

# Perioperative Management of Endocarditis

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## Objectives

- Clinical Presentation
- Classification, Diagnosis & Clinical Criteria
- Imaging
- Culture-Negative and NBTE
- Pathophysiology
- Etiology
- Epidemiology
- Outcomes
- Management
  - Current Guidelines
  - Antibiotics
  - Surgery
    - Timing
    - Repair vs Replace
  - Postoperative Management
  - Special Populations
    - Surgery with Stroke
    - IV Drug Users
- Alternative Therapies
  - Laser Lead Extraction
  - Angiovac

## Clinical Presentation

- 90% = Fever, chills, night sweats, fatigue, anorexia, weight loss, etc.
- Persistent bacteremia
- 85% have a murmur
- 40% are in acute heart failure
- Other symptoms
  - Petechiae
  - Splinter hemorrhages
  - Conduction abnormalities (usually heralds aortic root abscess)
- 25% = Embolic complications: coronaries, stroke (up to 30%), renal, splenic, pulmonary (usually silent if veg <4mm)
- Hematogenous spread: joints, osteo, psoas abscess

Rajani, et al. Clin Med 2020;20:31-35.  
Vilcant V, Hai O. Bacterial Endocarditis. StatPearls. 2022

## Classification

- Acute
  - Febrile, Toxic on presentation
  - Rapidly progressive symptoms (days to weeks)
  - High mortality
  - Organisms: *S. aureus*, B-hemolytic strep, GNRs
- Subacute
  - Slower, more indolent presentation
  - Develops over weeks to months
  - Can be complicated by major embolic event
  - Organisms: *S. aureus*, VGS, HACEK, enterococci
- Native vs Prosthetic Valve

Rajani, et al. Clin Med 2020;20:31-35.

## Diagnosis & Clinical Criteria

- Modified Duke's Criteria
  - Updated (modified) in 2015
    - Made *S. aureus* bacteraemia a major criterion whether community or hospital acquired (previously was only if community)
    - Modified the Q fever (*C. burnetti*) thresholds
    - Removed TTE minor criteria
    - Established definitive criteria for possible IE
  - Ongoing discussion for further changes
    - PCR-based testing for other rare organisms may be included in next update
    - Also other minor clinical criteria: elevated ESR/CRP, new splenomegaly, hematuria
  - 80% sensitivity
    - Lower in prosthetic IE or implantable device infections

Baddour, et al. Circulation 2015;132:1435-1486  
Habib, et al. Eur Heart J. 2015;36:3075-3128

## Diagnosis & Clinical Criteria

- Definite IE
  - Pathologic Criteria
    - Pathologic lesions such as vegetation or intracardiac abscess on histology
    - Microorganisms demonstrated by culture or histology of a vegetation or abscess
  - Clinical Criteria
    - 2 major criteria OR
    - 1 major + 3 minor criteria OR
    - 5 minor criteria
- Possible IE
  - 1 major + 1 minor criteria
  - 3 minor criteria

Habib, et al. Eur Heart J. 2015;36:3075-3128

**Table 34.3.** The Modified Duke Criteria for the Diagnosis of Endocarditis**Major Criteria**

- Blood culture positive for IE
  - Typical microorganisms consistent with IE from two separate blood cultures
    - Viridans streptococci: *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or
    - Community-acquired enterococci, in the absence of a primary focus
  - Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
    - At least two positive blood cultures of blood samples drawn >12 h apart; or
    - All of three or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
  - Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
- Evidence of endocardial involvement
- Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or
  - Abscess; or
  - New partial dehiscence of prosthetic valve
  - New valvular regurgitation (worsening or changing or preexisting murmur not sufficient)

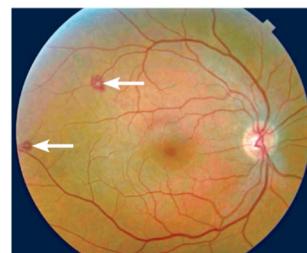
**Minor Criteria**

- Predisposition, predisposing heart condition or injection drug use
- Fever, temperature >38°C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena: Glomerulonephritis, Osler nodes, Roth's spots, and rheumatoid factor
- Microbiological evidence: Positive blood culture but does not meet a major criterion as noted previously (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organisms consistent with IE
- Echocardiographic minor criteria eliminated

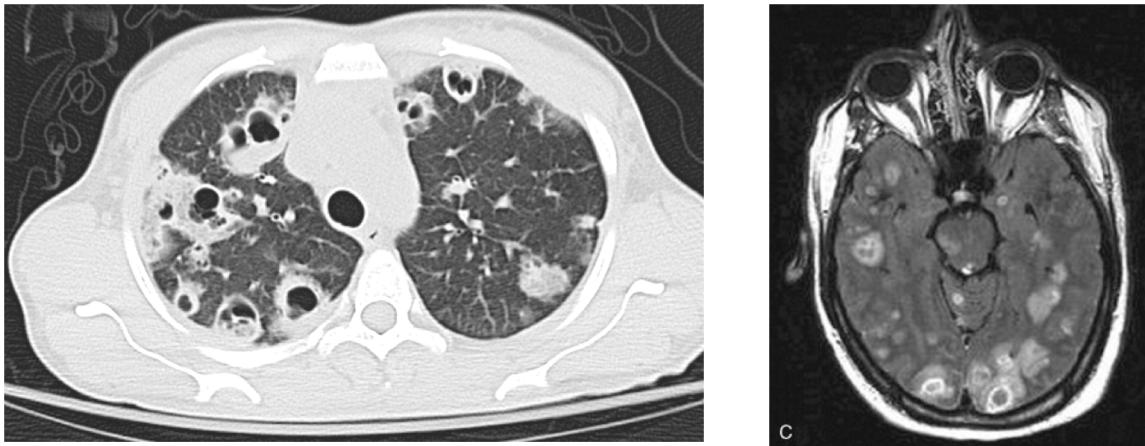
IE, Infective endocarditis; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.  
Modified from Li, J. S., Sexton, D. J., Mick, N., Nettles, R., Fowler, V. G., Ryan, T., et al. (2000). Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clinical Infectious Diseases, 30(4), 633–638.

**Janeway Lesions**

Painless, palms/soles,  
macular  
**Roth's spots**

**Osler's Nodes**

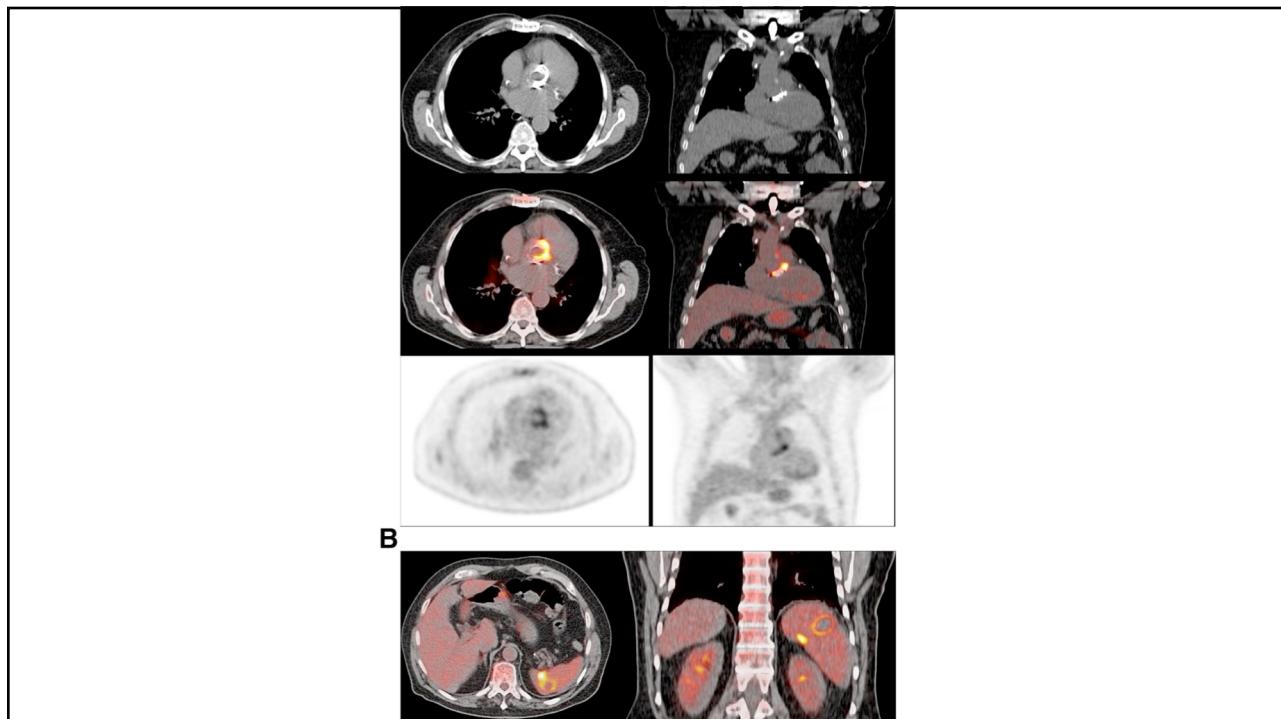
Painful, erythematous  
nodules, tips of fingers/toes



## Imaging

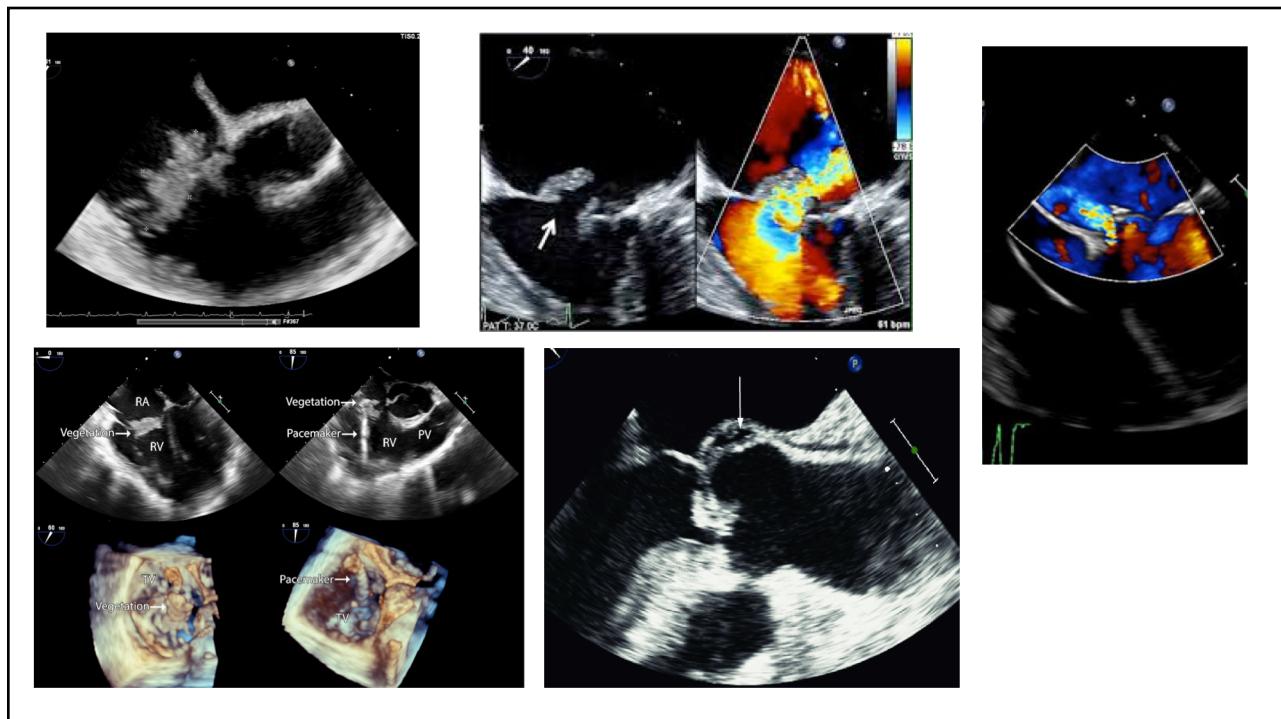
- Echo
  - TTE sensitive in 70%, but only 50% with prosthetic valves or implants
  - TEE = 90% specific/sensitive
- CTA Chest (helpful for perivalvular complications, especially with prosthetics that may obscure on echo)
- F-FDG-PET/CT
  - Uses  $^{111}\text{In}$  or  $^{99\text{m}}\text{Tc}$ -labeled autologous WBCs (infection imaging)
  - Particularly good for device-related endocarditis
  - Early identification before there is actual valvular damage
  - Also good in isolating to extracardiac components (pocket, LVAD driveline, etc) and identifying primary (non-cardiac) source in ambiguous cases
  - Sensitivity 73-100% and specificity 71-100% in prosthetic endocarditis (though only 22% in native); combined with Duke Criteria, sensitivity becomes 91-97%

Chen, et al. JACC Cardiovasc Imaging 2018;11:1679-1691  
Rajani, et al. Clin Med 2020;20:31-35.



## TEE Findings

- Vegetation = Oscillating mass in the heart
  - Usually on the upstream side (atrial or LVOT)
  - Moves into the originating chamber when valve closes
  - Vegetation directs the regurgitant jet
- Predominantly valvular regurgitation, but can have variable obstruction (ball-valve effect)
- Leaflet destruction or perforation
- Chordae rupture
- Abscess
- Fistula
- Dehiscence of prosthetic valve



## Pathophysiology

- Endothelial injury
  - Direct infection of valvular tissue by virulent organisms
  - Development of uninfected platelet-fibrin thrombus matrix which becomes a nidus for transient bacteremia
- Skin, mucosal, or previously infected sites seed the bloodstream and adhere to site of valvular damage or nonbacterial thrombus
- *Staph. aureus* can infect intact endothelium

## Etiology

- Most common infections
  - *Staph aureus* (25-50% of all comers, 60-70% of tricuspid disease)
  - Coag negative Staph (CoNS) = *S. epi*, *S. saprophyticus*, *S. haemolyticus*, *S. capitis*, *S. hominis*, *S. lugdunensis*
- Less common
  - Pseudomonas
  - HACEK organisms (Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella)
  - Fungal

Baddour, et al. Circulation 2015;132:1435-1486

## Etiology

- Left-sided infection is more common
  - Exception = IVDU
- Prosthetic valves
  - More common early in mechanical valves
  - Longterm, no difference
  - Less likely if stentless or allograft

Baddour, et al. Circulation 2015;132:1435-1486

## Culture-Negative Endocarditis

- No growth in 3 sets of blood cultures
- Incidence is 5-10% (but has been reported as high as 20%)
- Frequently due to early antibiotics (reduces recovery by 35-40%)
- Fastidious or late growing organisms
  - Coxiella, Legionella, Bartonella, Mycoplasma, Brucella, Chlamydia, fungi
- Can be hard to distinguish from non-bacterial thrombotic endocarditis (NBTE)

Rajani, et al. Clin Med 2020;20:31-35.

## Non-Bacterial Thrombotic Endocarditis

- Due to underlying clinical entities (cancer, AI disease, HIV), especially carcinomatosis
- Vegetations consistent of fibrin and platelets without inflammation or bacteria
- Life-threatening due to thromboembolism
- Rx = Correct underlying cause, no guidelines for surgery, but generally avoid

Asopa, et al. Eur J Cardiothoracic Surg 2007;32:696-701  
Rajani, et al. Clin Med 2020;20:31-35.

## IV Drug Abuse Patients

- 2-5% per year risk for each patient
- Predominantly right-sided valves
  - 46-78% tricuspid
  - 24-32% mitral
  - 8-19% aortic
- Underlying valve was NORMAL in 75-93% of patients

Rajani, et al. Clin Med 2020;20:31-35.

## Epidemiology

- Incidence:
  - 4.6/100,000 per year (reported as high as 10/100,000)
  - Significant linear increase
- Patient factors
  - M:F 1.54:1
  - Predominantly >60yo, with mean age 65.7
  - Community acquired = 58%, HC acquired = 38%, IVDU = 4%
  - Prosthetic = 30.6%
  - R-sided = 21%

Cresti, et al. Cardiovasc Diagn Ther 2017;7:27-35  
Rajani, et al. Clin Med 2020;20:31-35.

# Epidemiology

- Predisposing factors:
  - Known valvular disease (Rheumatic, Congenital)
    - Bicuspid AV, MVP, rheumatic, congenital (PDA, VSD)
    - Prior IE
    - Patients with implanted devices, indwelling catheters/lines
    - Patient with prosthetic valves
  - Comorbidities
    - Advanced age
    - CKD, particularly those on HD
    - Liver disease
  - Malignancy
  - Steroid use
  - Poorly controlled DM
  - Immunocompromised state (incl HIV)
  - Instrumentation of mucosa (oral/dental, urinary or GI tract)
  - Untreated dental disease (caries, abscess)
  - Extracardiac infections (lung, UTI, skin, abscess, etc)
  - Cardiac surgery
  - IV drug use

Cresti, et al. *Cardiovasc Diagn Ther* 2017;7:27-35  
 Rajani, et al. *Clin Med* 2020;20:31-35.

# Outcomes

- Major Non-Fatal Adverse Events
  - Hospitalization, pacemaker implantation, new Afib, sternal dehiscence, worsened LVEF, valvular dysfunction at follow-up
  - 34% had 1+ events
- Recurrence
  - 6% have one or more recurrences
  - Increased risk with *S. aureus*, R-sided IE, spondylodiscitis, IVDU
- Mortality
  - 24% in-hospital mortality (22.8% surgical, 26.4% medical)
    - 23% for native, 29% for prosthetic
  - 31.7% one-year mortality (30.4% surgical, 33% medical)
    - 29% for native, 38.5% for prosthetic
  - Higher mortality with higher age, IVDU, higher EUROSORE II and double valve infection; Strep had lower mortality

Cresti, et al. *Cardiovasc Diagn Ther* 2017;7:27-35  
 Scheggi et al. *BMC Cardiovasc Disor* 2021;21:1-9

## AHA Scientific Statement

**Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications**  
**A Scientific Statement for Healthcare Professionals From the American Heart Association**

*Endorsed by the Infectious Diseases Society of America*



Cochrane Database of Systematic Reviews

### Circulation

#### **ACC/AHA CLINICAL PRACTICE GUIDELINE**

**A comparison of different antibiotic regimens for the treatment of infective endocarditis (Review)**

**2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary**

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Marti-Carvajal AJ, Dayer M, Conterno LO, Gonzalez Garay AG, Martí-Amarista CE

## Recommendations for Diagnosis

- Blood cultures = 3 sets from different sites, with first and last drawn at least 1 hour apart (I;A)
- Expeditiously get an echo in patients suspected to have IE (I;A)
  - When Staph bacteraemia, must get an echo
  - Negative TTE does not r/o endocarditis
- If prosthetic valve, implanted device, or borderline TTE with high clinical suspicion, get TEE
- ID should be consulted to guide antibiotic therapy (I;B)
- TTE after antibiotic completion should be done for post-treatment baseline (IIa;C)

Baddour, et al. Circulation 2015;132:1435-1486

## Recommendations for Medical Management

- Count duration of therapy from the first day cultures were negative if they were initially positive (Iia;C)
- Get repeat cultures (2 sets) q24-48 hours until cleared (Iia;C)

Baddour, et al. Circulation 2015;132:1435-1486

## Summary of Antibiotic Therapy

- High dose, long duration Beta-lactams
- NVE = 4 weeks, PVE = 6 weeks
  - 2 weeks: R sided IE and combo therapy for viridans Strep NVE
- Postop:
  - 2 weeks (vs 6 weeks from negative BCx) if valve cx neg
  - Restart series if intraop culture is positive

Baddour, et al. Circulation 2015;132:1435-1486

## Summary of Antibiotic Therapy

- MSSA = no longer need Gent
- Rifampin no longer a useful adjunct for staph NVE
- Enterococcus = Amp/Gent or “double lactam” with Amp/CTX
- Partial PO therapy: L-sided, after 10-14 days
- Fungal = lifelong antibiotic suppression

Baddour, et al. Circulation 2015;132:1435-1486  
 Iversen K, et al. NEJM 2019;380:415-424

## VGS and *Strep gallolyticus (bovis)*

Highly PCN-Susceptible Native Valve	4 weeks of PCN G + CTX 2 weeks if Gent included (uncomplicated course, normal kidneys) 4 weeks of Vanc if PCN allergy
PCN Resistant (MIC 0.12-0.5) Native Valve	4 weeks of PCN G with 2 weeks of Gent 4 weeks of CTX alone could be considered 4 weeks of Vanc if PCN allergy
PCN Resistant (MIC >0.5) Native Valve	Amp or PCN G + Gent (treat like enterococcus) If Vanc used (PCN allergy), then no Gent CTX + Gent may be a reasonable alternative
Prosthetic Valve	6 weeks of PCN G or CTX +/- 2 weeks of Gent Can extend Gent to 6 weeks if MIC >0.12 Vanc ok for PCN or Gent intolerance

Baddour, et al. Circulation 2015;132:1435-1486

## *Strep pneumo, Strep pyogenes, Group B, C, F, and G Strep*

<i>S. pneumo</i> Native Valve	4 weeks of PCN G, Ancef, or CTX 4 weeks of Vanc if PCN allergy
<i>S. pneumo</i> Prosthetic Valve	6 weeks of therapy
PCN Resistant <i>S. pneumo</i>	Without meningitis: High-dose PCN or 3 <sup>rd</sup> Gen Cephalosporin With meningitis: High-dose Cefotax or CTX If Cefotax resistant (MIC >2): Consider adding Vanc + Rifampin
<i>S. pyogenes</i>	4-6 weeks of PCN G or CTX Vanc if PCN allergy
Group B, C, F, G Strep	4-6 weeks of PCN G or CTX +/- Gent

Baddour, et al. Circulation 2015;132:1435-1486

## *Staphylococcus*

MSSA L-sided Native Valve	6 weeks of Nafcillin or Oxacillin (longer if “complicated”) Consider combo therapy of Vanc + Oxacillin/Nafcillin until susceptibilities back Cefazolin or Vanc for PCN allergy (should do allergy challenge) Dapto is a reasonable Vanc alternative  PCN G not recommended (labs can't detect susceptibility) Gent not recommended (high resistance, no benefit, nephro/ototoxicity) Rifampin not recommended (rapid resistance, no benefit, hepatotoxicity) Clinda not recommended (high relapse rate)
MSSA R-sided Native Valve (IVDU)	2-4 weeks of IV therapy vs 4 weeks of PO therapy Gent not recommended (no benefit, may cause harm)

Baddour, et al. Circulation 2015;132:1435-1486

## *Staphylococcus*, continued

MSSA Prosthetic Valve	6 weeks Combo Therapy: Nafcillin or Oxacillin + Rifampin 2 weeks of Gent FQ if Gent resistant Early Surgical intervention
MRSA Prosthetic Valve	6 weeks Combo Therapy: Vanc + Rifampin 2 weeks of Gent (or FQ)
CoNS Prosthetic Valve	6 weeks of Vanc/Rifampin + 2 weeks of Gent Use alternative AG if Gent resistant Fluoroquinolone if pan-resistant to Gent
Vanc Resistance (hVISA, VISA, or VRSA)	Salvage situation: consult ID ?? Bactrim + Dapto, Linzeolid, Ceftaroline, Quiupristin-dalfopristin

Baddour, et al. Circulation 2015;132:1435-1486

## *Enterococcus (\*\*E. faecalis, E. faecium)*

All strains	Should routinely test for PCN/Vanc susceptibility and high-level Gent resistance + Dapto and Linezolid sensitivities if Vanc/AG, BL resistant Give Gent q8 instead of daily
Pansusceptible Native Valve	<3 months of symptoms = 4 weeks >3 months of symptoms = 6 weeks Amp or PCN G + Gent (4 weeks ok) If cannot use Gent: "Double Lactam" Amp + CTX (6 weeks) Vanc if PCN allergic
Pansusceptible Prosthetic Valve	6 weeks of therapy
PCN Resistant Native & Prosthetic	6 weeks of Vanc + Gent

Baddour, et al. Circulation 2015;132:1435-1486

## *Enterococcus, continued*

VRE (E. faecalis)	(only 3% are MDR, mostly PCN susceptible) Linezolid and Dapto are the only alternatives
VRE (E. faecium)	(95% are MDR to Vanc, AG, PCN) Salvage situation: consult ID Linezolid or high-dose Dapto (+/- Amp or Ceftaroline) Maybe Quinupristin-dalfopristin, Tigecycline, or Tedizolid

Baddour, et al. Circulation 2015;132:1435-1486

## *HACEK Organisms*

All organisms	Considered Amp and PCN resistant Gent not recommended (toxicity)
HACEK Native Valve	4 weeks CTX, Unasyn (or 3rd/4 <sup>th</sup> generation Cephalosporin) FQ as alternative for allergy
HACEK Prosthetic Valve	6 weeks

Baddour, et al. Circulation 2015;132:1435-1486

## Non-HACEK GNR

- Usually *E. coli*, Enterobacter and Pseudomonas
- Has been associated with *Salmonella*
- Usually have healthcare exposure
- Expedited surgery + 6 weeks of antibiotics (BL + AG or FQ)
- High resistance rates (and have inducible  $\beta$ -lactamase resistance) = consult ID

Baddour, et al. Circulation 2015;132:1435-1486

## Culture-Negative IE

- Deep history taking and ID consult to establish prior infections & best course of empiric therapy

Acute presentation Native Valve	<i>S. aureus</i> , B-hemolytic strep, aerobic GNRs Vanc + Cefepime
Subacute presentation Native Valve	<i>S. aureus</i> , VGS, HACEK, enterococci Vaanc + Unasyn
PVE <1 year postop	Staph, Enterococci, aerobic GNRs Vanc + Cefepime + Rifampin + Gent
PVE >1 year postop	Staph, VGS, Enterococci Vanc + CTX

Baddour, et al. Circulation 2015;132:1435-1486

## Fungal

- Mostly *Candida* >> *Aspergillus*
- *Candida* usually eventually culture positive; *Aspergillus* usually culture negative
- Risk factors = IVDU, Immunocompromised, Indwelling devices/lines, prostheses (43% >1 year out)
- Abysmal outcomes (survival <20%)
- Must have surgery (50% reduction in death) + >6 weeks of Amphotericin B + flucytosine
- Lifelong suppression with an oral azole

Baddour, et al. Circulation 2015;132:1435-1486

## Surgical Indications

- >50% of patients need surgery
- STS RISK-E Scoring system
- For all locations:
  - Highly resistant or fastidious organisms (fungi, MDR, non-HACEK GNRS)
  - Persistent bacteremia >5-7 days despite antibiotics
  - Recurrent emboli despite antibiotics

Baddour, et al. Circulation 2015;132:1435-1486  
Olmos C, et al. Heart 2017;103:1435-1442  
Pettersson GB, et al. Ann Cardiothorac Surg 2019;8:630-644

## Emergency Surgery

- Within 24-48 hours if:
  - Cardiogenic shock
  - Large mobile veg at imminent risk of embolism

Baddour, et al. Circulation 2015;132:1435-1486  
Pettersson GB, et al. Ann Cardiothorac Surg 2019;8:630-644

## Prosthetic Valve

- HF from dehiscence, fistula, or severe valve dysfunction
- Abscess, HB, or destructive penetrating lesion
- Relapsing PVE
- Mobile vegetation >10mm

Baddour, et al. Circulation 2015;132:1435-1486  
Pettersson GB, et al. Ann Cardiothorac Surg 2019;8:630-644

## Left-Sided Native Valve

- Valve dysfunction with HF symptoms
- Abscess, HB, or destructive penetrating lesion
- Persistent or enlarging vegetations
- Mobile veg >10mm + severe regurg
- Veg >10mm on the AL of MV

Baddour, et al. Circulation 2015;132:1435-1486  
Pettersson GB, et al. Ann Cardiothorac Surg 2019;8:630-644

## Right-Sided Native Valve

- Those with Complications:
  - RHF 2/2 severe TR with poor medical response
  - TV veg >20mm

Baddour, et al. Circulation 2015;132:1435-1486  
Pettersson GB, et al. Ann Cardiothorac Surg 2019;8:630-644

## Repair vs Replace

- TV and MV Repair are superior
  - No prosthetic material or need for reoperation
  - Better survival, lower risk of recurrent infection
  - Short and longterm benefit
- Allograft may be better for AV IE

Lee HA, Chou AH, Wu, VC, et al. J Thorac Cardiovasc Surg 2021;59:878-886

Lee HA, Cheng YT, Wu VC, et al. J Thorac Cardiovasc Surg 2018;156:1473-1483

Pettersson GB, et al. Ann Cardiothorac Surg 2019;8:630-644

Toyoda N, Itagaki S, Egorova NN, et al. J Thorac Cardiovasc Surg 2017;154:1906-1912

## Postoperative Management

- High dose inotropes are more likely required in:
  - Males
  - Preop inotropes or low baseline MAP
  - Preop sepsis or heart failure
  - Preop mechanical ventilation
  - Low GFR, Higher Creatinine
  - Higher ASA score
  - Thrombocytopenia, high INR, high LDH, high CRP
  - Multiple valves involved
  - Abscess or valvular perforation
  - Longer CPB, cross clamp, and surgical time

Bellotti J Cardiothorac Vasc Anesth 2018;32:2529-2536

## Surgery in Patients with Stroke

- Stroke is a RF for mortality
- Cardioembolic
  - Concern is hemorrhagic conversion
  - Similar to ?better outcomes for early surgery (<7 days)
- Hemorrhagic
  - Prohibitively high risk for at least 4 weeks
  - Concern for mycotic aneurysms
- Hold anticoagulation for 2 weeks in mechanical IE with embolic stroke
  - ASA/Antiplatelet are not recommended

Baddour, et al. Circulation 2015;132:1435-1486  
Pettersson GB, et al. Ann Cardiothorac Surg 2019;8:630-644

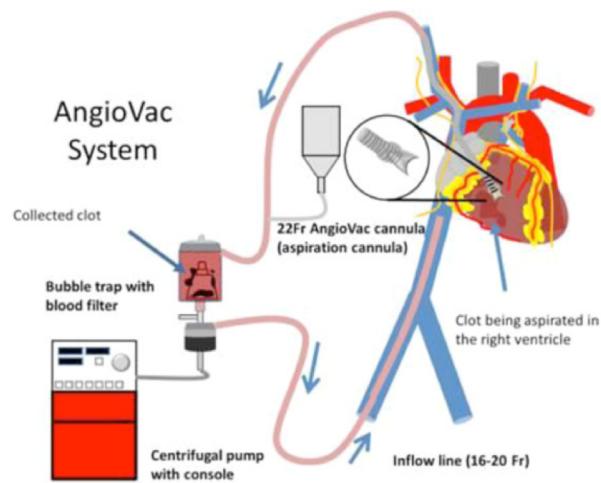
## IV Drug Abusers

- Must refer for substance abuse therapy
- Avoid surgery whenever possible → AngioVac
- No difference in mortality in the first 3 months or >6 months (3-6 month relapse window)
- No clear guidelines for reoperation if otherwise a good surgical candidate

Baddour, et al. Circulation 2015;132:1435-1486  
Elbatarny, et al. Gen Hosp Psychiatry 2019;57:44-49

## AngioVac

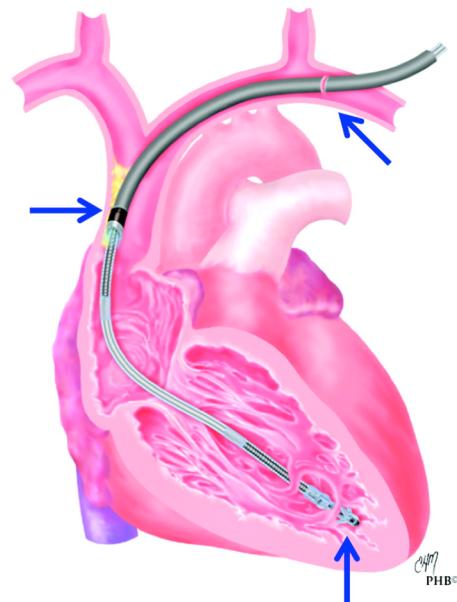
- Classically for R-sided vegetations, but has been deployed transtetally for MV disease
- Effective for debulking when surgical risk is prohibitive
  - 90% removal >50%
  - >80% cleared cultures
- Often worsens TR



Lu SY, et al. J Cardiothorac Vasc Anes 2021;35:1040-1045  
Mhanna, et al. Curr Probl Cardiol 2022;47:101353

## Laser Lead Extraction

- A laser sheath is placed encapsulating the lead
- Cool cutting Xe lasers lyses scar tissue under counter traction to facilitate lead removal
- Worse outcomes (esp. Strep) than fractured lead, particularly when delayed



Buch, et al. Circulation. 2011;123:e378-80  
Aleong, et al. J Am Heart Assoc 2020;9:e011473