Infective Endocarditis
Microbiological Aspect

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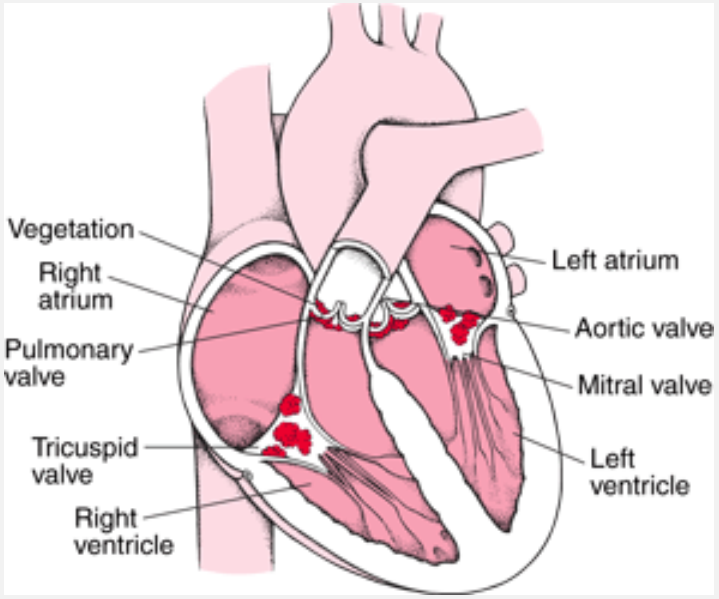
Infective Endocarditis

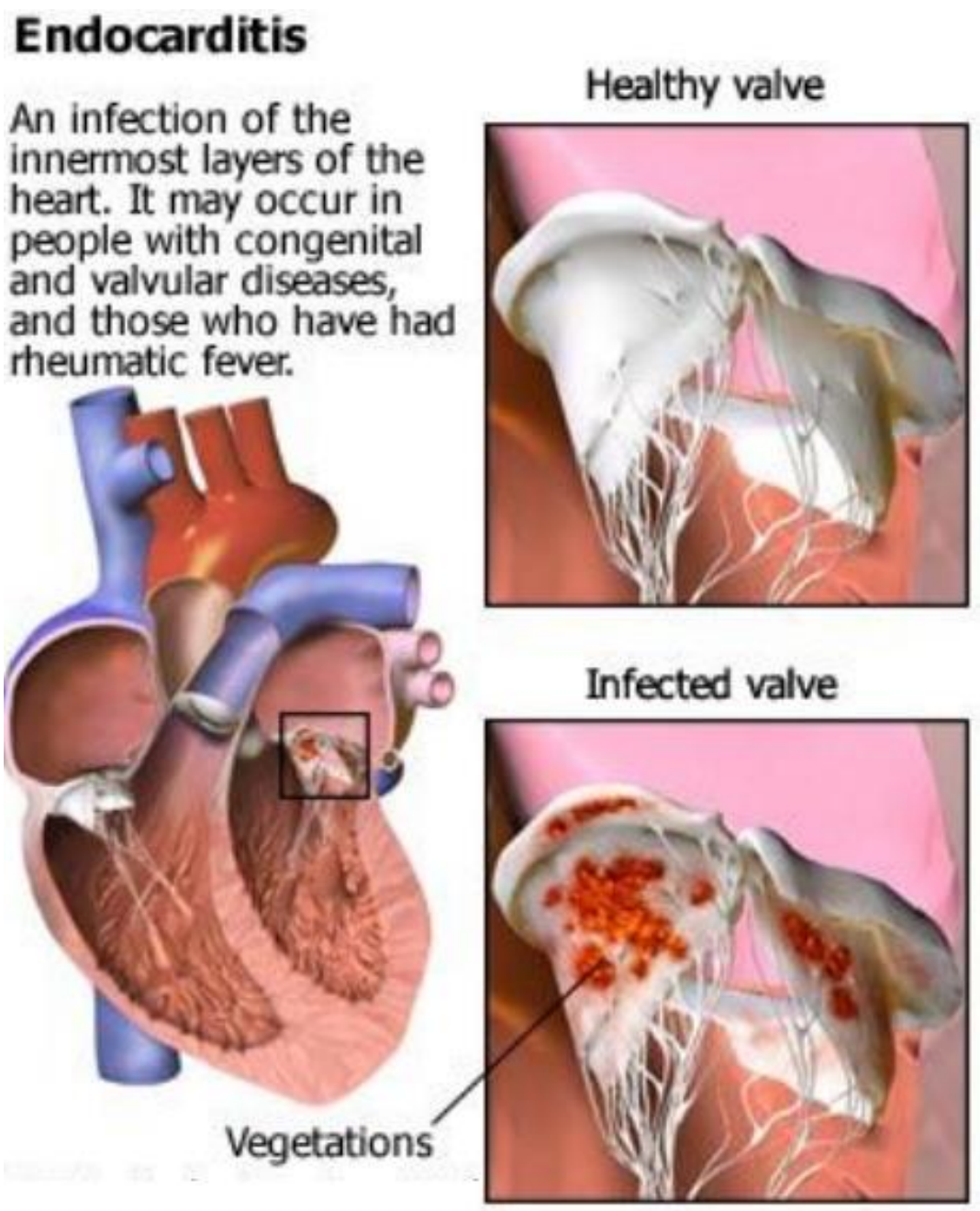
- IE - infection of the endocardial surface of the heart and implies the physical presence of microorganisms in the lesion.

Outline of the lecture

1. Introduction
2. Predisposing factors
3. Pathogenesis
4. **Organisms responsible**
    - Common bacterial causes
    - Other bacterial causes
    - Fungal causes
5. Laboratory diagnosis



- **IE**: infection of the endocardial surface of the heart



Introduction

- **Common sites**:

1. heart valve (most common)

   most often involves the **AV** or **MV**

   tricuspid valve involvement

   < 10% of cases

   often in association with **injection drug use**

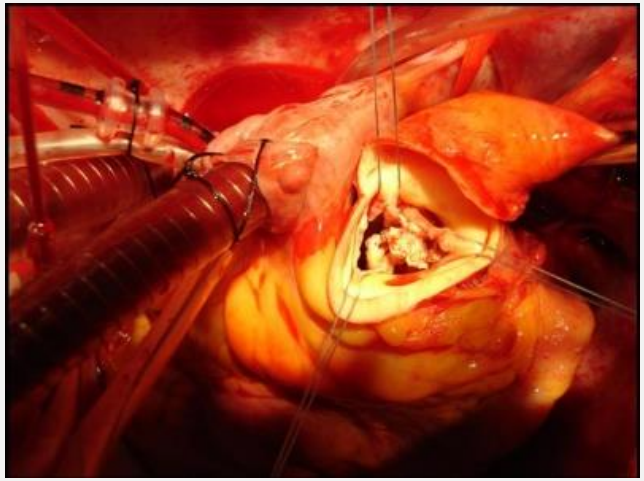
Introduction

2. may occur at → septal defect
   - chordae tendineae
   - mural endocardium

- The **mortality** of IE remains **high**, with > 1/3 of patients affected **dying within a year** following diagnosis
- More common in elderly (>50 years)

Classification

- Native valve / prosthetic valve



- Based on severity of presentation and progression

  - Acute

  - Subacute-chronic

Acute IE

- Infection of **previously normal heart valve**
- by a **highly virulent organism**
- Produces **necrotizing, ulcerative**, **destructive lesions**
- Difficult to cure with Abx & usually require Sx
- Death can occur within days to weeks

Sub-acute IE

- Usually via lower virulent organisms
- Insidious onset
- Infections of deformed (native) valves
- Less destructive
- Prolonged course: weeks to months
- More amenable to treatment with antibiotics

Predisposing factors

1. Previous **rheumatic** heart diseases
2. **Congenital** heart disease
3. **Athelesclerotic** aortic valve diseases
4. **Prosthetic** valve heart surgery
5. Severe **MVP**
6. **Drug addition** (IV)

Pathogenesis

- Transient bacteraemia occurs when a heavily colonised mucosal surface is traumatised,

  - Dental extraction, Periodontal surgery
  - Tooth brushing
  - Tonsillectomy
  - Operations involving the respiratory, GI or GU tract – mucosa
  - Biliary tract surgery

Pathogenesis……

High pressure gradient / turbulence around the valve / septal defect

↓

Damage the endothelium

↓

Roughen the endothelium

↓

Deposition of fibrin and platelets

Pathogenesis……

Bacteria reach the fibrin platelet layer

↓

Invasion of fibrin – platelet layer

↓

Covered by more fibrin

↓

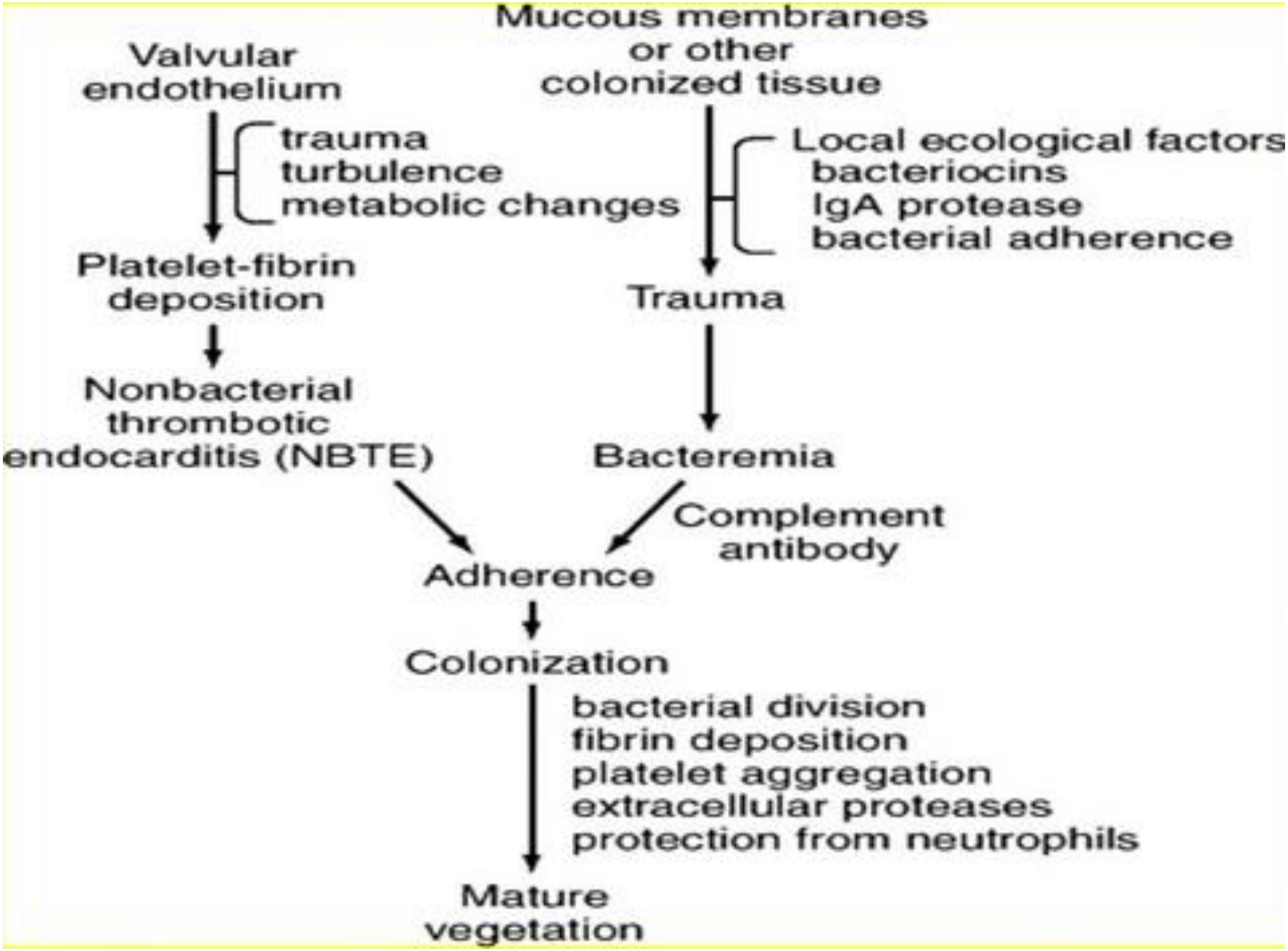
Protected from neutrophils

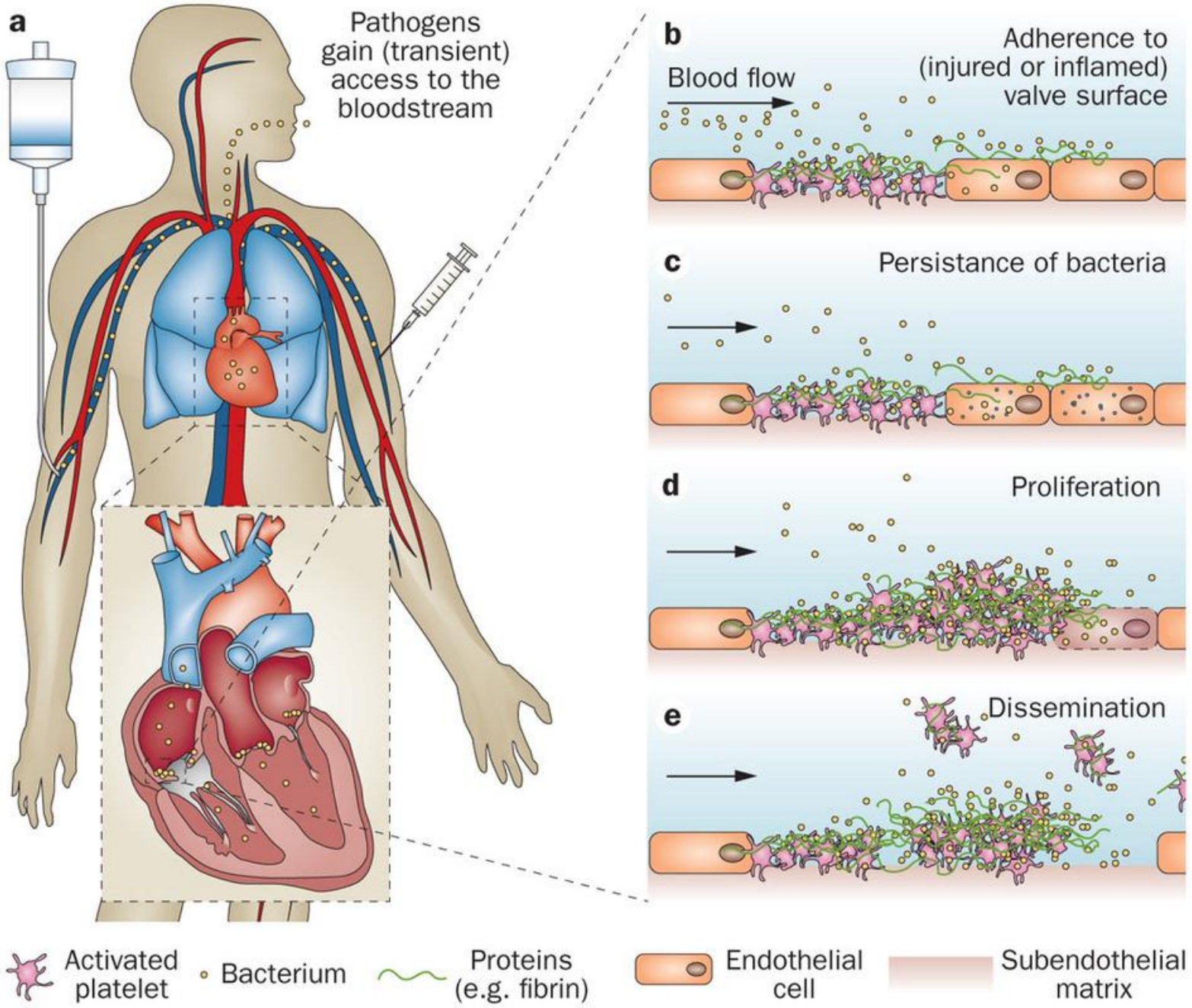
↓

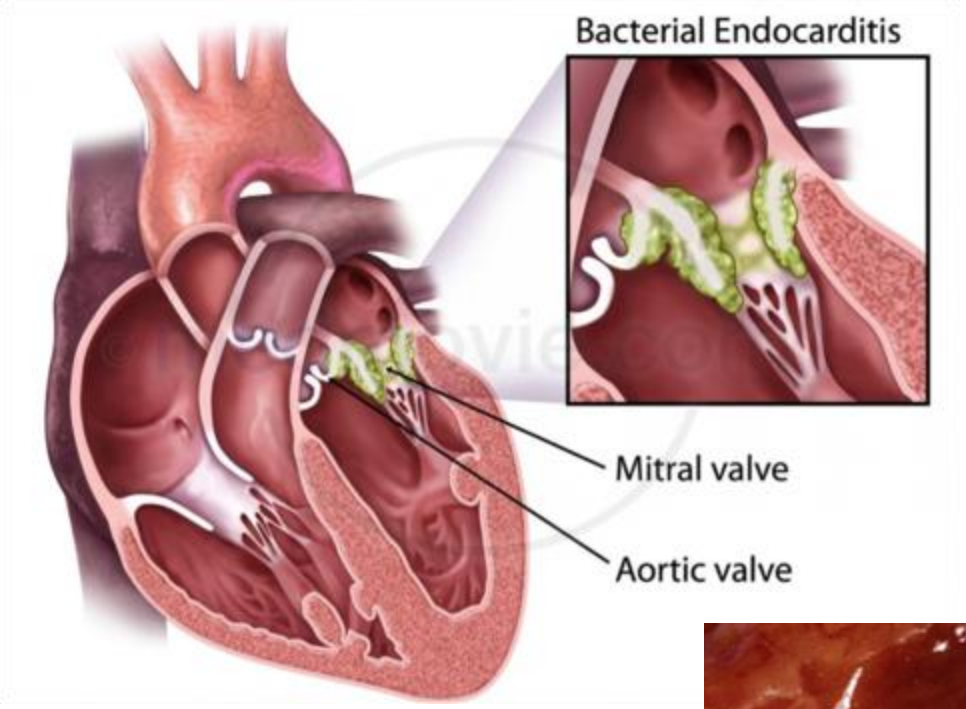
Division of bacteria

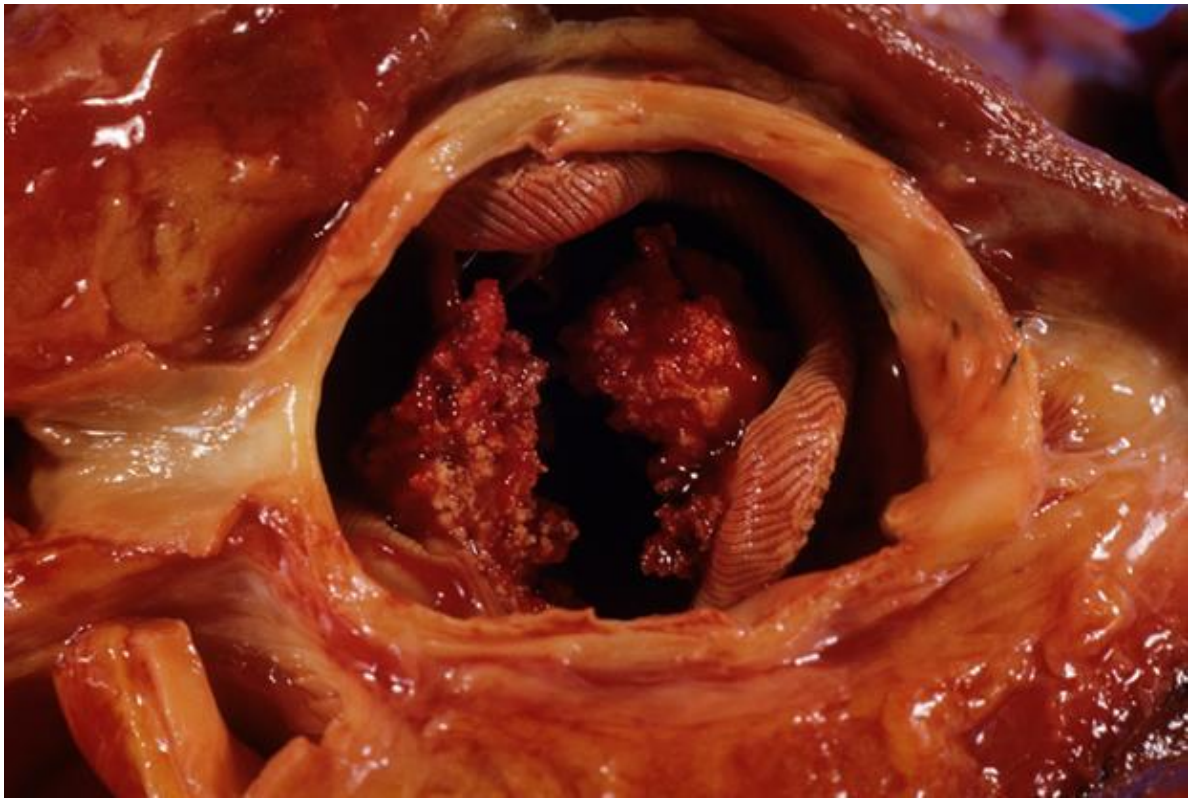
↓

Mature vegetation


Valvular endothelium
trauma
turbulence
metabolic changes
Platelet-fibrin deposition
Nonbacterial thrombotic endocarditis (NBTE)
Mucous membranes or other colonized tissue
Local ecological factors
bacteriocins
IgA protease
bacterial adherence
Trauma
Bacteremia
Complement
antibody
Adherence
Colonization
bacterial division
fibrin deposition
platelet aggregation
extracellular proteases
protection from neutrophils
Mature vegetation


a
Pathogens gain (transient) access to the bloodstream
b
Blood flow
Adherence to (injured or inflamed) valve surface
c
Persistance of bacteria
d
Proliferation
e
Dissemination
Activated platelet
Bacterium
Proteins (e.g. fibrin)
Endothelial cell
Subendothelial matrix


Bacterial Endocarditis
Mitral valve
Aortic valve



Organisms involve

Bacterial causes

- Most IE cases - bacterial (Gram positives)
- 90% of patients with proven IE have

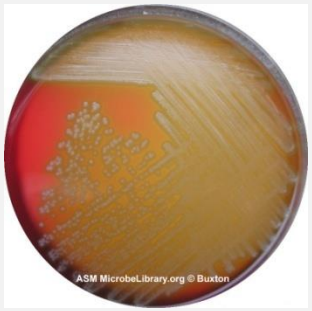
  - Staphylococci
  - Streptococci

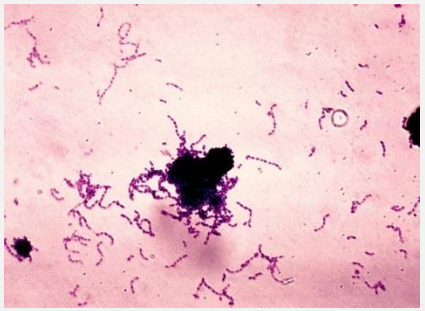
  } 80%

  - Enterococci

Streptococci

Viridans Streptococci





- Primarily viridans group streptococci, cause about 30% of cases
- **α heamolytic** streptococcal species in **oral flora**
- Etiologic agents for **community-acquired native valve endocarditis** (non- IDUs)

Streptococci……

- **Spp (Viridans strep)**

  S. sanguis

  S. oralis (mitis)

  S. salivarius

  S. mutans

- *S. bovis* -associated with colonic carcinoma

- Enter to blood stream following dental extraction
- Asymptomatic bacteraemia lasts for 2-20 min following extraction
- IE
- Has an **insidious onset**
- Lasts **many weeks**
- Most patients with viridians IE - have **previous heart lesion** & about quarter gives H_x of **recent dental extraction.**

S. pneumoniae, *S. pyogenes* and Groups B, C, and G Streptococci

- Relatively uncommon

Enterococci

- *Especially **Enterococcus faecalis**, account for **10%** of cases*
- More common among older male patients who have genito – urinary diseases
- Organism enter to blood flowing **manipulation of GUT / GIT**
- Most important as its reduced sensitivity to penicillin
- Occasionally - **highly resistant to gentamicin**

  some are multidrug resistant

  R to penicillin, ampicillin, aninoglycosides,

  rarely vancomycin , teicoplanin

Staphylococci

- ***S. aureus*** remains the dominant pathogen, associated with **25% to 30% of** cases, primarily **native valve endocarditis**
- Coagulase-negative staphylococci (**CoNS**) account for about 11% of cases cause primarily **prosthetic valve endocarditis**
- ***S. aureus* & CoNS** are frequently detected in **health care-associated** cases

S. aureus

- Usually runs an **acute cause**
- **Rapidly fatal** (mortality rates - 25% 40%)
- **MSSA** is more frequent in **community-acquired** IE
- **MRSA** is more related to **nosocomial infection**
- Clinical features often associated with
  - Staphylococcal **septicemia, DIC**
  - **Metastatic abscess** in lungs, brain and kidney

S. aureus

- Enter to blood originally from a **septic skin focus or from infected lungs**
- Attacks **previously healthy heart valve** (Sp aortic valve)
- **IV Drug addicts** are particularly at higher risk of *S. aureus* sepsis and IE
- **Tricuspid valve** infected in mainliners
- In **non-addicts** - involves **left** side of the heart

Coagulase-negative staphylococci

- Most common spp - ***S. epidermidis***
- Important cause of IE
  - **prosthetic** valve endocarditis
  - following **cardiac surgery**
- Causes great majority of early onset IE following cardiac surgery

Coagulase-negative staphylococci…

S. lugdunensis

- An important subset of patients with CoNS IE
- causes a substantially **more virulent form** of IE

Gram-negative bacilli

- GNB account for about **5% of** cases and include the HACEK group organisms

HACEK ORGANISMS

- Accounts for ≈5% to 10% of native valve community-acquired endocarditis in non -IDUs
- Fastidious Gram-negative bacilli
  - Heamophillus spp
  - *Aggregatibacter species*
  - *Cardiobacterium hominis*
  - *Eikenella corrodens*
  - *Kingella species*

HACEK ORGANISMS …

- **Grow slowly** in standard blood culture media, and recovery may require **prolonged incubation**
- Well recognized cause for initial **blood culture negative** endocarditis
- In cases - blood cultures are **initially negative** - retain blood cultures for **≥2 weeks** in all patients suspected of having IE

Non-HACEK Gram negative bacilli

- **Uncommon**

  Enterobacteriaceae &

  non-fermenting Gram-negative bacilli.

- Most are **health care associated** IE

Uncultivable / challenging to cultivate organisms

- *Coxiella burnetii*
- *Bartonella species*
- *Tropheryma whipplei*

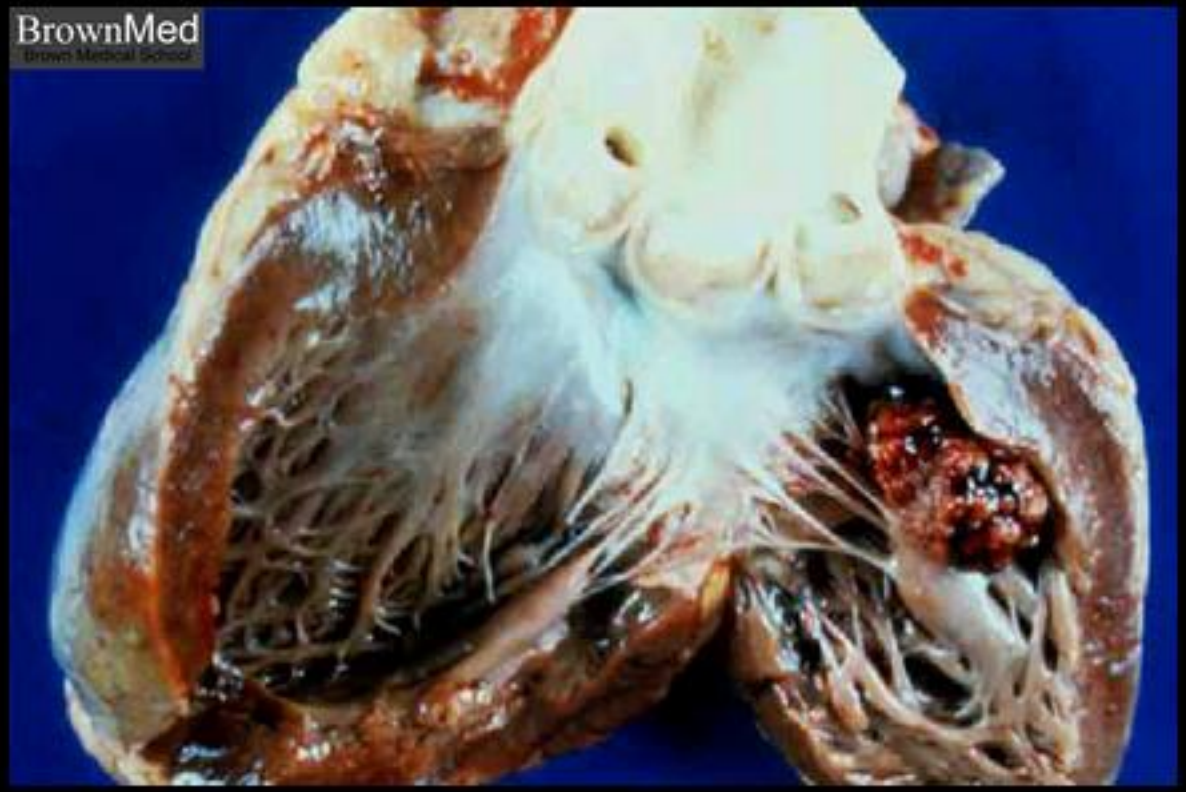
Other bacteria

Bartonella

- Unusual but important cause affecting native valve
- Spp *B. quintana*

  B. henselae
- Occasionally isolated after prolonged special blood culture techniques
- Usually diagnose via serological tests / PCR

Fungal endocarditis (*Candidiasis*)



The photo is from an immunocomprised patient with a fungus ball attached to the posterior leaflet of the mitral valve and to the chordae. Such a lesion predisposes to embolism.

Fungal endocarditis

- 1-3% of IE Fungi with **Candida** species being the most common.
- Associated with IVDU

  prosthetic valve

  long-term CVC

  immunocompromised status
- Needs to be considered in presence of

  Bulky vegetations, metastatic infection, perivalvular invasion

  Embolisation to large blood vessels despite -ve BC

Fungal endocarditis….

- Causes

  - Candida Spp - *C. albicans*

  - Aspergillus spp

- Survival rate -mold-related endocarditis

  <20%.

Microbial investigations

- Endocarditis is an **endovascular infection** associated with the **persistent** presence of infecting **microorganisms** in **blood**
- **Identification** of the specific underlying **microbial etiology** is **essential** for optimal patient management; **delays in microbial diagnosis** may contribute to late initiation of effective antimicrobial therapy, **influencing morbidity and mortality**.

Microbial investigations …

- The finding of **two (or more) blood cultures positive** for a typical microorganism consistent with IE is a **major criterion** for IE (modified Duke criteria)

Blood culture

- Draw 3 sets (aerobic and anaerobic) of blood cultures **before start of antibiotic therapy**
- **from different venipuncture sites, with at least 1 h between the first and last draw**
- Yield of blood cultures is directly related to **volume of blood cultured, (i.e., 10 ml of blood** per Bactec or BacT/Alert bottle) being essential

Blood culture

- Imp – Aseptic techniques
- Incubate at 37^0C for 5 days
- Subculture
- **Single positive** blood culture does **not** typically **represent** an endocarditis pathogen

Blood culture…..

- When initial routine blood cultures are negative **special techniques** might necessary for **HACEK** organisms and **Bartonella**

Interpretation of results

- Any organism isolated from 2 different blood culture sets - significant
- Imp – ***S. epidermidis*** and **Diphtheroids** are common skin **contaminants** that usually grow on one bottle
- Usually diagnosis can be made with the isolation of same organisms within few days of incubation from most bottles of first 2 or three days

Culture negative endocarditis

- 2% to 40% of cases of endocarditis
- **Causes**

  - Inadequate microbiological techniques

  - **Prior antibiotic therapy** (reduces the recovery rate of bacteria by 35% to 40%)

  - Infection with **highly fastidious bacteria** or nonbacterial pathogens

  - **HACEK** organisms

Culture negative endocarditis

Most common etiology of culture-negative endocarditis

- *- Coxiella burnetii*
- *- Bartonella species*

12 - 28%

- *- Tropheryma whipplei– 6%*
- *- Cutibacterium (formerly Propionibacterium) acnes*

Serology

- From cases of culture negative IE

  - *Coxiella burnetii*

    Best established **serologic test** for the diagnosis of **endocarditis**

    Included as a **major criterion** in the modified Duke criteria

    In chronic Q fever - anti-phase I IgG *C. burnetii* titers of **≥ 1:800** is **diagnostic**

Serology

- *Bartonella species*

- *Brucella* spp

Other Ix

- Microscopy and culture of

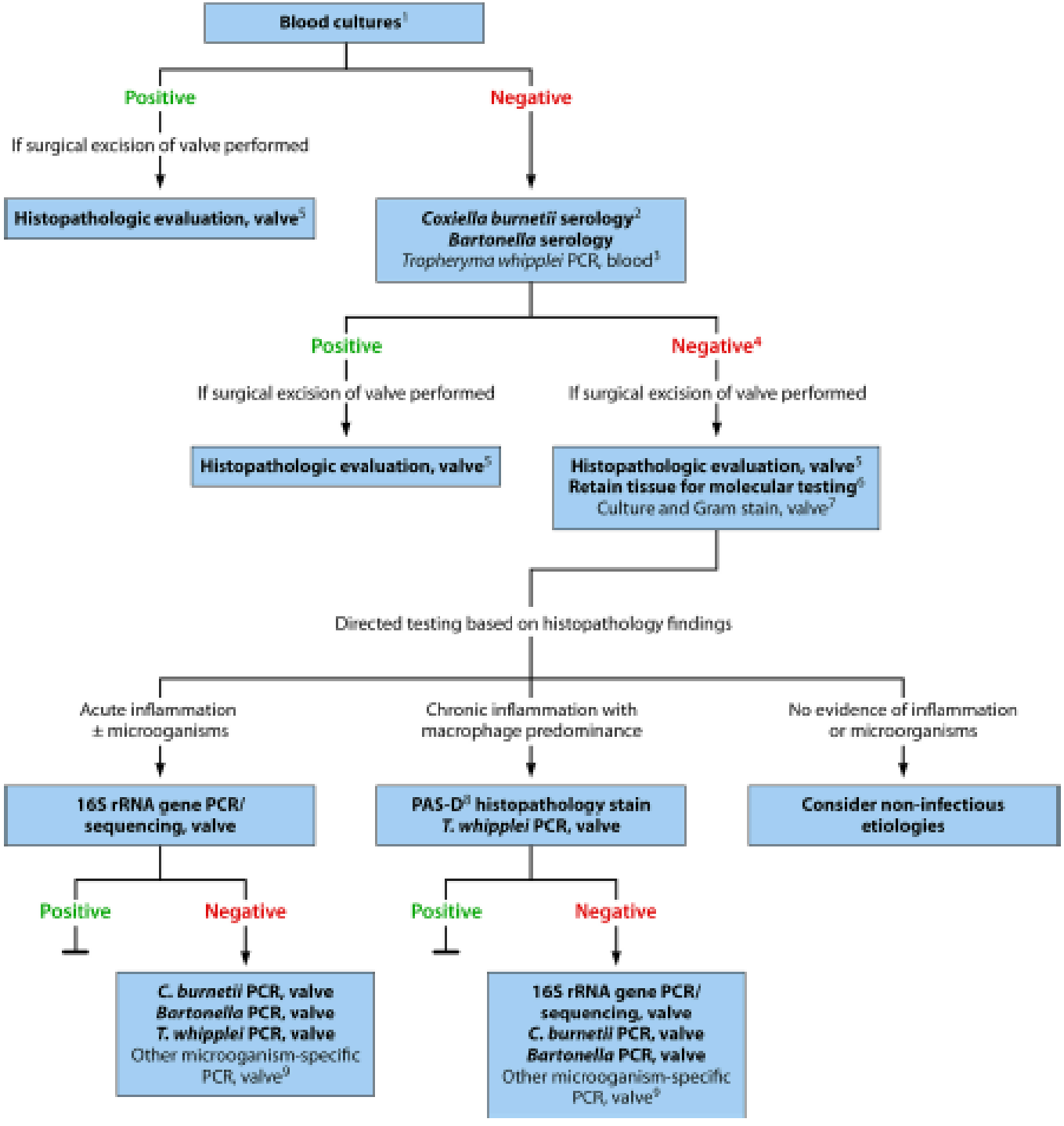
  - vegetations removed at the surgery

  - emboli lodged in blood vessels remove at Sx

  (particularly ass/w fungi)

- PCR - *C. burnetii*, Bartonella species*, T. whipplei,*

  C. acnes, and *M. hominis*


Blood cultures[1]
Positive
Negative
If surgical excision of valve performed
Histopathologic evaluation, valve[5]
Coxiella burnetii serology[2]
Bartonella serology
Tropheryma whipplei PCR, blood[3]
Positive
Negative[4]
If surgical excision of valve performed
If surgical excision of valve performed
Histopathologic evaluation, valve[5]
Histopathologic evaluation, valve[5]
Retain tissue for molecular testing[6]
Culture and Gram stain, valve[7]
Directed testing based on histopathology findings
Acute inflammation
± microorganisms
Chronic inflammation with
macrophage predominance
No evidence of inflammation
or microorganisms
16S rRNA gene PCR/
sequencing, valve
PAS-D[8] histopathology stain
T. whipplei PCR, valve
Consider non-infectious
etiologies
Positive
Negative
Positive
Negative
C. burnetii PCR, valve
Bartonella PCR, valve
T. whipplei PCR, valve
Other microorganism-specific
PCR, valve[9]
16S rRNA gene PCR/
sequencing, valve
C. burnetii PCR, valve
Bartonella PCR, valve
Other microorganism-specific
PCR, valve[9]

Antibiotic resistance

- Penicillin resistance among viridans group streptococci
- Methicillin resistance among *Staphylococcus aureus* (MRSA)

  community-acquired MRSA frequently seen.

  most alarming event - for *S. aureus*

  development of intermediate- and high-level resistance to vancomycin
- Vancomycin resistance among enterococci
- Increasing aminoglycoside resistance among enterococci

EMPIRICAL AND PROPHYLACTIC USE OF ANTIMICROBIALS

NATIONAL GUIDELINES 2016

The Sri Lanka College of Microbiologists
in Collaboration with other Professional Colleges in Healthcare
and
The Ministry of Health, Nutrition and Indigenous Medicine

Bacterial endocarditis

- Bacterial endocarditis essentially needs prolonged intravenous therapy throughout the course except in specific situations (eg. oral doxycycline for coxiella infections).
- Duration of therapy depends on the organisms isolated. Contact Microbiologist for advice.
- Defervescence might take 5-10 days despite appropriate antibiotic therapy.

Condition	Primary therapy	Alternative therapy	Comments
Native valve bacterial endocarditis	crystalline penicillin 3-4 MU IV 4 hourly + [2]gentamicin 1mg/ kg IV 8 hourly or ampicillin 2g IV 4 hourly + [2]gentamicin 1mg/kg IV 8 hourly	[1]In immediate penicillin or cephalosporin hypersensitivity [3]vancomycin 1g IV infusion (over 100 minutes) 12 hourly + [2]gentamicin 1mg/kg IV 8 hourly other penicillin hypersensitivities (excluding immediate type) ceftriaxone 2g IV daily + [2]gentamicin 1mg/kg IV 8 hourly	Obtain 3 blood cultures depending on the urgency to start antibiotics. These samples should be collected 12 hours apart. If the patient needs antibiotics urgently all samples can be collected within 1 hour (with first and last samples drawn at least 1 hour apart) from different venepuncture sites. Treatment should not be delayed if blood culture facilities are not available. Antibiotics and duration should be revised according to culture results. Discuss with the microbiologist.

ABST

- For Streptococci & Enterococci **- MIC is must** for penicillin and other antibiotics
- **Viridans Streptococci**
  - Fully sensitive to penicillin
    MIC ≤ 0.12mg /l
  - Reduced sensitivity to Penicillin
    Penicillin MIC 0.12 - 0.5 mg/l
  - Resistant to Penicillin
    Penicillin MIC >0.5 mg/l

Gentamycin Assay

- Need twice a week
- Minimize ototoxicity and nephrotoxicity
- As gentamicin is used for synergy, aim for a trough concentration of 0.5-1mg/ml and peak levels need not exceed

Pyrexia during therapy

Possibilities

1. Drug reaction
2. Super infection – contaminated IV line / drip site infection
3. Lack of control of original infection

paravalvular / embolic infection

Further blood cultures and culture of IV line are indicated

Case history

- A 22-year-old female with a history of mitral valve prolapse was admitted with complaints of intermittent fevers for 1 month and headaches for 3 weeks. Two weeks before symptoms developed, she had undergone a dental procedure.

Case history

- Four blood cultures were performed on admission.
- All four blood cultures demonstrated Gram-positive cocci in chains. The diagnosis was bacterial endocarditis

- 1**. What is significant in the patient's history?** (what situations do you think predisposed this person to infection?)

- heart valve anomaly
- recent dental procedure

What organism is most likely to be causing her infection?

What organism is most likely to be causing her infection?

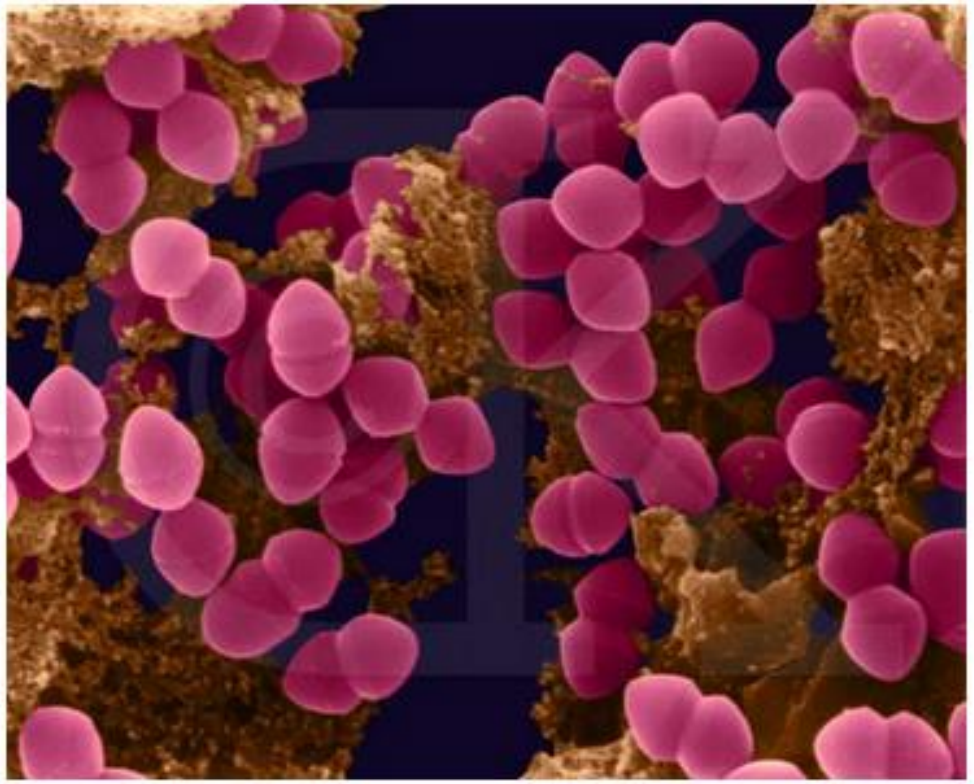
- streptococci.
- Two groups of streptococci are common causes of bacterial endocarditis
- They are **viridans streptococci**
- nonhemolytic streptococci (which include **Group D streptococci and the enterococci**).
- Because the individual had recently undergone a dental procedure, the organism causing the infection probably originated from the oral microbiota rather than the gut microbiota.

What organism is most likely to be causing her infection?

- The Group D streptococci and the enterococci are commonly found as part of the normal microbiota in the **gut**, whereas **the viridans streptococci** are common members of the **oral microbiota.**
- ***Streptococcus mutans***, a viridans streptococcus, was the organism recovered from this patient. It commonly resides on the **tongue** and **teeth**.

- The organisms that commonly cause this bacteremia are oral streptococci, which readily adhere to a variety of surfaces via a very sticky glycocalyx, so thick and sticky it is called a slime layer.
- In particular, abnormal heart valves may be affected because blood flow is slightly slowed and the streptococci have a better opportunity to adhere.
- Colonies may form and then endocarditis, or inflammation of the heart develops

Bacterial endocarditis



Streptococci