

# Bacterial Endocarditis

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## Objectives

- Identify which valves are commonly involved with endocarditis
- Identify common pathogens and the routes of acquisition associated with endocarditis
- Define what is meant by the terms right or left sided endocarditis & native valve vs prosthetic valve endocarditis
- Identify appropriate laboratory studies, specific parts of the physical exam, diagnostic procedures & diagnostic criteria (Duke) used in the diagnosis of endocarditis
- Identify appropriate treatment strategies & duration for specific pathogens or types of endocarditis

## Overview

- In pre-antibiotic era endocarditis was usually a fatal disease as a result of CHF
- Host defenses play minor role in disease
- Staphylococci and Streptococci usually responsible for  $\geq 75\%$  cases
  - *S. aureus* primary pathogen
- New Infective Endocarditis Guidelines
  - AHA Circulation 111:3167-3184, 2005
  - BSAC JAC 54:971-981, 2004

## Definitions

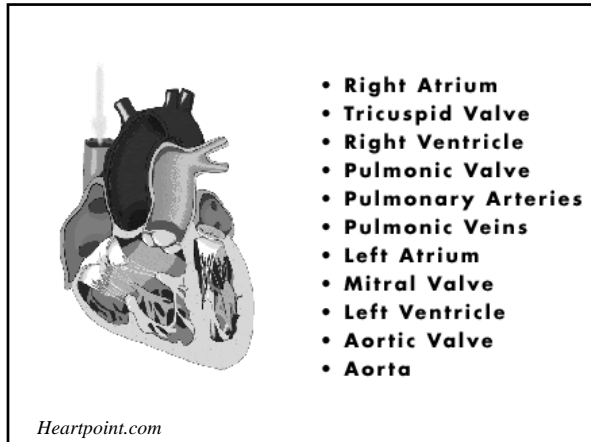
- Acute Bacterial Endocarditis (ABE):
  - Fulminating infection
  - High fever
  - Systemic toxicity
  - Death in < 6 weeks
- Subacute Bacterial Endocarditis (SBE):
  - Indolent infection
  - Prior to valvular disease
  - Death in 6 weeks – 3 months
- “Left-sided” endocarditis
  - Mitral valve

## Definitions

- “Right-sided” endocarditis
  - Involvement of the tricuspid valve
  - Related to IVDA and indwelling pacemakers
- “Native-valve” endocarditis
- “Prosthetic-valve” endocarditis
- “Culture-Negative” endocarditis
  - Bad isolation/identification technique
  - Fastidious isolate
  - Non-bacterial culprit
  - Antibiotics administration pre-culture

## Pathogenesis

- Valve surface altered through trauma or blood turbulence eroding endothelial lining
  - Fibrin and platelets deposited at the damaged site forming nonthrombotic vegetative lesion
  - Transient bacteremia seeds vegetative lesion
  - Bacteria enter exponential growth protected from WBC in the confines of the vegetation
  - Bacteria can begin to damage valve and seed bloodstream with bacteria

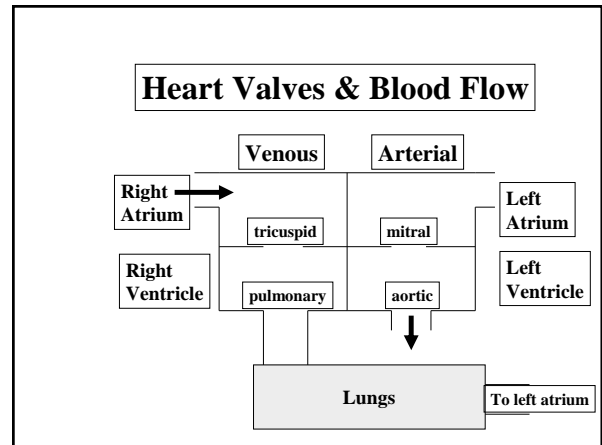


### Native Valve Endocarditis

- **Right Sided**
  - Tricuspid  $\leq 6\%$  (Most often IVDA)
  - Pulmonary  $< 1\%$
- **Left Sided**
  - Mitral 30 - 45%
  - Aortic 5 - 35%
  - Both valves  $\leq 35\%$

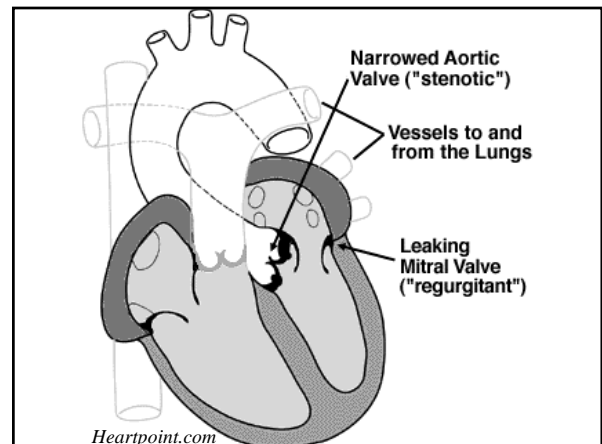
### Intravenous Drug Abuse (IVDA) Endocarditis

- **Disease of the right side of the heart**
- **May present as pulmonary syndrome**
  - Fever
  - Cough
  - Pleuretic chest pain
  - Hemoptysis
  - Pathogen a function of patient's IV drug practices
    - Contaminated water, drugs, or equipment



### Pathogenesis

- **Conditions contributing to the development of endocarditis**
  - Bacteremia (15-25%)
  - History of IV drug abuse
  - Body piercing / tattoos
  - Recent dental work
  - History of rheumatic heart disease
  - Congenital heart disease or malformations
  - Mitral valve prolapse or valvular insufficiency
  - Ventral septal defect
  - Valvular stenosis
  - Prosthetic valve



## Endocarditis

- **Common Bacterial Pathogens**
  - *S. aureus* (MRSA or MSSA)
  - *S. epidermidis* (MRSE or MSSE)
  - *S. viridans*
  - Enterococci
  - *S. pneumoniae*
  - HACEK organisms

## Staphylococcal Native Valve Endocarditis

Millar, BC et al JAC 61:1-7, 2008

	MSSA (248)	MRSA (43)	CA-MRSA (23)
Mean Age (yrs)	33	60	35
Male (%)	66	49	62
Diabetic (%)	7	28	9
IVDA (%)	55	14	43
Community Acq (%)	84	19	81
Location (%)			
Aortic	17	7	29
Mitral	18	39	29
Tricuspid	43	23	41
Embolism (%)	64	44	68
Mortality(%)	23	37	13

## Endocarditis

- **Bacterial Pathogens**
    - HACEK Group
      - *Haemophilus spp.*
      - *Actinobacillus actinomycetemcomitans*
      - *Cardiobacterium hominis*
      - *Eikenella corrodens*
      - *Kingella kingae*
- Slow growing, fastidious Gram negatives likely cause of Culture Negative Endocarditis

## Enterococci

- **Enterococci naturally tolerant to aminoglycosides**
  - MIC < 500 mg/L = “sensitive” or synergy likely
  - MIC > 2000 mg/L = “resistant”
  - Gentamicin or Streptomycin aminoglycosides of choice
  - Resistance to gentamicin does not always mean resistance to streptomycin (reverse also true)
  - Tobramycin or amikacin not reliable choice

## Culture Negative Endocarditis

- Misnomer as there may be a pathogen but organism recovery may not be possible with standard methods
  - Fungal
  - HACEK group
  - Rickettsiae
  - Chlamydiae
  - Anaerobes
  - Cysteine/Vitamin B6 dependent Streptococci
  - Brucella
  - Viral
  - Prior antibiotic therapy
  - Misdiagnosis

## Diagnosis of Endocarditis

## Diagnosis of Endocarditis

- **Duke Criteria** (Am J Med 96:200-209,1995)
  - **Definite Case of Endocarditis**
    - Must have 2 major criteria or 1 major criteria & 3 minor criteria or 5 minor criteria
  - **Possible Case of Endocarditis**
    - Patient appears to have endocarditis but does not have the necessary number of major and minor criteria
  - **Rejected Possibility of Endocarditis**
    - While possibility considered initially an alternative diagnosis established or pathologic diagnosis not established

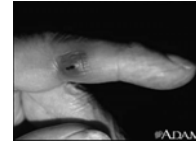
## Duke - Major Criteria

- **Positive blood cultures**
  - Typical pathogen frequently associated with endocarditis
  - Multiple positive cultures (75-100% of cultures positive)
  - Positive cultures obtained throughout the day
  - Positive serology
- **Evidence of endocardial involvement**
  - New evidence of valve regurgitation
  - Echocardiogram positive
    - Vegetation present
    - Evidence of intra-cardiac abscess
    - Dehiscence of prosthetic valve

## Duke - Minor Criteria

- **Fever  $\geq 38$  C (100.4 F)**
- **History of IVDA or predisposing heart disease**
- **Positive Blood culture but not typical pathogen**
- **Echo not meeting major criterion**
- **Immune**
  - +RF, Osler Node, Roth Spot, or Glomerulonephritis
- **Vascular**
  - PE, mycotic aneurysm, Janeway lesion, arterial emboli, intracranial hemorrhage, Flame hemorrhage

## Janeway Lesion



Janeway lesions are seen in people with acute bacterial endocarditis. They appear as flat, painless, red to bluish-red spots on the palms and soles

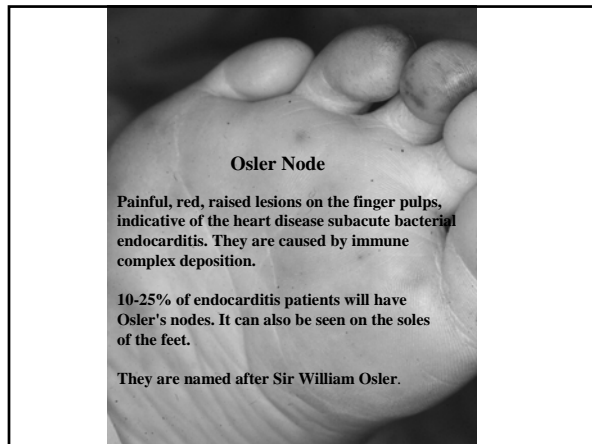


**Janeway Lesion:** Flat, painless, erythematous lesions seen on the palm of this patient's hand. While frequently associated with bacterial endocarditis, in this case, they are the result of an infected radial artery aneurysm (inflamed area proximal to thumb).  
Photo credit, Josh Fierer, M.D.



A white, round spot in the retina close to the optic disk, often surrounded by oval areas of haemorrhages.  
Seen in bacterial endocarditis, pernicious anaemia, and leukaemia

Roth Spot



### Diagnostic work-up

- CBC with differential, U/A, ESR
- $\geq 3$  sets of blood cultures drawn at different sites and times
- EKG & Echo
- Antibiotic sensitivity studies if +B/C's
- Peak / trough serum inhibitory titer (SIT) & serum bactericidal titer (SBT)
- Physical for classic findings of endocarditis
  - Neurologic (change in mental status or stroke)

### Echocardiography

- Attempt to visualize vegetation's on heart valve
  - Lesions must be  $> 2$ mm in size
- Negative test does not necessarily exclude endocarditis
  - Transesophageal (TEE)
    - Provides the most information but most invasive (approx 90% accurate in diagnosis)
  - Transthoracic (TTE)
    - Less invasive but harder to visualize valves

### Endocarditis Treatment

- For left sided endocarditis generally 4 to 6 weeks of antibiotic therapy recommended
- For right sided endocarditis shorter courses of antibiotics may be considered

### Therapeutic Goals

- Identify, if possible, the primary site of infection
- Identify infecting pathogen so as to direct therapy
- Sterilize the blood now and following therapy
- Prevent or limit valvular damage and resulting CHF
- Use a bactericidal antibiotic regimen
- Maintain optimal nutritional status of patient
- Prevent embolic disease
- Advise patient &/or family regarding future need for antibiotic prophylaxis

### Treatment Considerations

- Large bacterial inoculum
- Pathogens not in exponential growth phase compromising the effect of antibiotics
- Platelet fibrin network prevents WBC from confronting bacteria
- Antibiotics and surgery only real treatment options

## Staphylococci

- **Methicillin Resistant**
  - Vancomycin, Linezolid, Daptomycin or Q/D
- **Methicillin Sensitive**
  - Nafcillin
  - ± Gentamicin
  - ± Rifampin

## Daptomycin vs. Standard Therapy for *S. aureus* Bacteremia & Infective Endocarditis

V. Fowler, et al NEJM 355:653-665, 2006, 2006

- Daptomycin dosed at 6 mg/Kg/day vs semisynthetic penicillin or vancomycin with low dose gentamicin X 4 days
- TOC (42 days) 53/120 (44.2%) DAP vs. 48/115 (41.7%) COMP
- CPK elevation 25.0% DAP vs 12.5% COMP (p= 0.038)
  - Drug D/C'd due to CPK elevation in 3/120 (2.5%) DAP
- Worsening renal function 19.8% DAP vs. 46.8% COMP (p < 0.001)
  - Vancomycin troughs averaged just under 15 mg/L
- MIC elevations in 7 daptomycin patients (6/7 microbiologic failures)
- No difference between drugs in time to sterilize blood

## Vancomycin vs. Nafcillin *S. aureus* Endocarditis

Investigator	Antibiotic	+BC	Cure
Korzeniowski (1982)	N	Mean 3.4d	22/35 (63%)
Chambers (1988)	N+T	19/20 sterile 48hrs	47/50(94%)
	V+T	1 pt (+BC 12&14d)	1/3 (33%)
Small (1990)	V	2Pt(+BC 7-16d)	8/13(62%)
Levine (1991)	V	Median 7d	18/22(82%)
	V+R	Median 9d	18/20(90%)

Karchmer Ann Intern Med 1991

## Adjunct use of gentamicin for staphylococcus

- Data almost exclusively with right sided endocarditis, nafcillin, and *S. aureus*
- Data has been extrapolated to:
  - Left sided endocarditis
  - Bacteremia
  - *S. epidermidis*
  - Vancomycin
  - Other beta-lactam antibiotics

## Adjunct Therapy of *S. aureus* with Gentamicin

- **Questionable practice**
  - No difference in morbidity (other than duration of fever) or mortality
  - Addition of gentamicin reduces duration of bacteremia by approximately 1/2 day
  - Greatly increases risk of nephrotoxicity (NEJM 335:653-665, 2006)
- **If decision is made to use gentamicin**
  - Duration of therapy ≤ 5 days
  - Maintain Cpmax 3-5 mg/L & Cpmin < 1 mg/L
  - Present data would not support SDD

## Adjunct Use of Rifampin

- **Rifampin added for “synergy”**
  - In-vitro data suggests possible synergy, antagonism, or indifference
- **Levine suggests that the addition of rifampin to vancomycin offers no therapeutic advantage**
  - Drug might be useful in patients unable to lyse *S. aureus* inside WBC

## Enterococci

- **Beta-lactam sensitive**
  - Ampicillin or Penicillin G (+ aminoglycoside if sensitive)
- **Vancomycin Resistant**
  - Daptomycin (6 mg/Kg/day)
  - Linezolid
  - Quinupristin/dalfopristin (E. faecium only)
  - Doxycycline/Minocycline
  - Chloramphenicol
- **Aminoglycosides**
  - Gentamicin or streptomycin if sensitive (+ cell wall agent)
  - Maintain gentamicin C<sub>max</sub> 3-5 mg/L & C<sub>min</sub> < 1 mg/L
  - Maintain streptomycin C<sub>max</sub> approximately 20 mg/L

## *S. pyogenes* & *S. bovis*

- **Can use any of the following**
  - Penicillin G for 4 weeks
  - Penicillin G and gentamicin for 2 weeks
  - Penicillin G for 4 weeks and gentamicin for 2 weeks
    - MIC must be between 0.1- 0.5 mg/L
  - Ceftriaxone daily for 4 weeks
- **Outcomes are essentially equal**

## Aminoglycosides and Endocarditis

- **Aminoglycosides are ototoxic and nephrotoxic**
- **Want to limit therapy to as short a period of time as possible to avoid toxicity**
  - Staphylococci  $\leq$  5 days
  - Enterococci will require 4-6 weeks
  - Control peak and trough concentrations
- **Elderly and/or renally impaired patients treated for extended periods of time are at greatest risk**

## Role of Anticoagulants in Endocarditis

- **No anticoagulation if patient in NSR with uncomplicated endocarditis (native or bioprosthetic valve)**
- **Recommended long term in patients with PVE (mechanical) unless there are contraindications**
- **Embolism during therapy for native or bioprosthetic valve endocarditis uncertain & depend on circumstances**

## Surgical Indications in Endocarditis

- **Hemodynamically unstable**
  - New or worsening CHF
  - Valvular dysfunction
- **Uncontrolled infection**
  - + Blood cultures > 3 days
  - Fungal endocarditis
  - Perivalvular or myocardial abscess
- **Eliminate primary site of infection**

## Relative Indications for Surgery

- **Vegetation >10mm**
- **Recurrent systemic emboli ( $\geq$  2)**
- **Mitral valve preclosure**
- **Ruptured chordae tendineae, papillary muscle, ventricular septum**
- **Heart block**
- **Infection relapse**

## **Endocarditis - Cause of Death**

- CHF
- Embolic phenomena
- Mycotic aneurysm rupture
- Complications from cardiovascular surgery
- PVE
- Inadequate response to antibiotics

## **Antibiotic Prophylaxis**

American Heart Assoc. JAMA 277:1794,1997

- One hour prior to procedure:
  - 2 Gm Amoxicillin orally or
  - 600 mg Clindamycin orally or
  - 2 Gm Cephalexin orally or
  - 500 mg Clarithromycin orally or
  - 2 Gm Ampicillin intramuscularly

## **Conclusions**

- Despite changing pathogen picture for endocarditis, >75% still caused by staphylococci & streptococci
- Increasing use of prosthetic devices increasing the prevalence of MRSE
- Changing patterns of IVDA may alter the spectrum of bacterial pathogens
- Resistance with Gram positive pathogens may make us more dependent on new drugs