Infective endocarditis

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Summary

Infective endocarditis (IE) is an infectious inflammation of the endocardium that affects the heart valves. The condition is a result of bacteremia, which is most commonly caused by dental procedures, surgery, distant primary infections, and nonsterile injections.

IE clinically presents with either an acute or subacute course. Acute disease is usually caused by *Staphylococcus aureus* and causes rapid endocardium destruction. Subacute progression is most commonly caused by viridans streptococci species and generally affects individuals with pre-existing damage to the heart valves, structural heart defects, or the presence of prosthetic valves.

Unlike acute disease, in which patients develop symptoms over a period of hours to days, subacute disease is associated with a progression of symptoms over weeks to months. Clinical features include constitutional symptoms (fatigue, fever/chills, malaise) in combination with signs of pathological cardiac changes (e.g., new or changed heart murmur, heart failure signs) and possibly manifestations of subsequent damage to other organs (e.g., glomerulonephritis, septic embolic stroke).

Diagnosis is made based on the Duke criteria, whose main features include positive blood cultures and evidence of endocardial involvement in echocardiography. Initial treatment of IE consists of empiric IV antibiotic therapy, which is then adapted to blood culture results and continued for four to six weeks. Prophylaxis is only administered in specific circumstances, e.g., in patients with preexisting heart conditions undergoing dental or surgical procedures. If left untreated, infective endocarditis can be fatal within a few weeks.

Etiology
Pathogens

Main pathogens	Characteristics
• **Staphylococcus aureus (45–65%)**	• Most common cause of acute IE for all groups (including IV drug users and patients with prosthetic valves or pacemakers/ICDs) • Affects previously healthy valves • Usually fatal within 6 weeks (if left untreated)

Main pathogens	Characteristics
• **Viridans streptococci (30%): S. sanguinis, S. mutans, S. mitis**	• Most common cause of subacute IE, especially in predamaged native valves (mainly the mitral valve • Common cause of IE following dental procedures • Produce dextrans that facilitate binding fibrin-platelet aggregates on damaged heart valves

Main pathogens	Characteristics
• **Staphylococcus epidermidis**	• IE transmitted via infected peripheral venous catheters • Common cause of subacute IE in patients with prosthetic heart valves or pacemakers/ICDs

Main pathogens	Characteristics
• **Enterococci, especially Enterococcus faecalis (< 10%)**	• Multiple drug resistance • Common cause of IE following nosocomial urinary tract infections (UTIs) • Following gastrointestinal or genitourinary procedures

Main pathogens	Characteristics
• **Streptococcus gallolyticus**	• S. gallolyticus is associated with colorectal cancer • If S. gallolyticus is detected, colonoscopy is indicated

Main pathogens	Characteristics
• **Gram-negative HACEK group**	• Physiological oral pharyngeal flora (~ 3% of cases of IE) • In patients with poor dental hygiene and/or periodontal infection

Main pathogens	Characteristics
• **Candida species** • **Aspergillus fumigatus**	• Causes IE in immunosuppressed patients • Causes IE in IV drug abusers • Cause of IE after cardiosurgical interventions

Risk factors

- **Demographics**
  - Male sex
  - Age > 60 years

- **Preexisting conditions**
  - Previous IE
  - **Predamaged** or **prosthetic heart valves**
  - **Congenital heart defects**
  - Need for chronic hemodialysis
  - Impaired immune function (e.g., HIV infection)

- **Bacteremia**
  - Infected peripheral venous catheters, surgery, dental procedures
  - Non-sterile venous injections (e.g., **IV drug abuse**)
  - Bacterial infections of various organs (e.g., UTIs, spondylodiscitis)

Pathophysiology

- **Pathogenesis**: localized infection or contamination → bacteremia → **bacterial colonization** of damaged valve areas → **formation of fibrin clots** encasing the vegetation → **valve destruction with loss of function**
  - Preexisting valvular endothelial damage or prosthetic valves predispose to bacterial colonization, especially of those that cause subacute IE
  - Frequency of valve involvement: mitral valve > aortic valve > tricuspid valve > pulmonary valve

- **Clinical consequences**
  - Bacterial thromboemboli from bacterial vegetation → vessel occlusion with infarctions
  - Formation of immune complexes and antibodies against tissue antigens → glomerulonephritis, Osler nodes

Clinical features
Course of disease

	Acute bacterial endocarditis	Subacute bacterial endocarditis	Prosthetic valve endocarditis
Course	• Acute onset • Rapid, fulminant progression (days to weeks) • More severe constitutional symptoms (e.g., high fever)	• Insidious onset • Slow progression (weeks to months) • Less severe constitutional symptoms (e.g., low fever possible, often absent)	• Early-onset: < 60 days after surgery • Late-onset: ≥ 60 days after surgery

	Acute bacterial endocarditis	Subacute bacterial endocarditis	Prosthetic valve endocarditis
Main pathogens	• Most common: S. aureus • Others: group A hemolytic streptococci, S.pneumoniae, N.gonorrhoeae	• Most common: viridans streptococci species • Others: nonenterococcal group D streptococci and enterococci	• Early onset: S. epidermidis or S. aureus (most common) • Late-onset: S. epidermidis (most common)

Constitutional symptoms

- **Fever and chills** (~ 90% of cases), **tachycardia**
- **General malaise**, weakness, night sweats, weight loss
- Dyspnea, cough, pleuritic chest pain
- Arthralgias, myalgias

Cardiac manifestations

- New heart murmur development or change to a preexisting one
  - **Mitral valve** regurgitation → **holosystolic** murmur, loudest at the heart's apex, and radiates to the left axilla
  - **Tricuspid valve** regurgitation → **holosystolic** murmur; loudest at the left sternal border ; seen in **IV drug users** and concomitant **HIV infection**, immunosuppressed pati ents, and patients with central venous catheters
  - **Aortic valve** regurgitation → **early diastolic** murmur; loudest at the left sternal border

- Signs of progressive heart failure (e.g., **dyspnea**, edema)
- Signs of acute cardiac decompensation (pulmonary edema)
- Arrhythmias
  - Suspect perivalvular abscess in patients with infective endocarditis who develop a new conduction abnormality (e.g., a third-degree atrioventricular block)

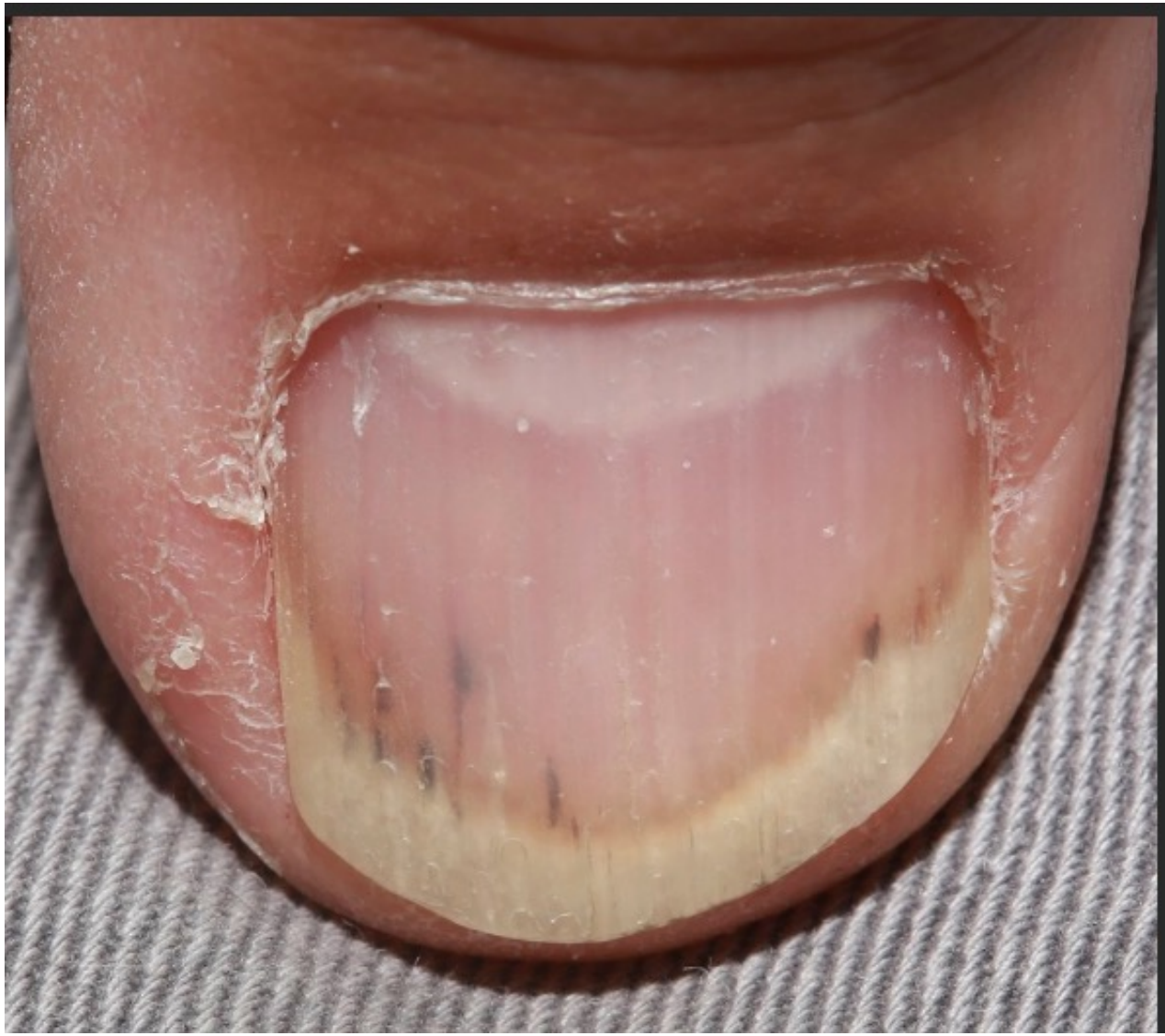
Extracardiac manifestations

- These manifestations are mainly caused by bacterial microemboli and/or the precipitation of immune complexes .
- **Petechiae**; especially **splinter hemorrhages** (hemorrhages underneath fingernails)
- **Janeway lesions**: non-tender, erythematous macules on palms and soles (due to microemboli and microabscesses with neutrophilic capillary infiltration)
- **Osler nodes**: painful nodules on pads of the fingers and toes

- **Roth spots**: retinal hemorrhages with pale centers
- Signs of **acute renal injury**, including hematuria and anuria
- Splenomegaly and possible LUQ pain
- Neurological manifestations (e.g., seizures, paresis)
- Signs of pulmonary embolism (e.g., dyspnea)
- Possible arthritis

Infective endocarditis should always be considered as a cause of fever of unknown origin (FUO), especially if a new heart murmur develops!

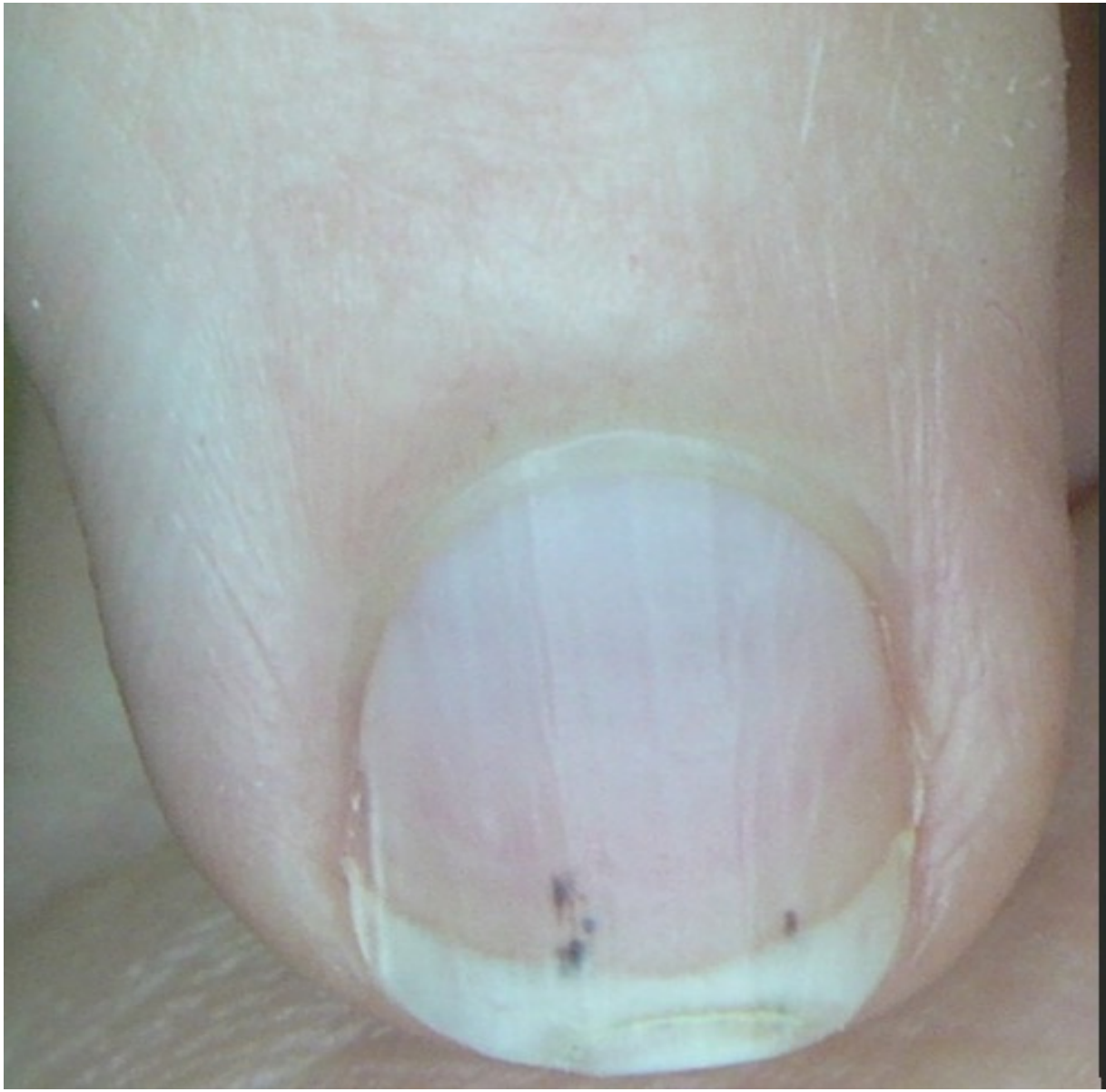
FROM JANE - **F**ever, **R**oth's spots, **O**sler nodes, **M**urmur, **J**aneway lesions, **A**nemia, **N**ail bed hemorrhage, **E**mboli



Splinter hemorrhages

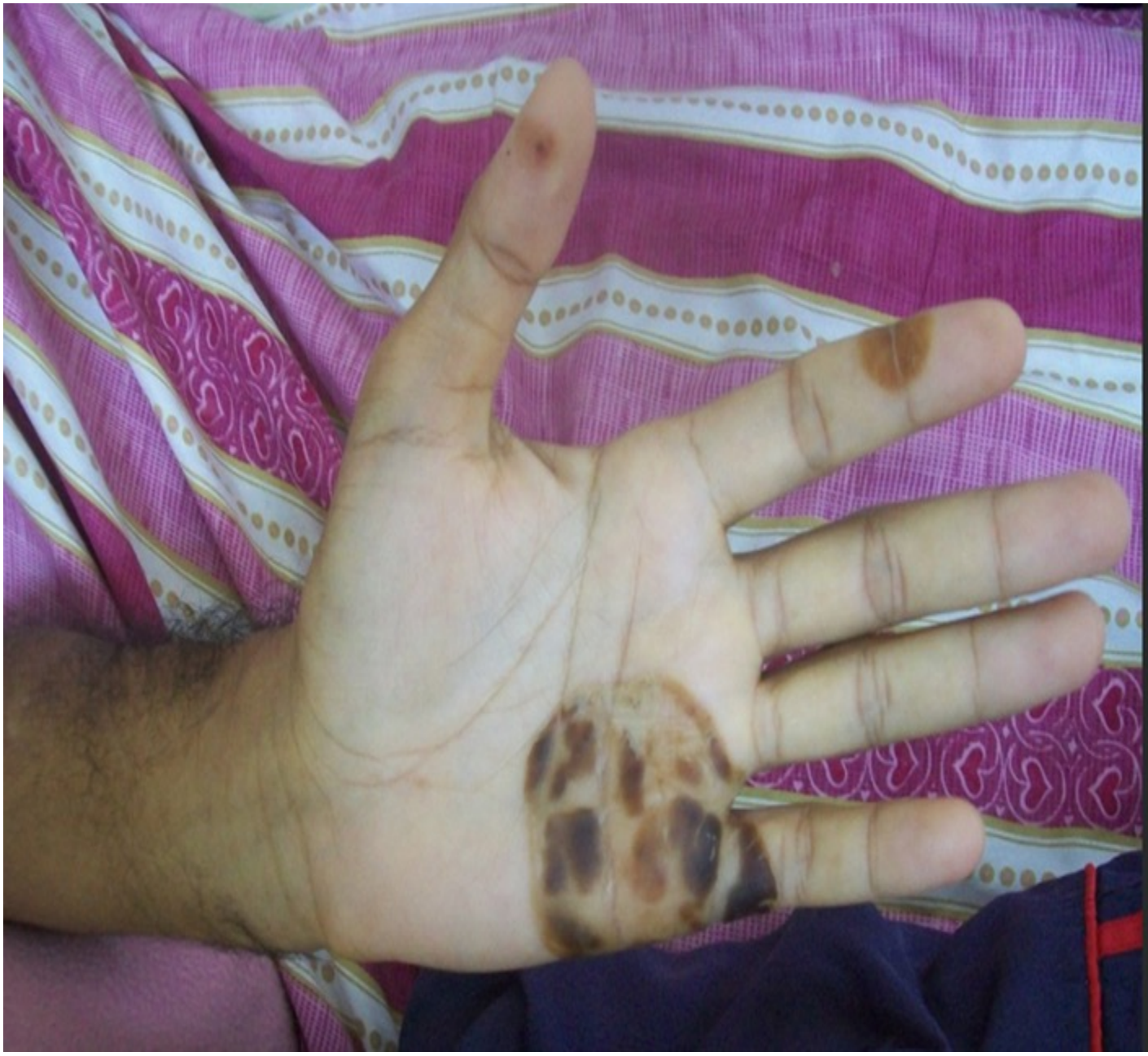
Photograph of a fingernail

Multiple bluish–black longitudinal lesions (resembling splinters) are seen underneath the fingernail. These lesions do not blanch on pressure.



Splinter hemorrhages in endocarditis

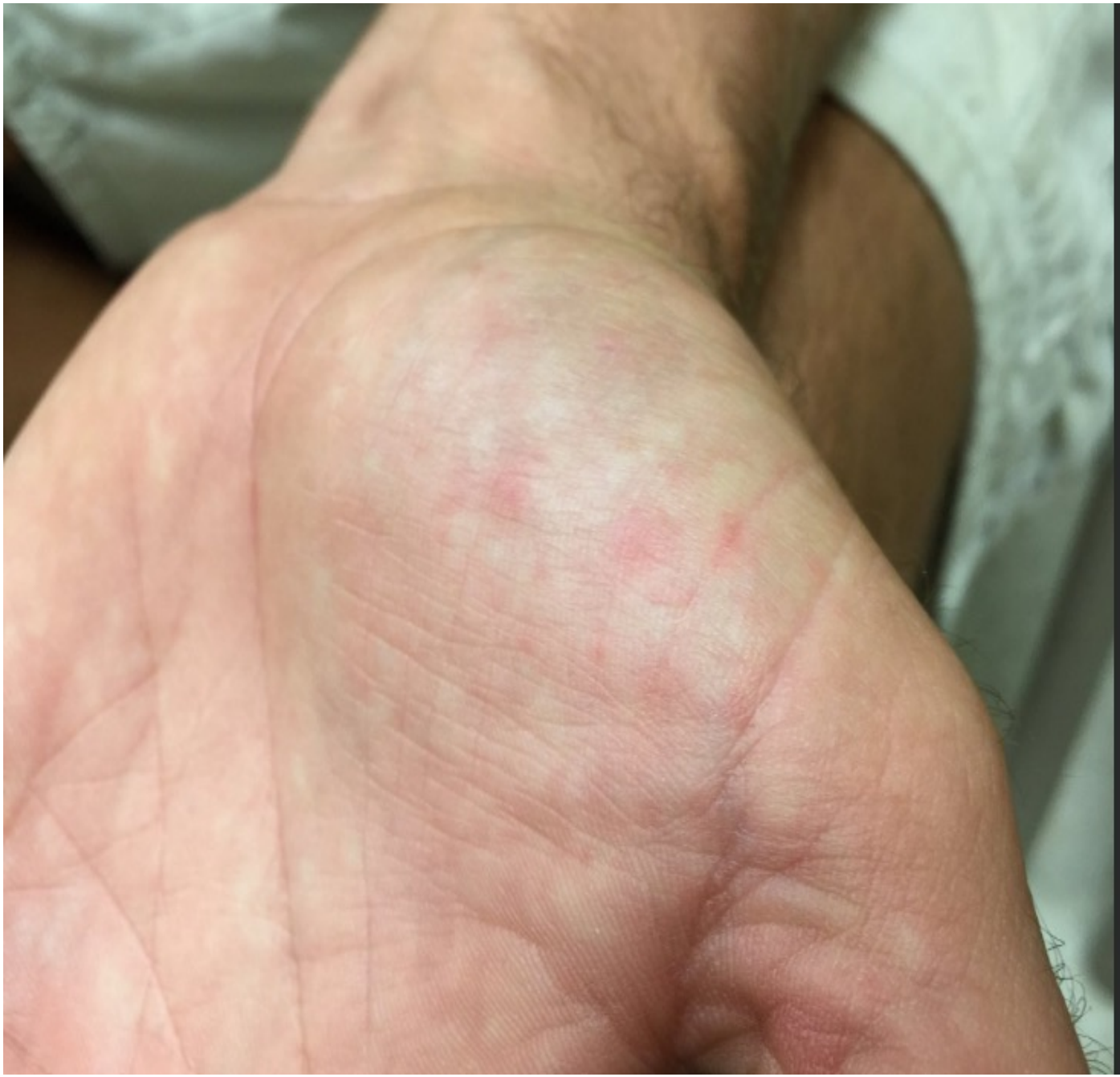
The vertical hemorrhages underneath this patient's fingernails are most commonly caused by trauma but can also occur as a result of immune complex deposition or microthrombosis in subacute, infective endocarditis, SLE, or rheumatoid arthritis.



Osler nodes on hand

Multiple papules and nodules on the palm of the hand and on the palmar aspects of the first and second digits. The lesions appear dark reddish-brown, indicating subcutaneous hemorrhages.

This is the typical appearance of Osler nodes (caused by infective endocarditis).



Janeway lesions

Multiple erythematous macules typical of Janeway lesions (caused by infective endocarditis) on the thenar eminence and the base of the thumb.

Diagnostics

Laboratory studies

- Best initial test: **blood cultures**
- **Leukocytosis** (with left shift), ↑ **ESR**, ↑ CRP

Echocardiography

- Detects **valve vegetations** , new valvular regurgitation, abscess.
- Transthoracic echocardiography (TTE) usually performed first (sensitivity: ~ 75%)
- Transesophageal echocardiography (TEE) higher sensitivity (> 90%) than TTE

(Modified) Duke criteria

- The Duke criteria help to diagnose infective endocarditis. To confirm the diagnosis, one of the following requirements must be met:
  - Two major criteria
  - One major and three minor criteria
  - Five minor criteria

- **Major diagnostic criteria**
  - Two separate blood cultures positive for typical pathogens (see “Etiology” above)
  - Evidence of endocardial involvement in echocardiography
  - A new valvular regurgitation (worsening of a pre-existing murmur is not sufficient)

- **Minor diagnostic criteria**
  1. Predisposition: underlying heart disease or IV drug abuse
  2. Fever ≥ 38°C (100.4F)
  3. Vascular abnormalities
  4. Immunologic disorder
  5. Microbiology

Only negative findings on transesophageal echocardiography (TEE) can reliably rule out endocarditis, as transthoracic echocardiography (TTE) is not sensitive enough!

Pathology

Pathogenesis

- Acute disease (leading to valve insufficiency, septic embolic infarcts, tendinous cord rupture)
  1. Erosion → fibrin deposits on valves
  2. Ulceration
  3. Perforation → adaptation of valve edges not possible

- Chronic disease (leading to valve insufficiency and valve stenosis)
  1. Granulation tissue → valve scarring/fibrosis
  2. Calcification → thickened and/or shortened tendinous cords

Differential diagnoses

Nonbacterial thrombotic endocarditis

- Rare, non-infectious form of endocarditis due to sterile platelet thrombus formation on the heart valves (usually aortic and mitral valves)
- Most commonly associated with underlying malignancy, hypercoagulable states, or rheumatologic conditions (SLE, rheumatoid arthritis, etc.)

- Compared to infectious endocarditis, vegetations are easily dislodged and embolization is common; most patients are asymptomatic until embolization occurs
- Definitive diagnosis can only be made pathologically: shows vegetations on either surface of the valve that are composed of immune complexes.
- **Libman-Sacks endocarditis**: describes especially large vegetations, also referred to as verrucous vegetations

Prosthetic valve thrombosis

- **Etiology**
  - Occurs if **insufficient anticoagulatory therapy** after valve replacement
  - Usually affects **mechanic valves**
  - Rare if anticoagulation is adequate

- **Clinical course of prosthetic valve thrombosis**
  - Signs of **acute heart failure**
    - Left heart failure: dyspnea and cough
    - Right heart failure: edema and jugular venous distention
  - Deterioration of general condition, cardiac arrhythmias, cerebral emboli (stroke)

- **Diagnostics**: transesophageal echocardiography
- **Treatment**: anticoagulation and fibrinolysis, surgical valve replacement

Treatment
Empirical therapy

Condition /Patient group	Antibiotic therapy

• **Native valves**	• Initial intravenous empiric antibiotic treatment with vancomycin → adapt intravenous antibiotics according to resistogram results from blood cultures
	• The duration of treatment depends on the patient's profile, and the patient's response to treatment.
	  • 4-week treatment
	  • Drug of choice: penicillin G
	  • Alternatives: ampicillin, IV ceftriaxone, IV vancomycin
	  • 2-week treatment regimens
	  • Drug of choice: gentamicin + penicillin G
	  • Alternative: gentamicin + ceftriaxone

Condition/ Patient group	Antibiotic therapy

• **Prosthetic valves**	• Generally the same antibiotic regimen as for native valves, but longer duration (at least 6 weeks)
	• Exceptions for staphylococci
	  • Methicillin-susceptible: nafcillin (or oxacillin, cefazolin) + rifampin + gentamicin
	  • Methicillin-resistant: vancomycin + rifampin + gentamicin

Condition/ Patient group	Antibiotic therapy

• **IV drug users**	• Intravenous empiric antibiotic treatment with vancomycin
	• After confirmation of a susceptible pathogen
	  • IV nafcillin (2 weeks)
	  • PO cloxacillin (2 weeks)

• **Indications for surgery: congestive heart failure, uncontrolled infection, systemic embolization, prosthetic valve, fungal endocarditis**	

If infective endocarditis is suspected:
1. Obtain blood cultures → 2. Start empiric antibiotic therapy immediately → 3. Adapt the therapy according to culture results

Targeted therapy

HACEK organisms

- **Drug of choice**
  - First-line: 3rd or 4th generation IV cephalosporin (e.g., ceftriaxone, cefotaxime)
  - Second-line : IV fluoroquinolone

- **Duration of therapy**
  - Native valve infectious endocarditis: 4 weeks
  - Prosthetic valve endocarditis: 6 weeks

Prevention

Endocarditis prophylaxis:

- Indicated for high-risk patients undergoing procedures with risk of bacteremia
- Regimens
  - Usually **PO amoxicillin** (administer 1 hour before procedure)
  - Patients who are unable to take oral medication: IV ampicillin
  - Patients with penicillin allergy: PO clarithromycin or azithromycin