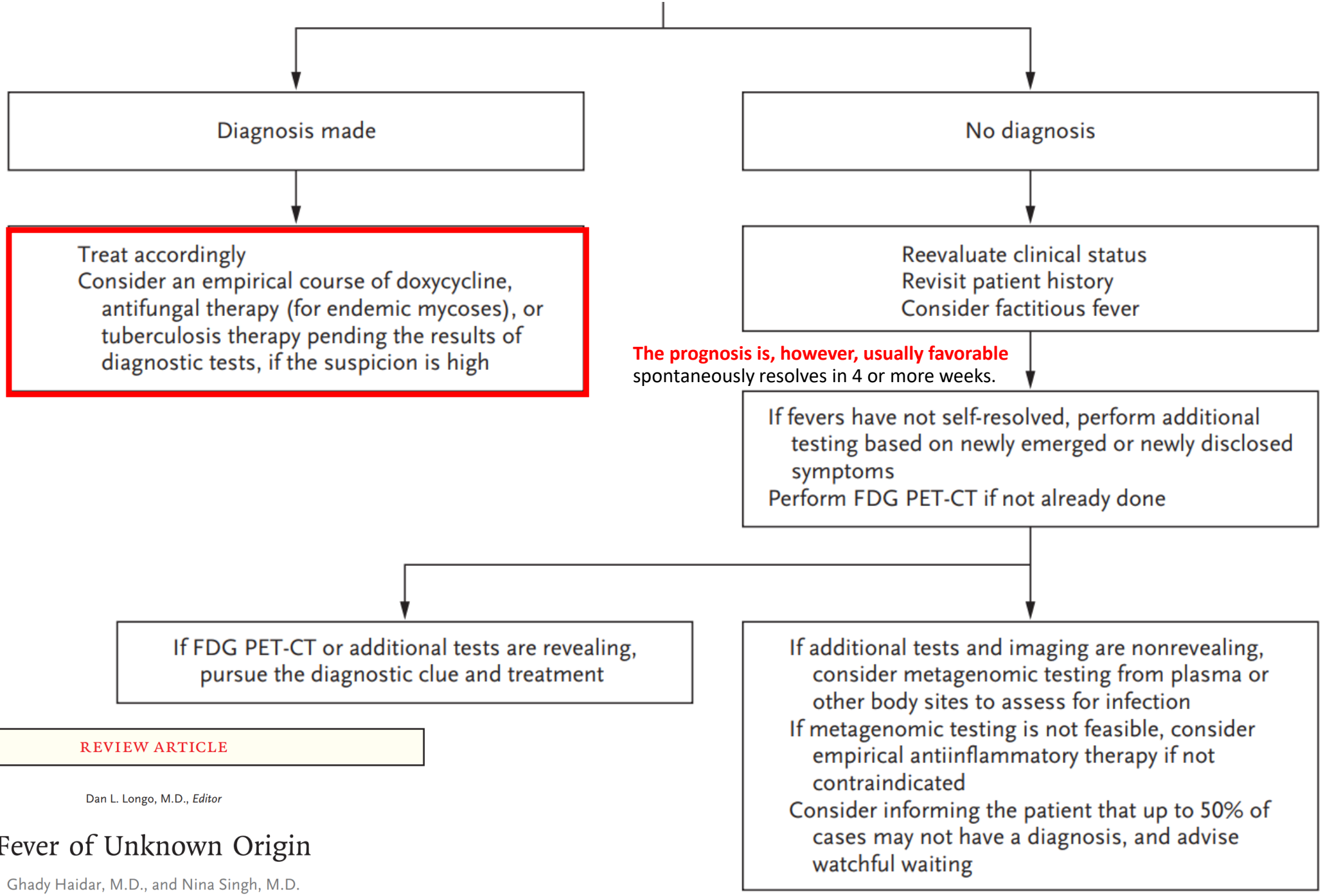

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Management

- **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.

Rate of TB Infection in Thailand (2021)

Thailand Operational Plan
To End Tuberculosis, Phase 2
(2023 - 2027)

- In 2021, Thailand had an estimated tuberculosis incidence of 143 cases per 100,000 persons in the general population, (decreased from 150 in 2018).
  - 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 7.6% **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.

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**

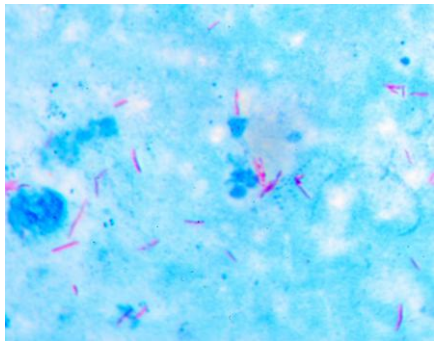
Cannot distinguish dead or viable organism

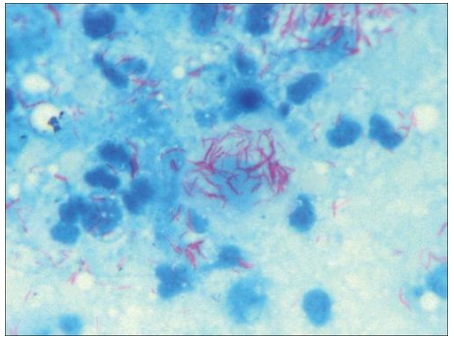
WHO recommendation since 2013 for the use of rapid molecular tests as the initial TB test for all

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.

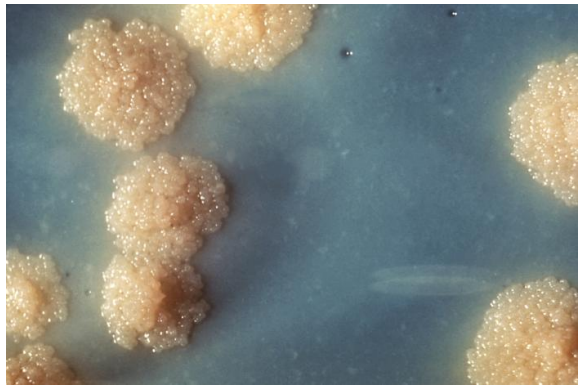
Study	# positive smears	% of total positives detected by:		
		1st smear	2nd smear	3rd smear
Ipuge et al. [25]	11,650	83.4	12.2	4.4
Nelson et al. [26]	53	77.4	15.1	7.5
Walker et al. [27]	166	77.1	15.0	7.9
Mathew et al. [28]	19	89.4	5.3	5.3
Wilmer et al. [29]	64	89.1	7.8	3.1
Khogali et al. [30]	60	93	5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

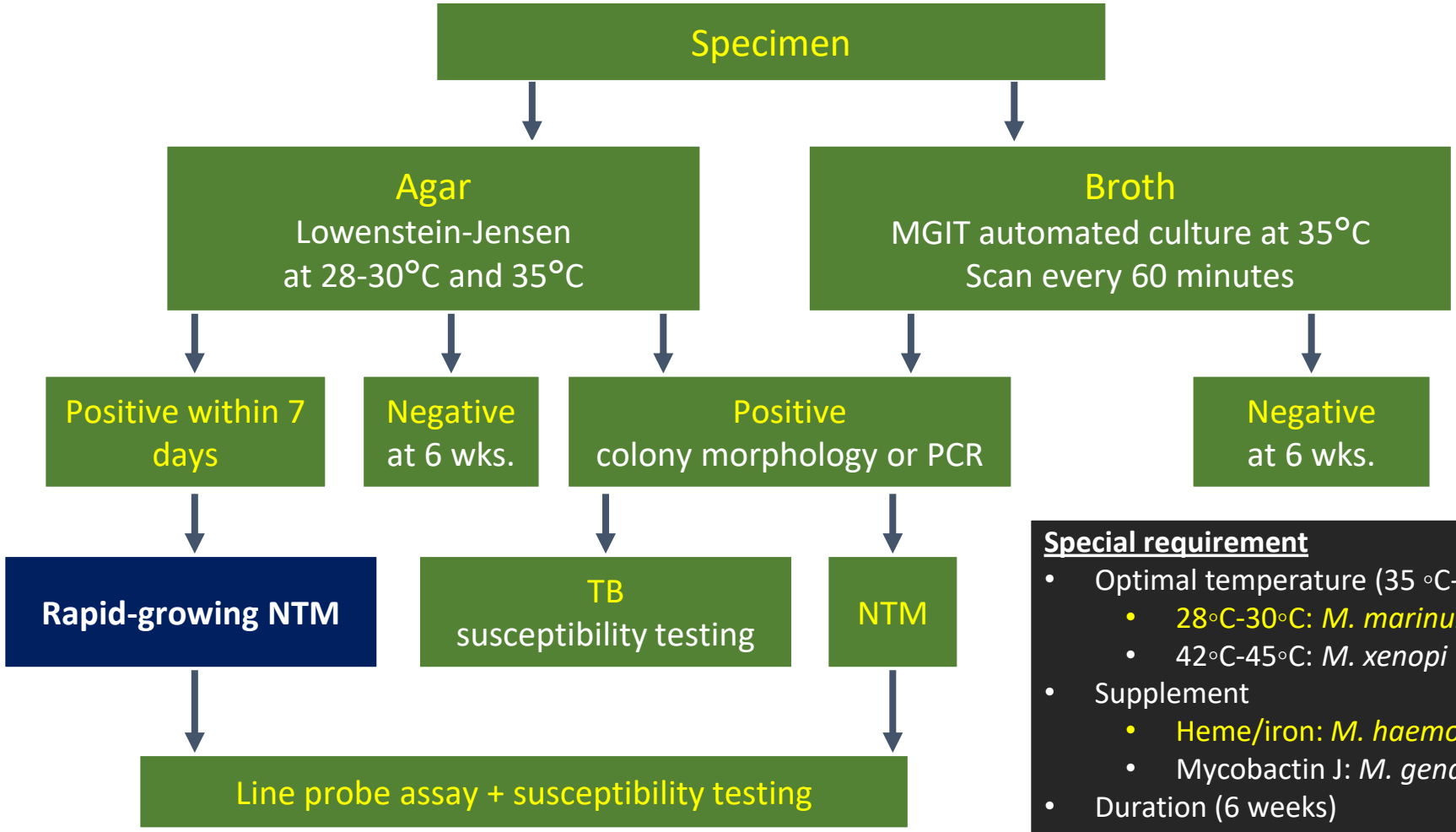


Liquid media (broth) (~2 wks.)

- 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*

Rapid molecular test	Sensitivity* (sputum)[35]	Specificity* (sputum)[36]	Cost (USD)	Manufacturer	WHO recommendation[37]
Xpert MTB/RIF	MTB: 85% RIF: 96%	MTB: 98% RIF: 98%	$10[38]	Cepheid	Xpert MTB/RIF and Xpert MTB/RIF Ultra are recommended as the initial tests for pulmonary and extrapulmonary TB and rifampicin resistance in adults and children.
Xpert MTB/RIF Ultra	MTB: 90% RIF: 94%	MTB: 96% RIF: 99%	$10[39]	Cepheid	
Truenat MTB**	MTB: 73%	MTB: 98%	$9[40]	Molbio	Truenat MTB, MTB Plus, and MTB-RIF Dx are recommended as the initial tests for pulmonary TB and rifampicin resistance in adults and children.
Truenat MTB Plus**	MTB: 80%	MTB: 96%	$12[41]	Molbio	
Truenat MTB-RIF Dx**	RIF: 84%	RIF: 97%	N/A (included in the price of MTB chips)	Molbio	

Hints

- Xpert MTB/RIF Ultra (10-100 organisms/mL)
- Pulmonary (any smear) and extrapulmonary
- Detect RR (94-99%)
- MTB vs NTM

*Accuracy estimates for pulmonary TB using the microbiological reference standard (MRS); see Box 5 below for Xpert MTB/RIF and Xpert MTB/RIF Ultra accuracy estimates for extrapulmonary TB and children
**Truenat sensitivity and specificity based on limited data including results from the microscopy center level

Abbreviations:
MTB: *Mycobacterium tuberculosis*; RIF: rifampicin

Xpert MTB/RIF and Xpert MTB/RIF Ultra

MTB complex and *rpoB* detection

Recommendation

- initial test for TB and rifampicin resistance
- pulmonary and extrapulmonary (~50% in pleural)
- Xpert MTB/RIF Ultra is a more sensitive but less specific test (due to additional probes capable of detecting very small concentrations)
- requires air-conditioned temperatures ≤ 30°C, limiting its use closer to the point-of-care.

WHO Xpert MTB/RIF Implementation manual 2014.
Dheda K, et al. Respirology. 2013 Feb;18(2):217-32.

In adults and children with signs and symptoms of extrapulmonary TB, Xpert Ultra may be used in lymph node aspirate and lymph node biopsy as the initial diagnostic test rather than smear microscopy/culture

People with extrapulmonary TB

The WHO recommends using rapid molecular tests Xpert MTB/RIF and Xpert MTB/RIF Ultra for extrapulmonary TB in samples including

- cerebrospinal fluid specimens
- lymph node aspirate (low certainty)
- lymph node biopsy
- pleural fluid (moderate certainty, Xpert MTB/RIF 50%, Ultra 71%)
- urine (low certainty)
- synovial fluid (low certainty, Xpert MTB/RIF 97%)
- peritoneal fluid (low certainty)
- pericardial fluid (very low certainty)
- blood

Xpert MTB/RIF Ultra sensitivity ranges from 71% for pleural fluid to 100% for urine, and its specificity also ranges from 71% for pleural fluid to 100% for urine.

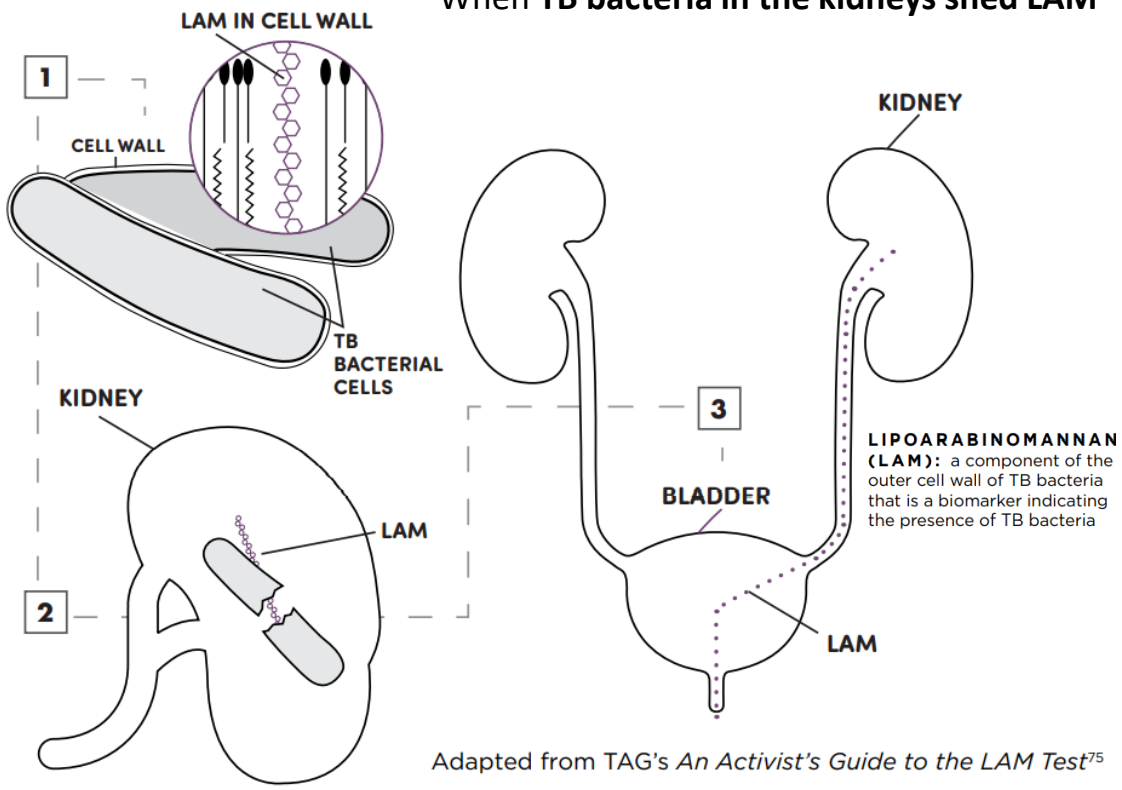
Main sample types testing positive for TB (n)	Gold standard for TB diagnosis	Xpert sensitivity, % (95% CI)	Xpert specificity, % (95% CI)	Ref.
Tissue biopsies/fine-needle aspirates (94); pleural fluid (18); gastric aspirates (61); pus (55); CSF (14); urine (16); peritoneal/ synovial/pericardial fluid (10)	Culture (solid and liquid) or suggestive radiology/ histology with documented positive response to TB treatment	81.3 (76.2–85.8)	99.8 (99.4–100)	[5]
LNs (16); pleural (7); bone (5)	Culture (solid and liquid media)	53.1 (34.7–70.9)	NA	[6]
Tissue biopsies (18); CSF (6); gastric aspirates (8); pleural fluid (4); purulent exudates (5)	Culture (solid and liquid media)	95.1 (83.5–99.4)	100 (98.8–100)	[7]
Pleural fluid (25)	Culture (liquid media)	25.0 (8.7–49.1)	100 (47.8–100)	[8]
Tissue (30); gastric aspirate (8); urine (5)	Culture (solid and liquid media)	77.3 (60.5–87.1)	98.2 (96.0–98.9)	[9]
Fine-needle aspiration LN biopsy	Composite standard: positive cytology + AFB and/or culture of MTB	96.6 (86.6–100)	88.9 (69.6–100) (note: only 18 samples)	[10]
All smear-negative. Pleural fluid (26); LNs (34); abscess aspirates (17); tissues (12)	Culture (solid and liquid media)	58.3 (48.5–67.8)	100 (91.4–100)	[11]
Tissue biopsies (105); pus (98); body fluids (24)	Composite of smear, culture, clinical, radiology and histology	80.6 (75.5–85.0)	99.6 (97.8–100)	[12]

Expert Rev Anti Infect Ther. 2012 June ; 10(6): 631–635.

World Health Organization. WHO consolidated guidelines on tuberculosis. Module 3: diagnosis - rapid diagnostics for tuberculosis detection.

Urine LAM tests to support rapid TB diagnosis among PLWHA

Disseminated TB, or TB spread throughout the body
When **TB bacteria in the kidneys shed LAM**



Adapted from TAG's *An Activist's Guide to the LAM Test*[75]

Urine LAM tests detect the TB biomarker LAM, **a component of the outer cell wall of TB bacteria.**

- The urine lipoarabinomannan (LAM) test is a rapid point-of-care TB test for use among PLWHA.
- only TB test that has been shown to reduce deaths.
- LAM testing uses urine as a sample, which is easily obtainable for PLWHA with advanced HIV disease

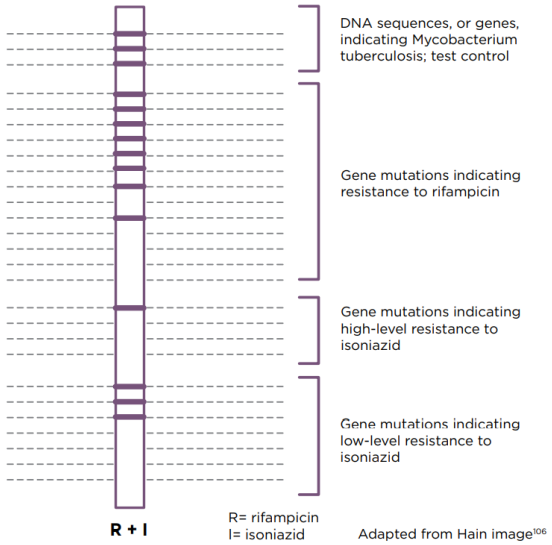
Hints

- disseminated infection
- **AIDS (CD4 < 100)**
- Sn 56%, Sp 93.6%
- **reduced mortality**

Trans R Soc Trop Med Hyg. 2016 Mar; 110(3):180–5.

Line probe assays (LPA)

- In 2016, the WHO recommended the use of line probe assays (LPAs) as the initial DST for first- and second-line TB drugs—rather than liquid culture—because LPAs are highly accurate and rapidly produce results within one day
- LPAs recommended by the WHO include
  - Hain's GenoType MTBDRplus Version 2.0 and Nipro's Genoscholar NTM+MDRTB II that test for resistance to first-line drugs **rifampicin and isoniazid**
  - Hain's GenoType MTBDRsl Version 2.0 that tests for resistance to the **fluoroquinolones** and to second line injectable agents, such as **amikacin.**



World Health Organization. The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin.
World Health Organization. The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs.

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

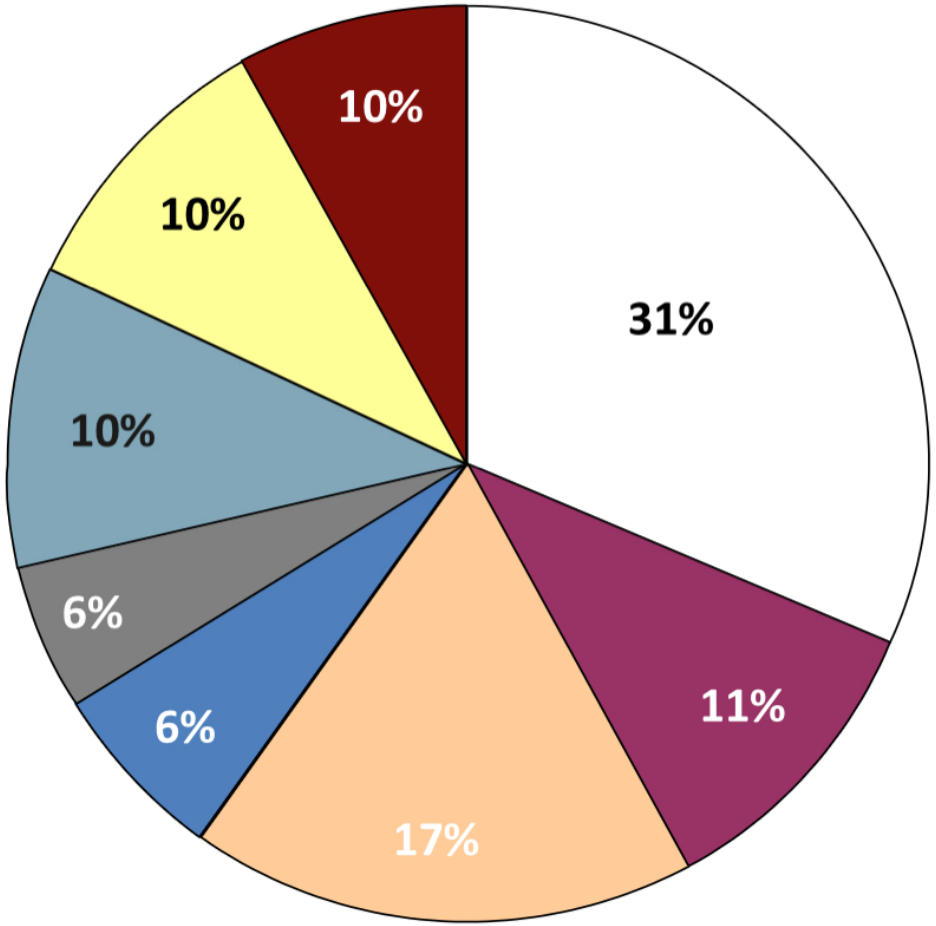
ตารางที่ 5.3 ระยะเวลาการรักษาวัณโรคในผู้ติดเชื้อเอชไอวี

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

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

Groups matter?

- sanguinis, mutans, bovis*, *Abiotrophia*
- mitis*, *Granulicatella, Aerococcus urinae*
- anginosus, salivarius, *S. dysgalactiae, S. agalactiae*
- *S. pyogenes, S. pneumoniae*

*might differ for some species

Top reasons for culture negative IE (5-15%)

- Prior antimicrobial therapy (33-50%)
- Fastidious microorganisms
- Uncultivable microorganisms
- Emerging, undefined pathogens
- Chronic endocarditis
- Not infectious
- Not endocarditis

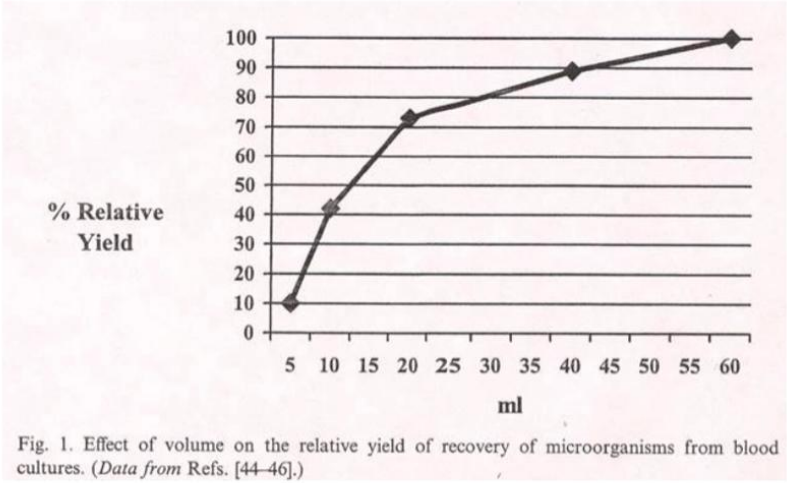


Fig. 1. Effect of volume on the relative yield of recovery of microorganisms from blood cultures. (*Data from* Refs. [44–46].)

Towns ML, Reller LB. Current best practices and guidelines for isolation of bacteria and fungi in infective endocarditis. Infect Dis Clin Am *2002;16:363-376.*

HACEK
- Median 3.4 days. No growth 10-14 days.
- Petti et al.

Brucella spp.
Abiotrophia spp.
Bartonella spp.
Legionella spp.

Hints (Extended culture)

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		

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

EUROPEAN SOCIETY OF CARDIOLOGY®

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.

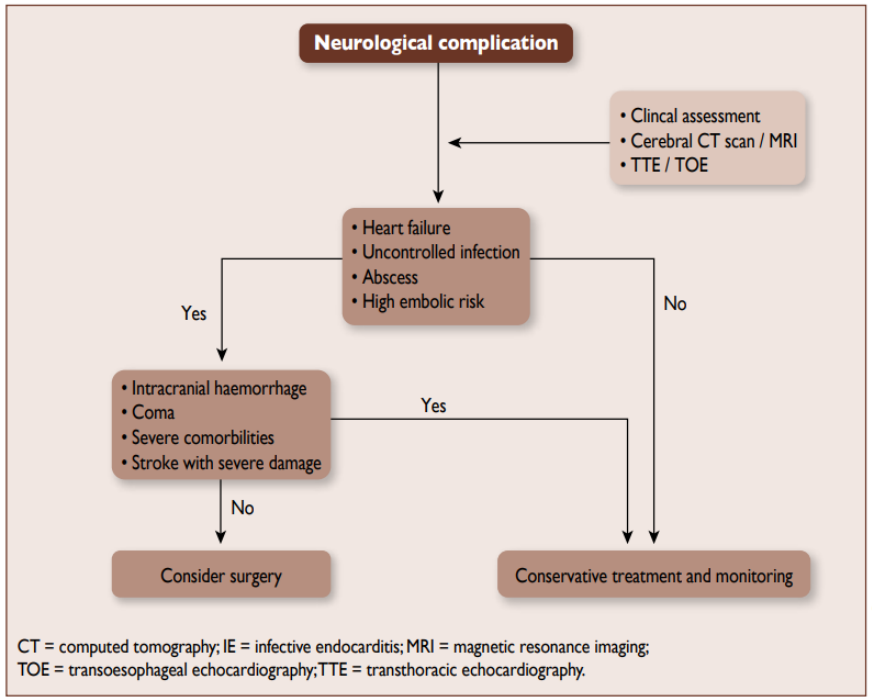
The three main indications for early surgery in IE are its 3 main complications, i.e. HF, uncontrolled infection, and prevention of embolic events.

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.

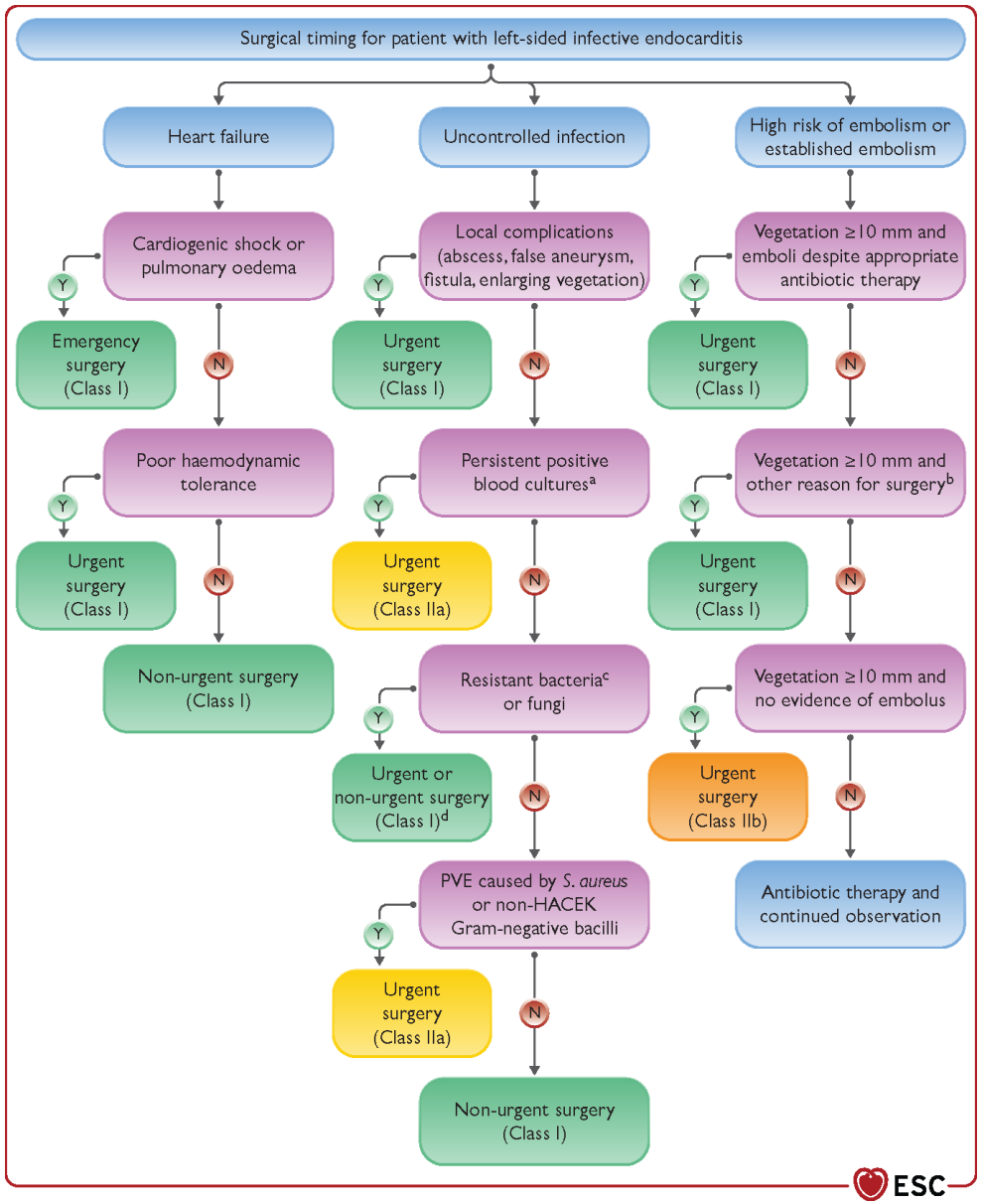
Therapeutic strategy for patients with IE and neurological complications



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

Figure 10

Proposed surgical timing for infective endocarditis



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(European Heart Journal; 2023 – doi: 10.1093/eurheartj/ehad193)

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).

Hints

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

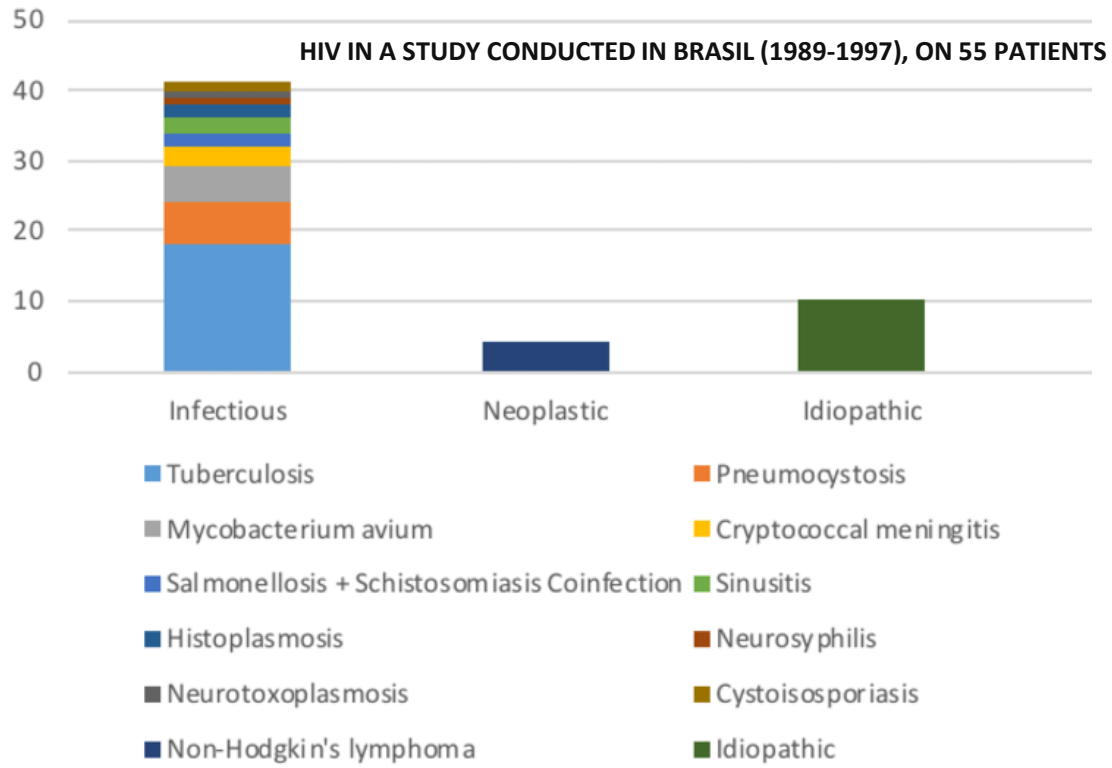
TABLE 128-8 Antibiotic Regimens for Prophylaxis of Endocarditis in Adults with High-Risk Cardiac Lesions[a,b]
A. Standard oral regimen
Amoxicillin: 2 g PO 1 h before procedure
B. Inability to take oral medication
Ampicillin: 2 g IV or IM within 1 h before procedure
C. Penicillin allergy
1. Clarithromycin 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).

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%)



Case (2)

She had **travelled to Phuket** recently and recollected being bitten by mosquitoes. **She had history of recreational drug use and multiple sexual contact**, and she was not taking any regular medication.

Anti HIV (ELISA 4th gen.) : Reactive

Eur J Intern Med 2009;20: 474–7

Opportunistic infections (OIs)

Bacteria	Fungus	Mycobacterium	Virus	Parasites
• *Salmonella*	• *Cryptococcus*	• TB	• CMV	• *Toxoplasma*
• Rhodococcosis	• *Histoplasma*	• MAC	• JC virus	• *Cryptosporidium*
	• *Talaromyces*		• HHV-8	• *Cyclospora*
	• PCP			• *Cystoisospora*
	• *Microsporidium*			

CD4 cell count (cells/mm^3)	OIs
<50	• MAC, PCNSL, CMV, *cryptosporidium*
<100	• *Toxoplasma*, PML, *Talaromyces*, *Histoplasma*
<200	• *Cryptococcus*, PCP
Any	• SY, TB, bacterial infection

Hints

- 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

CDC

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

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)

Markers of immunosuppression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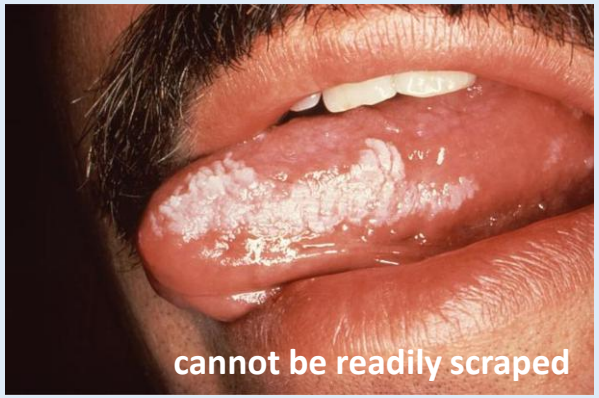
Oral candidiasis

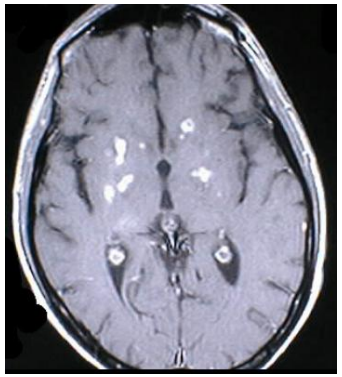


Oral hairy leukoplakia

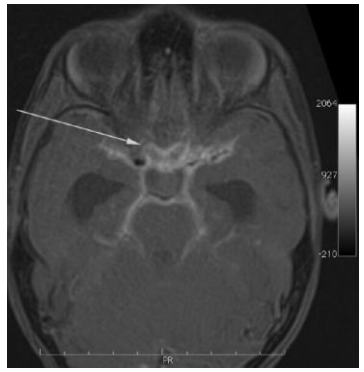
N Engl J Med. 1987;316:61–66.

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

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

CMV disease (CNS)

Ventriculoencephalitis

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

Polyradiculopathy

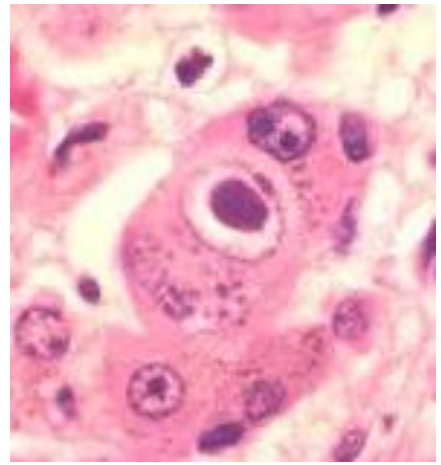
- Progressive lower extremity weakness (~GBS),pain, spasticity, areflexia, urinary retention & hypoesthesia
- CSF finding: PMN pleocytosis and low glucose level

Diagnosis

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

Treatment early with GCV and foscarnet

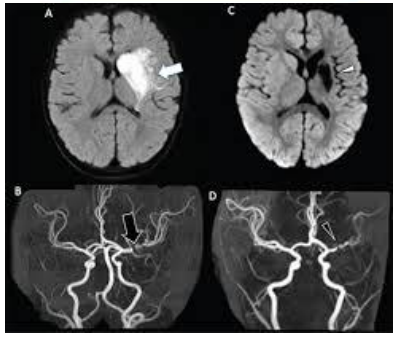
- No clinical trials, but found some poor respond with GCV alone

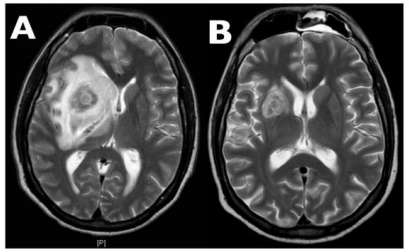


"owl eye" morphology

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

Pulmonary opportunistic infections

- The immune dysregulation associated with HIV results in an increased incidence of respiratory infection at all CD4 T-cell counts.
  - Early reports of the dramatic increased risk of PCP in advanced HIV disease have tended to overshadow the finding that other respiratory pathogens
- The widespread use of prophylaxis against opportunistic infections together with HAART has **reduced the risk of life-threatening infection**

- It has **not returned to the background** levels present in HIV-sero negative populations

BHIVA Guideline 2011

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

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

Relevant factors include;

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

1. Patient use of **effective OI prophylaxis or HAART**
2. Recent discharge from hospital or current hospital admission 45 days (nosocomial infections)
3. Country/place of residence and travel history
4. History of active injecting drug use
   - since these individuals are at increased risk of bacterial pneumonia and TB
5. **Level of host immunity (CD4)**
6. Neutropenia
7. Use of prolonged courses of immune modulators (e.g., corticosteroids).

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

Common radiographical appearances of pulmonary infections in HIV patients

Chest radiograph or CT abnormality	Acute or subacute onset	Chronic onset
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*	

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.

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

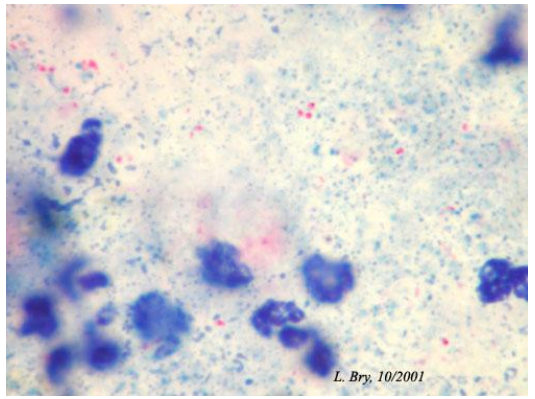
- Pulmonary (80%)
  - Subacute pneumonia (H/C pos 50%)
  - **CXR: TB-like disease; cavity** (single or multiple, thick wall, air-fluid level), nodules, infiltration, effusion (UL)
  - **Complications:** lung abscess, empyema, pneumothorax, mediastinitis
- Extrapulmonary (20%)
  - Disseminated disease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

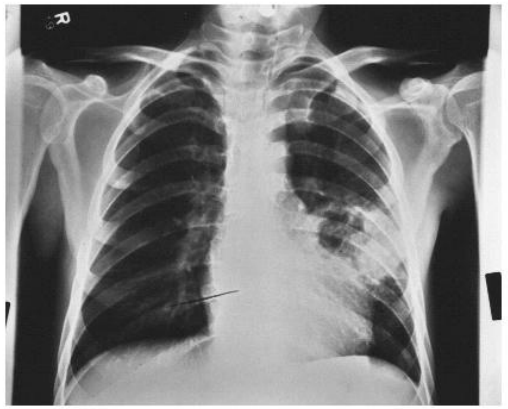
Immunocompromised, serious infection: at least 2 from the following

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.

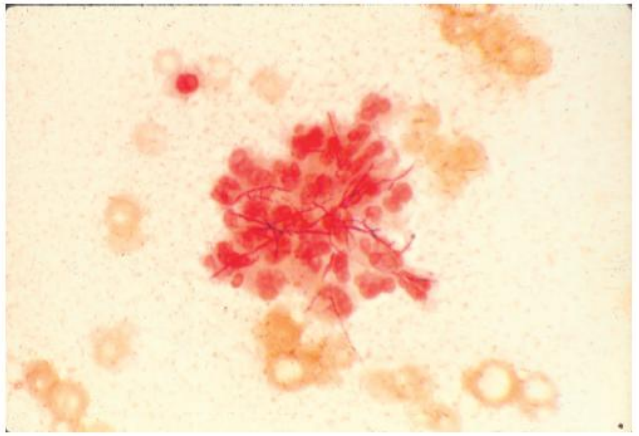
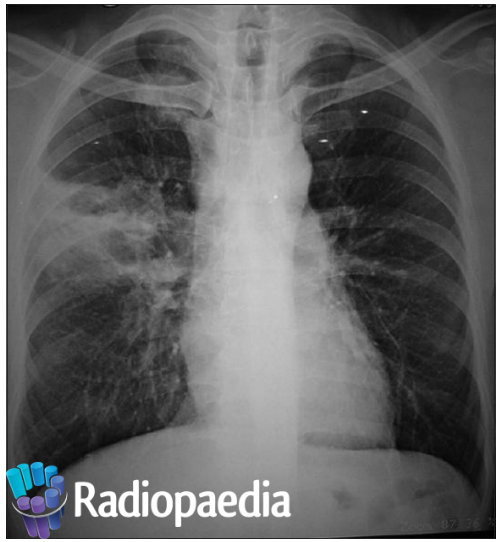


FIG. 253.1 **Pulmonary nocardiosis.** Photomicrograph of direct Gram-stained smear from a patient with pulmonary nocardiosis, showing typical branching rods.

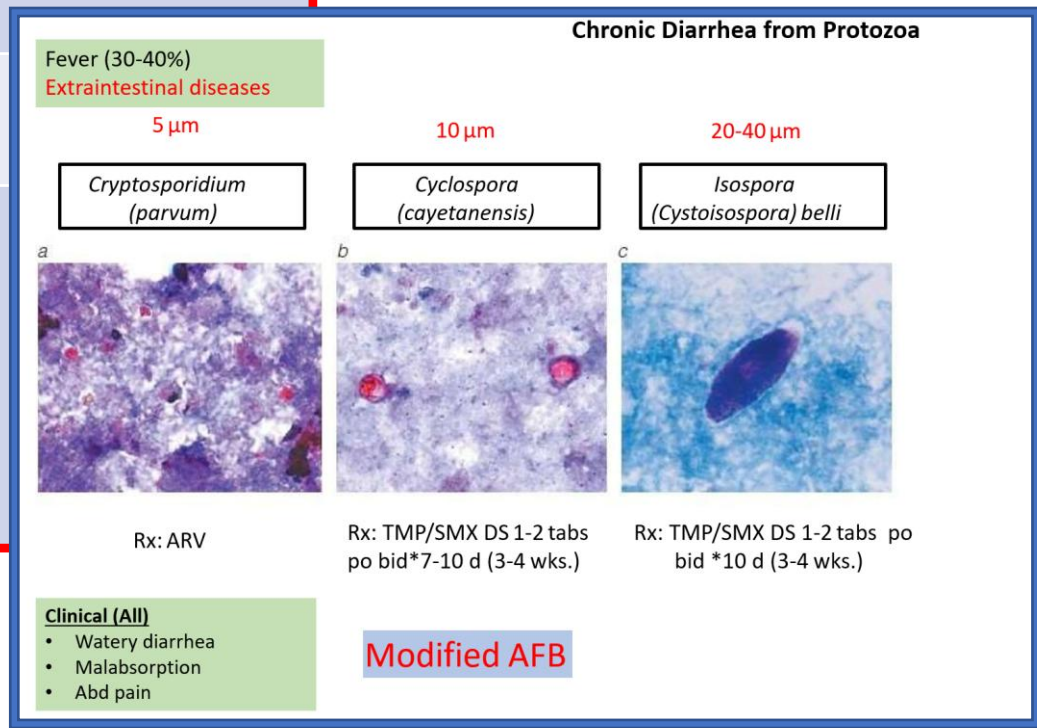


1. lobar or multilobar consolidation
   - abscess formation cavitation in 30%
2. solitary lung masses and/or nodules
3. reticulonodular infiltrates [9]
4. mediastinal or hilar lymphadenopathy is **not** a feature of nocardiosis

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 Penicilliosis

- **Cellular immunity**
- **Dimorphic fungi**
  - Yeast at 37°C
  - Mold at 25- 30°C
- Penicilliosis
  - *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: penicilliosis (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%)

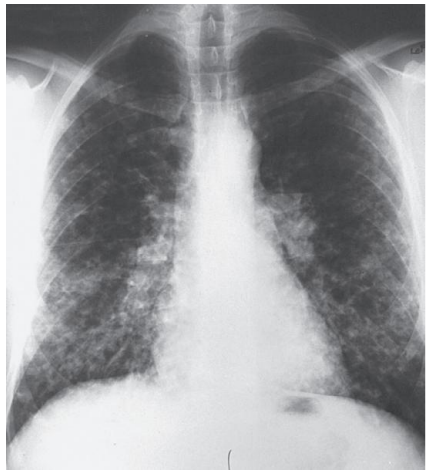
TABLE 263.1 Spectrum of *Histoplasma capsulatum*–Induced Disease

MANIFESTATIONS	ACUTE PULMONARY DISEASE	CHRONIC CAVITARY PULMONARY DISEASE	PROGRESSIVE DISSEMINATED DISEASE
Clinical	Often asymptomatic	Fever, productive cough, chest pain	Fever, weight loss, hepatosplenomegaly, hematologic disturbances[a]
Immunologic			
Positive skin test	>90%	70%–90%	30%–55%
Lymphocyte transformation	+++	+ to +++	±
Antibody to *Histoplasma capsulatum*[b]	25%–85%[c]	75%–95%	70%–90%
Antigenuria	20%[c]	40%	60%–90%
Pathologic			
Positive culture from lungs	<25%	5%–70%	50%–70%
Histology	Caseating and noncaseating granulomas, few yeasts, giant cells	Noncaseating granulomas, interstitial fibrosis, necrosis, yeasts, cavities, few to moderate yeasts	Diffuse macrophage proliferation, abundant few giant cells

Cavitary lesions were found in the **upper lobes (90%)**

8% of clinically recognized cases

- **Acute** – infants, immunocompromised
- Subacute
- Chronic – normal adults



Pulmonary Histoplasmosis

ACUTE PULMONARY HISTO: usually asymptomatic or an influenza-like illness, but can be severe

- Most symptoms **resolve within 10 days**
- Acute pulmonary infection can be accompanied by several **rheumatologic** manifestations.
  - Arthralgias, **erythema nodosum, and erythema multiforme** are present in approximately **6%**

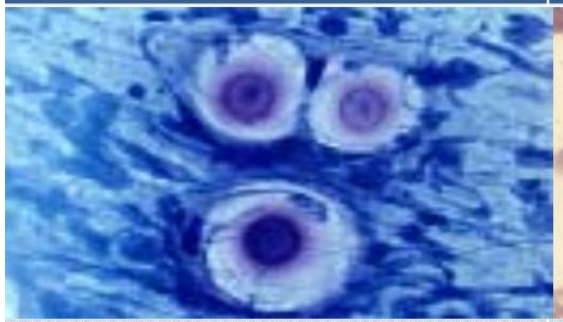
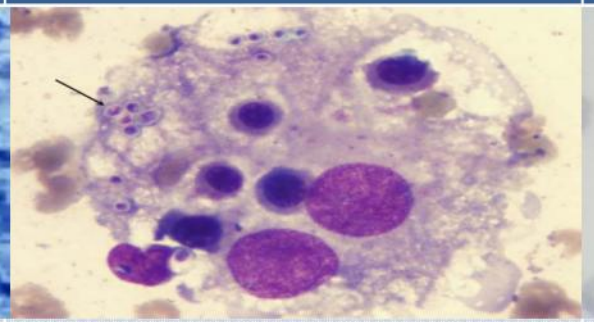
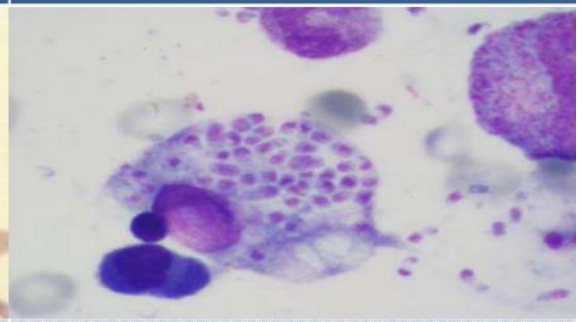
Disseminated Histoplasmosis

Can be new exposure or reactivation disease. Progressive disseminated disease most common in older patients, persons with HIV/AIDS, solid organ transplant recipients, those on TNF-alpha antagonists

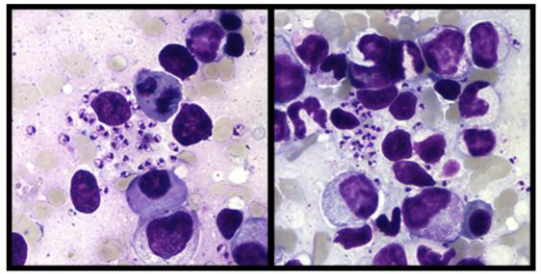
- The major risk factors manifestation of histoplasmosis **age older than 54 years and immunosuppression.**
- **GI (70%), adrenal (10%), CNS (5-20%) and skin (10%)**

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?)

Cryptococcosis	Histoplasmosis	Penicilliosis
		
Extracellular, large round encapsulated yeast cells with or without budding, varying in size	Intracellular or extracellular, monomorphous small round to oval yeast cells Small (2–5 µm) narrow **budding yeasts** of *H. capsulatum*	Intracellular or extracellular, small round to oval yeast cells and sausage or elongated forms, with transverse or central clear septum

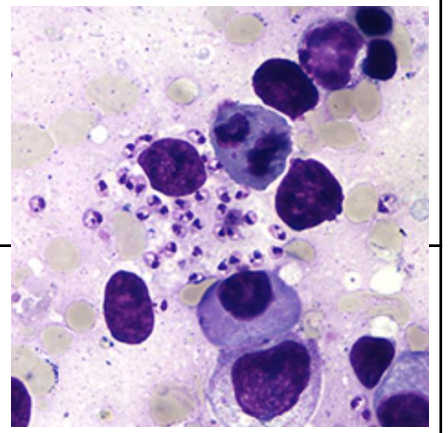
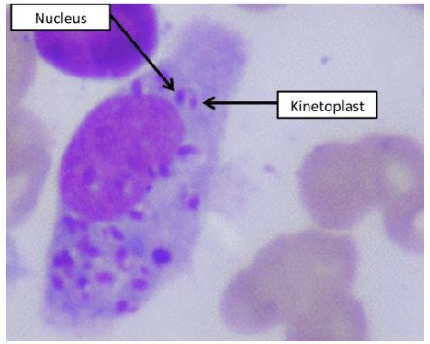
Serum LDH levels higher than 600 IU/mL are highly likely to have disseminated histoplasmosis.
Elevated serum ferritin levels are strongly suggestive of histoplasmosis.



Leishmania amastigotes in bone marrow biopsy specimens from patients with visceral leishmaniasis. Note the nucleus and kinetoplast in each amastigote.

Hints (Leishmania, southern part, Thailand)
- HIV (risk visceral form)
- **Splenomegaly**
- Cytopenia
- Yield > Splenic > **BM aspiration**
- PCR / Culture (Gold standard)
- Rx L-AmB

Clin Microbiol Rev. 2007;20:115–132.

	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?)	

Treatment of Histoplasmosis (disseminated)

OIs	Induction phase	Consolidation phase	Maintenance phase
Histoplasmosis or Penicillosis	Ampho B 0.6-0.7 MKD for 7-14 d	10-12 wks (Loading 600 mg/d x 3 d then 400 mg/d)	Itraconazole 200 mg/d, CD4 ≥100 (penicilliosis) or ≥ 150 (histoplasmosis) for 6 mo

Within 1 to 2 weeks, most patients are symptomatically, and laboratory improved

Mild to moderate disease

Start with itraconazole 400 mg/d

not associated with hemodynamic instability or severe illness

- **Itraconazole is contraindicated in pregnancy**
- **Capsule (with food)**
- **Solution (with fasting)** cyclodextrin oral liquid formulation increases absorption by 50%
- **TDM~ keep itraconazole level >1 mg/L**

PREVENTION

Prophylaxis of Immunocompromised Persons

For immunosuppressed patients who have a high risk of acquiring histoplasmosis from the environment because of their work or their residence, itraconazole, 200 mg/day, is useful. Such patients would include those with AIDS whose CD4 cell count is less than 150/μL or those who require potent immunosuppressive therapy. In the former group, prophylaxis with itraconazole reduced the incidence of infection by more than twofold. Another indication for prophylaxis in immunosuppressed patients would be residence in an area that has a high incidence of infection, as defined by at least 10 cases per 100 patient-years.[84]

Thai guideline

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

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

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

Hints : favor azithromycin

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

WHICH REGIMEN (S)

Prevent
AIDS event
- Infection : TB
- CA : Lymphoma, KS

Non-AIDS event
Prevent transmission

ตารางที่ 2.4 สูตรยาต้านเอชไอวีที่แนะนำเป็นสูตรแรกและสูตรทางเลือก

NRTIs backbone
แนะนำ
(TDF หรือ TAF) ร่วมกับ (3TC หรือ FTC)
หรือทางเลือก
ABC + 3TC
AZT + 3TC

+

ยาตัวที่ 3
แนะนำ
DTG[1]
หรือทางเลือก
EFV หรือ RPV

[1] ควรใช้ยารวมเม็ด

ตารางที่ 2.5 คำแนะนำการใช้ยาสูตรสองตัว กรณีไม่สามารถหายาสูตรสามตัวที่เหมาะสมได้

ยา	คำแนะนำ
DTG+3TC[1]	• ใช้ในกรณีไม่สามารถหายาสูตรสามตัวที่เหมาะสมได้ เช่น มีโรคไต ไม่สามารถใช้ TDF หรือ TAF ได้ • โดยควรพิจารณาใช้ในกลุ่มที่ - HBs Ag – negative และ - Baseline VL < 500,000 copies/mL หรือ CD4 > 200 cell/mm^3 และ - ไม่มีการดื้อต่อ 3TC

ควรเริ่มยาต้านเอชไอวีภายในวันเดียวกันกับวันที่วินิจฉัย (same day ART) หรือกรณีที่ทำไม่ได้ควรพิจารณา เริ่มยาต้านเอชไอวีโดยเร็วที่สุด ภายในเวลา 7 วัน (rapid ART)

Essential side effects of ARV

- **NNRTI**
  - NVP > EFV – SJS/TEN (NVP: Fulminant hepatitis)
- **NRTI**
  - ABC – Hypersentivity reaction (HLA B*5701)
  - AZT - BM suppression (High MCV),myopathy
  - TDF – Nephrotoxicity, osteoporosis, Fanconi syndrome
  - ddI – Pancreatitis
  - d4T, AZT – DM, insulin resistance
  - d4T, ddI – Peripheral neuropathy
- **PIs**
  - IDV/ATV – Nephrolithiasis (GS : ATV/r)
  - Pis – Hyperlipidemia (LPV/r)
  - Pis – MI & CVA, Increased Bleeding in Hemophilia

When to Start ARV in Ois

Hints : ARV
- 2 wks. after treatment ois except CNS ois 4-6 wks. (CNS IRIS)

ตารางที่ 2.7 ระยะเวลาเริ่มยาต้านเอชไอวีภายหลังรักษาโรคติดเชื้อฉวยโอกาส

โรคติดเชื้อฉวยโอกาส	ระยะเวลาเริ่มยาต้านเอชไอวี
วัณโรคทุกระดับ CD4	เริ่มภายใน 2 สัปดาห์ อย่างช้าไม่เกิน 4 สัปดาห์
วัณโรคระบบประสาท	เริ่มหลังรักษาวัณโรคระบบประสาท แล้วอย่างน้อย 4 สัปดาห์ อย่างช้าไม่เกิน 8 สัปดาห์
Cryptococcal meningitis	ระหว่าง 4-6 สัปดาห์
Non-CNS Cryptococcosis	ระหว่าง 2-4 สัปดาห์
Cerebral toxoplasmosis	ระหว่าง 2-4 สัปดาห์
โรคติดเชื้อ cytomegalovirus	ชะลอการเริ่มยาต้านเอชไอวีได้ 2 สัปดาห์ โดยเฉพาะผู้ป่วยที่มี chorioretinitis และ encephalitis
โรคติดเชื้อฉวยโอกาสอื่น ๆ	เร็วที่สุดภายใน 2 สัปดาห์

Which ARV ? (Rifampicin)

ตารางที่ 5.11 สูตรยาต้านเอชไอวีหลังเริ่มยาวัณโรคในผู้ใหญ่

การรักษาวัณโรค	คำแนะนำสูตรยาต้านเอชไอวี
กรณีที่ไม่มียา rifampicin ในสูตรยารักษา วัณโรค	• ให้พิจารณาเริ่มสูตรยาต้านเอชไอวีตามปกติ
กรณีที่มียา rifampicin ในสูตรยารักษาวัณโรค	• เริ่มสูตรยาต้านเอชไอวีด้วยยาในกลุ่ม NRTIs 2 ชนิด ร่วมกับเลือกใช้ยาชนิดที่ 3 ดังนี้ 1. EFV 400-600 มก. วันละครั้ง หรือ 2. DTG 50 มก. วันละ 2 ครั้ง
* Rifampicin ทำให้ระดับยาของ TAF ลดลง ยังมีข้อมูลจำกัดเรื่องปฏิกิริยาระหว่างยาที่อาจมีผลต่อระดับยา TAF ยังไม่แนะนำให้ใช้ TAF ร่วมกับ rifampicin จนกว่าจะมีข้อมูลมากกว่านี้	

STOP OIs Prophylaxis

1. Asymptomatic
2. Sustained CD4 response
3. On ART with sustained viral suppression
4. Completed course of treatment

ตารางที่ 5.19 สรุปเกณฑ์ CD4 ในการหยุด Primary และ Secondary Prophylaxis ของโรคติดเชื้อฉวยโอกาสในผู้ใหญ่

โรคติดเชื้อฉวยโอกาส (Opportunistic Infections)	การป้องกันโรคแบบปฐมภูมิ (Primary prophylaxis)	การป้องกันโรคแบบทุติยภูมิ (Secondary prophylaxis)
PCP	• CD4 > 200 cells/mm^3 นานกว่า 3 เดือน • CD4 100-200 cells/mm^3 แต่มี HIV VL undetectable นานกว่า 3-6 เดือน	• CD4 > 200 cells/mm^3 นานกว่า 3 เดือน • CD4 100-200 cells/mm^3 แต่มี HIV VL undetectable นานกว่า 3-6 เดือน
Cryptococcosis	หยุดยาได้เมื่อเริ่มรักษาด้วยยาต้านเอชไอวี	• ได้รับ secondary prophylaxis อย่างน้อย 1 ปี และ CD4 ≥ 100 cells/mm^3 นานกว่า 3 เดือน และ HIV VL undetectable
Candidiasis	-	ได้รับยาต้านเอชไอวีจนมีจำนวน CD4 > 200 cells/mm^3
Toxoplasmosis	• CD4 > 200 cells/mm3 นานกว่า 3 เดือน • CD4 100-200 cells/mm3 แต่มี HIV VL undetectable นานอย่างน้อย 3-6 เดือน	CD4 > 200 cells/mm^3 นานกว่า 6 เดือน
Talaromycosis/ Histoplasmosis	หยุดยาได้เมื่อเริ่มรักษาด้วยยาต้านเอชไอวี	• CD4 > 100 cells/mm^3 (สำหรับ talaromycosis) และ > 150 cells/mm^3 (สำหรับ histoplasmosis) นานกว่า 6 เดือน • HIV VL undetectable นานกว่า 6 เดือน
MAC	หยุดยาได้เมื่อเริ่มรักษาด้วยยาต้านเอชไอวี	ได้รับการรักษา MAC อย่างน้อย 12 เดือน และไม่มีอาการของโรค และ CD4 > 100 cells/mm^3 นานกว่า 6 เดือน
CMV retinitis	Not applicable	ได้รับการรักษา CMV retinitis นานกว่า 3-6 เดือน และ CD4 > 100 cells/mm^3 อย่างน้อย 3-6 เดือน

สรุปเกณฑ์ CD4 ในการหยุด primary และ secondary prophylaxis

2.13 การสร้างเสริมภูมิต้านทานด้วยวัคซีน

ผู้ใหญ่ที่ติดเชื้อเอชไอวีมีโอกาสเสี่ยงเป็นโรคติดเชื้ออื่น ๆ ที่สามารถป้องกันได้ด้วยการฉีดวัคซีน แต่ภาวะภูมิคุ้มกันบกพร่องที่เกิดขึ้นในผู้ติดเชื้อที่มีจำนวน CD4 ต่ำ อาจทำให้การตอบสนองต่อวัคซีนบางชนิดลดลง อย่างไรก็ตามการให้วัคซีนในผู้ติดเชื้อเอชไอวีที่มีจำนวน CD4 สูง หรือปกติ หรือเมื่อรักษาด้วยยาต้านเอชไอวีจน CD4 เพิ่มขึ้น จะสามารถตอบสนองต่อวัคซีนได้เหมือนผู้ที่ไม่ได้ติดเชื้อเอชไอวี มีรายงานว่าการฉีดวัคซีนอาจกระตุ้นให้มีการเพิ่มขึ้นของจำนวนเชื้อเอชไอวีในกระแสเลือดชั่วคราว แต่ยังไม่มีหลักฐานว่าทำให้การดำเนินโรค เร็วขึ้นหรือแย่ลง เมื่อคำนึงถึงประโยชน์ที่จะได้รับจากการฉีดวัคซีนซึ่งมีมากกว่า จึงแนะนำการสร้างเสริมภูมิคุ้มกันโรคด้วยวัคซีน โดยยึดหลักการว่า ไม่ควรให้วัคซีนชนิดเชื้อเป็นอ่อนฤทธิ์ (live-attenuated vaccine) แก่ผู้ที่ติดเชื้อเอชไอวี แต่อาจพิจารณาให้วัคซีนบางชนิดได้ ถ้ามีจำนวน CD4 มากกว่า 200 เซลล์/ลบ.มม. และได้รับการรักษาด้วยยาต้านเอชไอวีแล้ว รวมถึงไม่มีโรคติดเชื้อฉวยโอกาสที่เพิ่งได้รับการรักษา (active)

วัคซีนชนิดเชื้อเป็นอ่อนฤทธิ์ ได้แก่ วัคซีนป้องกัน measles, mumps, rubella, varicella และ zoster live ไม่แนะนำให้วัคซีนเชื้อเป็นอ่อนฤทธิ์ในหญิงตั้งครรภ์ การฉีดวัคซีนเชื้อตาย (inactivated vaccine) สามารถให้พร้อมกันได้ ในครั้งเดียวมากกว่า 1 ชนิด ส่วนการฉีดวัคซีนชนิดเชื้อเป็นอ่อนฤทธิ์ สามารถให้พร้อมด้วยกันเอง หรือพร้อมกับวัคซีนเชื้อตายได้ แต่ถ้าไม่ได้ให้วัคซีนชนิดเชื้อเป็นอ่อนฤทธิ์มากกว่า 1 ชนิดพร้อมกัน ต้องเว้นระยะห่างอย่างน้อย 4 สัปดาห์

Conclusion : FUO

- **Initial evaluation** reveals diagnostic clues that strongly support certain diagnosis
- **High quality diagnostic workup** after reasonable amount of time (rule out self-limited fevers)
- **Clinical judgment** should be used in deciding whether to pursue **therapeutic challenges**

GOOD LUCK IN YOUR EXAMS!

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

Prophylactic antibiotic regime for high-risk dental procedures

Situation	Antibiotic	Single-dose 30–60 min before procedure	
		Adults	Children
No allergy to penicillin or ampicillin	Amoxicillin	2 g orally	50 mg/kg orally
	Ampicillin	2 g i.m. or i.v.	50 mg/kg i.v. or i.m.
	Cefazolin or ceftriaxone	1 g i.m. or i.v.	50 mg/kg i.v. or i.m.
Allergy to penicillin or ampicillin	Cephalexin	2 g orally	50 mg/kg orally
	Azithromycin or clarithromycin	500 mg orally	15 mg/kg orally
	Doxycycline	100 mg orally	<45 kg, 2.2 mg/kg orally >45 kg, 100 mg orally
	Cefazolin or ceftriaxone	1 g i.m. or i.v.	50 mg/kg i.v. or i.m.

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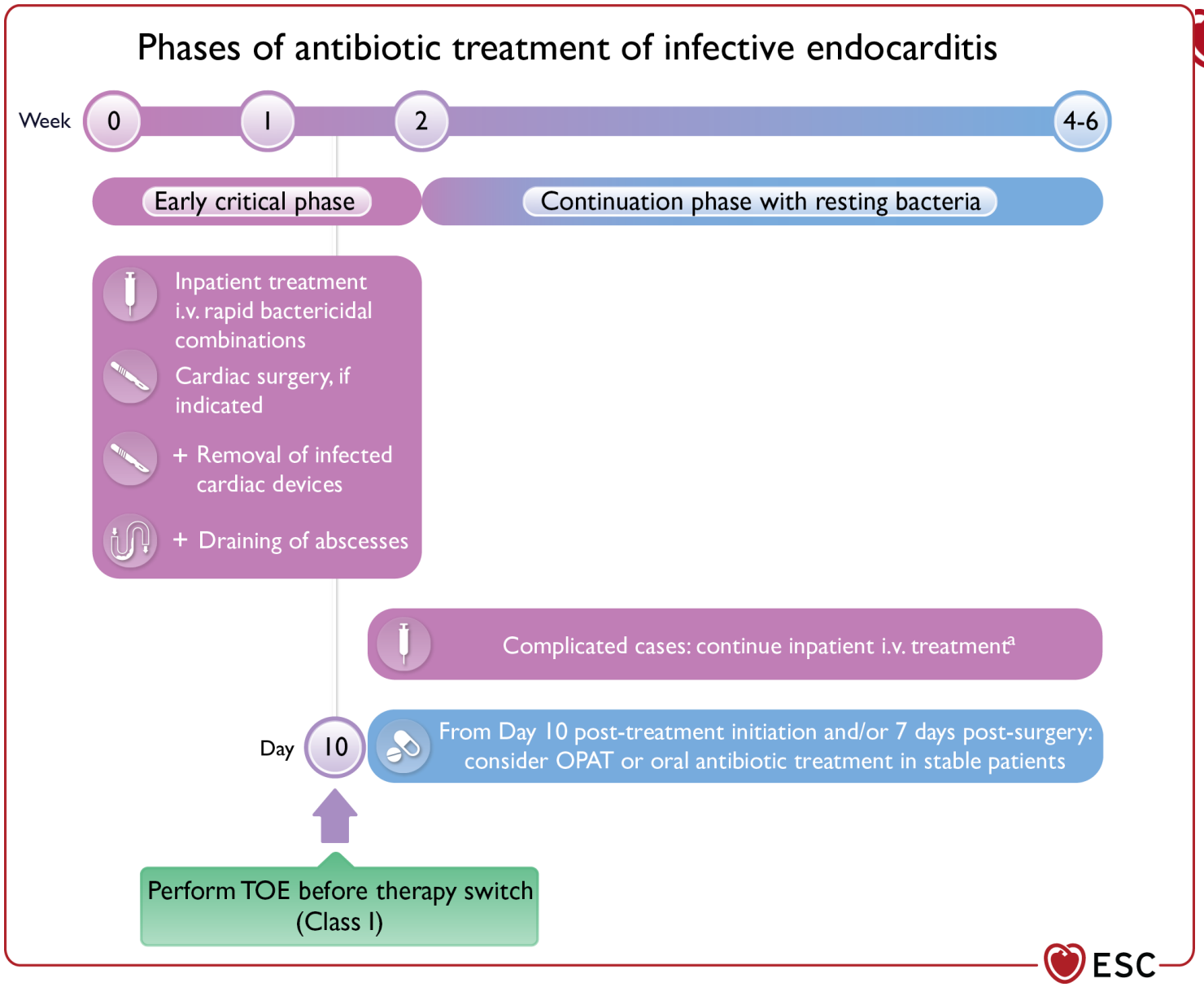
Figure 8

Phases of antibiotic treatment for infective endocarditis in relation to outpatient parenteral antibiotic therapy and partial oral endocarditis treatment



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Recommendations for antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus gallolyticus* group (1)

Recommendations		Class	Level
Penicillin-susceptible oral streptococci and Streptococcus gallolyticus group			
Standard treatment: 4-week duration in NVE or 6-week duration in PVE			
In patients with IE due to oral streptococci and S. *gallolyticus* group, penicillin G, amoxicillin, or ceftriaxone are recommended for 4 (in NVE) or 6 weeks (in PVE), using the following doses:		I	B
Adult antibiotic dosage and route			
Penicillin G	12–18 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Paediatric antibiotic dosage and route			
Penicillin G	200 000 U/kg/day i.v. in 4–6 divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg/day i.v. in 1 dose		

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Recommendations for antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus gallolyticus* group (2)

Recommendations		Class	Level
Penicillin-susceptible oral streptococci and Streptococcus gallolyticus group			
Standard treatment: 2-week duration (not applicable to PVE)			
2-week treatment with penicillin G, amoxicillin, ceftriaxone combined with gentamicin is recommended only for the treatment of non-complicated NVE due to oral streptococci and *S. gallolyticus* in patients with normal renal function using the following doses:		I	B
Adult antibiotic dosage and route			
Penicillin G	12–18 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Penicillin G	200 000 U/kg/day i.v. in 4–6 divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg i.v. in 1 dose		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose or 3 equally divided doses		

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Recommendations for antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus gallolyticus* group (3)

Recommendations		Class	Level
Penicillin-susceptible oral streptococci and Streptococcus gallolyticus group			
Allergy to beta-lactams			
In patients allergic to beta-lactams and with IE due to oral streptococci and *S. gallolyticus*, vancomycin for 4 weeks in NVE or for 6 weeks in PVE is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 or 3 equally divided doses		

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Recommendations for antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus gallolyticus* group (4)

Recommendations		Class	Level
Oral streptococci and Streptococcus gallolyticus group susceptible, increased exposure or resistant to penicillin			
In patients with NVE due to oral streptococci and *S. gallolyticus*, penicillin G, amoxicillin, or ceftriaxone for 4 weeks in combination with gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	12 g/day i.v. in 6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		

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Recommendations for antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus gallolyticus* group (5)

Recommendations		Class	Level
Oral streptococci and Streptococcus gallolyticus group susceptible, increased exposure or resistant to penicillin (continued)			
In patients with PVE due to oral streptococci and *S. gallolyticus*, penicillin G, amoxicillin, or ceftriaxone for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	12 g/day i.v. in 6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		

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Recommendations for antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus gallolyticus* group (6)

Recommendations		Class	Level
Oral streptococci and Streptococcus gallolyticus group susceptible, increased exposure or resistant to penicillin (continued)			
Allergy to beta-lactams			
In patients with NVE due to oral streptococci and *S. gallolyticus* and who are allergic to beta-lactams, vancomycin for 4 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		

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Recommendations for antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus gallolyticus* group (7)

Recommendations		Class	Level
Oral streptococci and Streptococcus gallolyticus group susceptible, increased exposure or resistant to penicillin (continued)			
Allergy to beta-lactams (continued)			
In patients with PVE due to oral streptococci and *S. gallolyticus* and who are allergic to beta-lactams, vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		

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Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp (1)

Recommendations		Class	Level
IE caused by methicillin-susceptible staphylococci			
In patients with NVE due to methicillin-susceptible staphylococci, (flu)cloxacillin or cefazolin is recommended for 4–6 weeks using the following doses:		I	B
Adult antibiotic dosage and route			
(Flu)cloxacillin	12 g/day i.v. in 4–6 doses		
Cefazolin	6 g/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
(Flu)cloxacillin	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Cefazolin	300-600 mg/kg/day in 3-4 doses		

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Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp (2)

Recommendations		Class	Level
IE caused by methicillin-susceptible staphylococci (continued)			
In patients with PVE due to methicillin-susceptible staphylococci, (flu)cloxacillin or cefazolin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
(Flu)cloxacillin	12 g/day i.v. in 4–6 doses		
Cefazolin	6 g/day i.v. in 3 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
(Flu)cloxacillin	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Cefazolin	300-600 mg/kg/day in 3-4 doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		

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Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp (3)

Recommendations		Class	Level
IE caused by methicillin-susceptible staphylococci (continued)			
Allergy to beta-lactams			
In patients with NVE due to methicillin-susceptible staphylococci who are allergic to penicillin, cefazolin for 4–6 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Cefazolin	6 g/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
Cefazolin	300-600 mg/kg/day in 3-4 doses		

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Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp (4)

Recommendations		Class	Level
IE caused by methicillin-susceptible staphylococci (continued)			
Allergy to beta-lactams (continued)			
In patients with PVE due to methicillin-susceptible staphylococci who are allergic to penicillin, cefazolin combined with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Cefazolin	6 g/day i.v. in 3 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
Cefazolin	300-600 mg/kg/day in 3-4 doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		

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Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp (5)

Recommendations		Class	Level
IE caused by methicillin-susceptible staphylococci (continued)			
Allergy to beta-lactams (continued)			
In patients with NVE due to methicillin-susceptible staphylococci who are allergic to penicillin, daptomycin combined with ceftaroline or fosfomycin may be considered.		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Ceftaroline OR Fosfomycin	1800 mg/day i.v. in 3 doses OR 8–12 g/day i.v. in 4 doses		

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Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp (6)

Recommendations		Class	Level
IE caused by methicillin-susceptible staphylococci (continued)			
Allergy to beta-lactams (continued)			
In patients with PVE due to methicillin-susceptible staphylococci who are allergic to penicillin, daptomycin combined with ceftaroline or fosfomycin or gentamicin with rifampin for at least 6 weeks and gentamicin for 2 weeks may be considered using the following doses:		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Ceftaroline OR Fosfomycin	1800 mg/day i.v. in 3 doses OR 8–12 g/day i.v. in 4 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		

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Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp (7)

Recommendations		Class	Level
IE caused by methicillin-resistant staphylococci			
In patients with NVE due to methicillin-resistant staphylococci, vancomycin is recommended for 4–6 weeks using the following doses:		I	B
Adult antibiotic dosage and route			
Vancomycin	30–60 mg/kg/day i.v. in 2–3 doses		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2–3 equally divided doses		

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Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp (8)

Recommendations		Class	Level
IE caused by methicillin-resistant staphylococci (continued)			
In patients with PVE due to methicillin-resistant staphylococci, vancomycin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Vancomycin	30–60 mg/kg/day i.v. in 2–3 doses		
Rifampin	900–1200 mg/day i.v. or orally in 2 or 3 divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2–3 equally divided doses		
Rifampin	20 mg/kg/day i.v. or orally in 2 or 3 divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		

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Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp (9)

Recommendations		Class	Level
IE caused by methicillin-resistant staphylococci (continued)			
In patients with NVE due to methicillin-resistant staphylococci, daptomycin combined with cloxacillin, ceftaroline or fosfomycin may be considered using the following doses:		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Cloxacillin	12 g/day i.v. in 6 doses		
OR	OR		
Ceftaroline	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin	8–12 g/day i.v. in 4 doses		

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Recommendations for antibiotic treatment of infective endocarditis due to Enterococcus spp. (1)

Recommendations		Class	Level
Beta-lactam and gentamicin-susceptible strains			
In patients with NVE due to non-HLAR Enterococcus spp., the combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. in 2 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. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		

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Recommendations for antibiotic treatment of infective endocarditis due to Enterococcus spp. (2)

Recommendations		Class	Level
Beta-lactam and gentamicin-susceptible strains (continued)			
In patients with PVE and patients with complicated NVE or >3 months of symptoms due to non-HLAR Enterococcus spp., the combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. in 2 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		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		

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Recommendations for antibiotic treatment of infective endocarditis due to Enterococcus spp. (3)

Recommendations		Class	Level
High-level aminoglycoside resistance			
In patients with NVE or PVE due to HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin and ceftriaxone for 6 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Ampicillin	12 g/day i.v. in 4–6 doses		
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. or i.m. in 2 doses		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg i.v. or i.m. in 2 doses		

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Recommendations for antibiotic treatment of infective endocarditis due to Enterococcus spp. (4)

Recommendations		Class	Level
Beta-lactam resistant Enterococcus spp. (E. faecium)			
In patients with IE due to beta-lactam resistant *Enterococcus* spp. (*E. faecium*), vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2–3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		

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Recommendations for antibiotic treatment of infective endocarditis due to Enterococcus spp. (5)

Recommendations		Class	Level
Vancomycin-resistant Enterococcus spp.			
In patients with IE due to vancomycin-resistant *Enterococcus* spp., daptomycin combined with beta-lactams (ampicillin, ertapenem, or ceftaroline) or fosfomycin is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	12 g/day i.v. in 4 doses		
Ceftaroline	1800 mg/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose (age-adjusted)		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	2–3 g/day i.v. in 1 dose		
Ceftaroline	24–36 mg/kg/day in 3 doses		
Ertapenem	1 g/day i.v. or i.m. in 1 dose [if younger than 12 years, 15 mg/kg/dose (to a maximum of 500 mg) twice daily]		

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Antibiotic treatment of blood culture-negative infective endocarditis (1)

Pathogens	Proposed therapy	Treatment outcome
Brucella spp.	Doxycycline (200 mg/24 h) plus cotrimoxazole (960 mg/12 h) plus rifampin (300–600 mg/24 h) for ≥3–6 months orally	Treatment success defined as an antibody titre <1:60. Some authors recommend adding gentamicin for the first 3 weeks
C. Burnetii (Q fever agent)	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h) orally (>18 months of treatment)	Treatment success defined as anti-phase I IgG titre <1:400, and IgA and IgM titres <1:50
Bartonella spp.	Doxycycline 100 mg/12 h orally for 4 weeks plus gentamicin (3 mg/24 h) i.v. for 2 weeks	Treatment success expected in ≥90%

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Antibiotic treatment of blood culture-negative infective endocarditis (2)

Pathogens	Proposed therapy	Treatment outcome
Legionella spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 weeks or clarithromycin (500 mg/12 h) i.v. for 2 weeks, then orally for 4 weeks plus rifampin (300–1200 mg/24 h)	Optimal treatment unknown
Mycoplasma spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 months	Optimal treatment unknown
T. whipplei (Whipple's disease agent)	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h) orally for ≥18 months	Long-term treatment, optimal duration unknown

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