23 – Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices

Speaker: Henry Chambers, MD

Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices

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Disclosures of Financial Relationships with Relevant Commercial Interests

- Equity: Moderna
- Data Monitoring Committee: Merck
- Consultant: Janssen

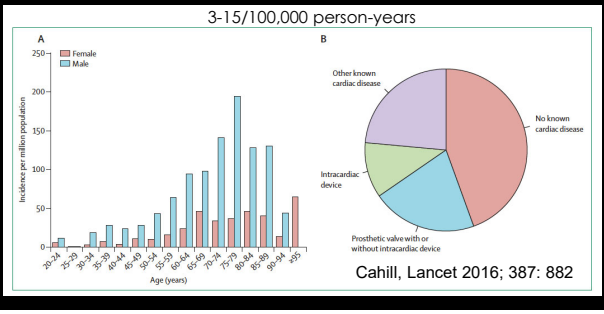
Topics for Discussion

- Diagnosis of endocarditis
- Native valve endocarditis
- Culture-negative endocarditis
- Prosthetic valve and device-related infections

Diagnosis of Endocarditis

Epidemiology

3-15/100,000 person-years



Cahill, Lancet 2016; 387: 882

Clinical Signs and Symptoms

Finding	Approximate Prevalence, %
Fever	90
Murmur	70-85
New murmur	50
Worsening old murmur	20
Peripheral stigmata (e.g., Osler's)	20% or less
Heart failure, cardiac complications	20-50
CNS complications	20-40

Arch Intern Med. 2009;169:463-473

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Q1. Which one of the following statements is correct?

1. Staphylococcus aureus is the most common cause of bacterial endocarditis
2. Dental procedures carry a substantial risk for streptococcal endocarditis for patients with predisposing cardiac lesions
3. Three-quarters of patients with endocarditis have a known underlying cardiac predisposing condition
4. Fever and a new cardiac murmur are present in the majority of patients with endocarditis

Microbiology

Organisms	Approximate % of Total
Staphylococci	**40-50**
S. aureus	30-40
Coag-neg	10
Streptococci	**25-30**
Viridans group	20
S. gallolyticus	5
Groups B, C, D	5
Enterococcus	**10**
HACEK	**1-2**
Culture-negative	**3-5**

Arch Intern Med. 2009;169:463; Antimicrob Agents Chemother. 2015;60:1411; Clin Infect Dis. 2018;66:104; Lancet 2016; 387: 882

Modified Duke Criteria for Diagnosis of Endocarditis

Definite pathologic diagnosis	Definite Clinical Diagnosis	Possible Clinical Diagnosis
Organisms on histology or culture of vegetation, intracardiac abscess or peripheral embolus OR Evidence of a vegetation or intracardiac abscess, confirmed by histology showing active endocarditis	Two major criteria OR Five minor criteria OR One major plus three minor criteria	Three minor criteria OR One major plus one minor criteria

If criteria either for definite or for possible endocarditis are not met, the diagnosis of infective endocarditis is rejected.

Duke Major Clinical Criteria for Diagnosis of Endocarditis

Positive blood cultures	Positive Echocardiogram	Regurgitant murmur
Typical microorganisms* from 2 separate blood cultures OR Persistently positive blood cultures (two > 12h apart, all of 3 or majority of ≥ 4) OR Single positive blood culture for Coxiella burnetii or phase I IgG antibody titer >1:800	Vegetation, defined as an oscillating intracardiac mass on a valve or supporting structure OR Abscess OR New partial dehiscence of a prosthetic valve	New (worsening old murmur does not count)

**Staphylococcus aureus*, viridans group streptococci, *Streptococcus gallolyticus*, HACEK species (*Hemophilus* species, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*), and community-acquired enterococci in absence of a primary focus.

Duke Minor Clinical Criteria for Diagnosis of Endocarditis

- Presence of predisposing cardiac condition or intravenous drug use
- Temperature ≥38.0ºC (100.4ºF)
- Vascular phenomena: systemic arterial emboli, septic pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor
- Positive blood cultures that do not meet major criteria, OR serologic evidence of active infection with organism consistent with infective endocarditis

Modified Duke Criteria for Diagnosis of Endocarditis

Definite pathologic diagnosis	Definite Clinical Diagnosis	Possible Clinical Diagnosis
Organisms on histology or culture of vegetation, intracardiac abscess or peripheral embolus OR Evidence of a vegetation or intracardiac abscess, confirmed by histology showing active endocarditis	Two major criteria OR Five minor criteria OR One major plus three minor criteria	Three minor criteria OR One major plus one minor criteria

Sensitivity: 70% (definite), 95% definite + possible
Specficity: 95%

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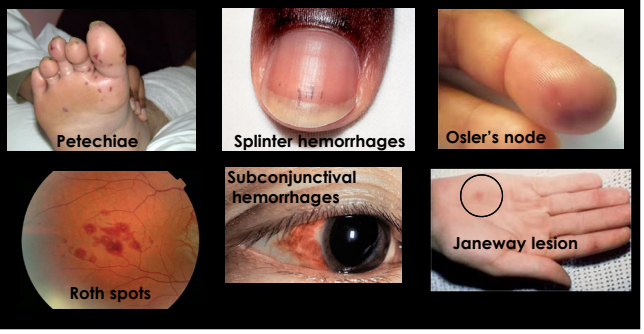
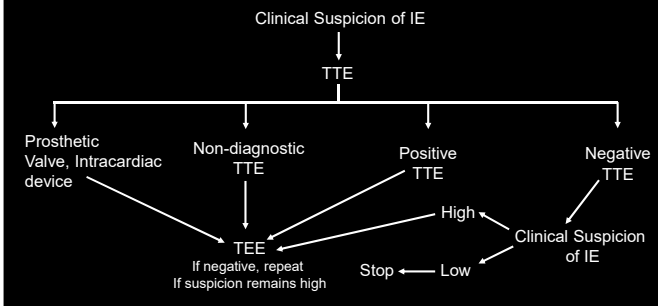
Microvascular/Immunologic Phenomena



Role of Echocardiograpy



European Heart Journal (2015) 36, 3075–3123

Harmonic TTE vs TEE for Diagnosis of IE

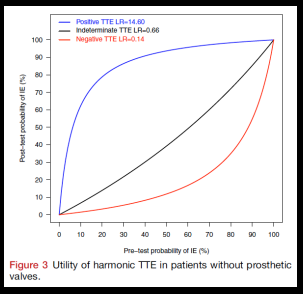


Figure 3 Utility of harmonic TTE in patients without prosthetic valves.

- Conclusively negative harmonic TTE useful to r/o native valve IE
- TTE less sensitive than TEE for detecting prosthetic IE vegetations, dehiscence, abscess
- Indeterminant TTE not useful to r/o endocarditis
- TTE insensitive for abscess, IE of implantable cardiac device
- Specificity of TTE is ~95%

Bai, J Am Soc Echocardiogr 2017; 30:639-646.e8

High Risk Factors for Proceeding to TEE

- High risk patients (examples)
  - Prosthetic valve
  - Congenital heart disease
  - Previous endocarditis
  - New murmur, heart failure, heart block, stigmata of IE
- High risk TTE (examples)
  - Large or mobile vegetations, anterior MV leaflet veg
  - Valvular insufficiency, perivalvular extension, valve perforation
  - Ventricular dysfunction

Native Valve Endocarditis

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

Larry M. Baddour, MD, FAHA, Chair; Walter R. Wilson, MD; Arnold S. Bayer, MD; Vance G. Fowler, Jr, MD, MHS; Imad M. Tleyjeh, MD, MSc; Michael J. Rybak, PharmD, MPH; Bruno Barsic, MD, PhD; Peter B. Lockhart, DDS; Michael H. Gewitz, MD, FAHA; Matthew E. Levison, MD; Ann F. Bolger, MD, FAHA; James M. Steckelberg, MD; Robert S. Baltimore, MD; Anne M. Fink, PhD, RN; Patrick O'Gara, MD, FAHA; Kathryn A. Taubert, PhD, FAHA; on behalf of the American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council

Circulation. 132:1435-86, 2015

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Q2. A 63 y/o. man with no significant past medical history presents with a week of fever, rigors, and progressive dyspnea on exertion.

- Exam : BP 160/40 P110 , 39.5
  - Rales ½ way up bilaterally
  - Loud diastolic decrescendo murmur, lower left sternal border
- Labs and studies
  - WBC 23,000 90% PMNS, HCT 30. Platelets 110.
  - Creatinine 1.6 mg/dl
  - TTE 1.5 cm oscillating mass, on bicuspid AV with severe aortic regurgitation
- 3/3 blood cultures: Gram positive cocci in clusters.

Q2. What antibiotic regimen would you recommend pending further information about Gram-positive cocci?

1. Nafcillin
2. Vancomycin
3. Vancomycin + nafcillin
4. Vancomycin + gentamicin
5. Vancomycin + gentamicin + rifampin

Native Valve Staph. aureus IE

Regimen	Duration	Comments
MSSA		
Nafcillin or oxacillin	6 wk	2 wk uncomplicated R-sided IE (IDU)
Cefazolin	6 wk	Pen-allergic naf-intolerant patient (equivalent to naf)
MRSA		
Vancomycin	6 wk	For MSSA if beta-lactam hypersensitivity
Daptomycin	6 wk	≥ 8 mg/kg/day, vanco alternative

No gentamicin, no rifampin

Q3. A 63 y/o woman with a history of mitral valve prolapse presents with 3 weeks of low-grade fever, fatigue, generalized weakness, weight loss, arthralgias. She is first chair violinist for the local orchestra

- Exam: BP 135/90 P100 , 38.2°C
  - 3/6 holosystolic murmur, radiating the the axilla
  - Lungs are clear, no peripheral stigmata of endocarditis
- Serum creatinine 1.2 mg/dl
- TTE: mitral valve prolapse with 0.5 cm vegetation on anterior leaflet, moderate regurgitation
- 3/3 blood cultures from admission positive for *Streptococcus mitis*, penicillin MIC = 0.25 μg/ml, ceftriaxone MIC = 0.25 μg/ml.

Q3. What antibiotic regimen would you recommend for definitive therapy of this patient's infection?

1. Penicillin for 6 weeks
2. Penicillin + gentamicin for 4 weeks
3. Ceftriaxone for 4 weeks
4. Penicillin + gentamicin for 2 weeks then penicillin for 2 weeks
5. Ceftriaxone + gentamicin for 2 weeks then ceftriaxone for 2 weeks

Treatment of VGS and Strep. gallolyticus Native Valve Endocarditis

- Pen MIC ≤ 0.12 μg/ml
  - Penicillin or ceftriaxone + gent x 2 weeks
  - Penicillin, ceftriaxone, vancomycin x 4 weeks
- Pen MIC > 0.12 μg/ml, < 0.5 μg/ml
  - Penicillin or ceftriaxone (4 wk) + gent (2 wk)
  - Ceftriaxone or vancomycin (4 wk)
- Pen MIC ≥ 0.5 μg/ml (Gemella and nutritionally deficient species, Abiotrophia and Granulicatella)
  - Penicillin or ceftriaxone + gent
  - Vancomycin
  - Duration 4-6 weeks (two weeks of gent may be sufficient)

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Q4. A 72 y/o man type 2 diabetes mellitus, stage II chronic kidney disease (CKD), and a history of mild aortic stenosis is admitted to the hospital with fever, dysuria, and urinary frequency.

- Exam: T38.9°C, Pulse 110 , BP 145/95 mm Hg.
  - Lungs are clear
  - 3/6 systolic ejection murmur at the right upper sternal boarder.
- Lab results
  - Serum glucose 340 mg/dl
  - Serum creatinine 1.7 mg/dl, BMP otherwise normal
  - UA: 3+ protein, 20-50 wbcs/high power field, 4+ glucose.
  - Two blood cultures and a urine culture are positive for ampicillin-susceptible *Enterococcus faecalis*.

Q4. What antibiotic regimen would you recommend for definitive therapy of this patient's infection?

1. Ampicillin for 2 weeks
2. Penicillin + gentamicin for 4 weeks
3. Ampicillin + gentamicin for 4 weeks
4. Ampicillin + ceftriaxone for 6 weeks
5. Daptomycin for 8 weeks

Enterococcal Endocarditis

Regimen	Duration	Comments
Pen or amp + gent	4-6 wk	Pen S, Gent 1 mg/kg q8h, 6 wk for PVE, symptoms >3 mo*
Amp + ceftriaxone	6 wk	Pen S, aminoglycoside susceptible or resistant
Pen or amp + strep	4-6 wk	Gent resistant, strep synergy, ClCr ≥ 50
Vanco + gent	6 wk	Pen resistant or beta-lactam intolerant (toxic!)
Linezolid or dapto	> 6 wk	VRE: Dapto 10-12 mg/kg & combo with amp or ceftaroline

*Limited data that 2 weeks of gent is sufficient

HACEK Organisms

- Haemophilus species
- Aggregatibacter species
- Cardiobacterium hominis
- Eikenella corrodens
- Kingella species

Antimicrobial Therapy of HACEK Endocarditis

Regimen	Comments
Ceftriaxone	Regimen of choice NO GENT: nephrotoxic
Levofloxacin	Levo or FQ as single agent OK as alternative regimen NO GENT: nephrotoxic
Ampicillin	Avoid: assume amp or pen resistant if no reliable MIC NO GENT: nephrotoxic

Culture-Negative Endocarditis

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Culture-Negative Endocarditis

- Prior antibiotics
- Fastidious organisms
  - HACEK
  - Abiotrophia defectiva, et al
- "Non-cultivatable" organism
  - *Bartonella quintana* > *henselae*
  - *Coxiella burnetii*, *Tropheryma whipplei*, *Legionella* spp.
- Fungi (molds)
- Not endocarditis
  - Libman-Sacks, myxoma, APLS, marantic

Culture-Negative Scenarios

- **Coxiella burnetii (Q fever)**: Direct or indirect animal contact, hepatosplenomegaly, abnormal or prosthetic valve. **Rx:** Doxycycline + hydroxychloroquine x 18 mo.
- **Bartonella quintana**: Homeless, indolent, valve normal or abnormal, louse vector. **Rx:** 6 wks doxycycline plus two wks gentamicin or plus 6 wks rifampin, then doxy for another 6 wk (resected valve) to 3 mo (no valve surgery).
- **Tropheryma whippeli:** Indolent, protracted course with arthralgias, diarrhea, malabsorption, weight loss, CNS involvement . **Rx:** Doxycycline + hydroxychloroquine x 12 mo, then more doxy…

Tools for Diagnosis of Culture-Negative Endocarditis

Organism	Clinical clues	Serology	Specific PCR	Universal 16s/18s rRNA PCR
HACEK, strep, etc	Prior antibiotics			X
Legionella spp.	Immunocompromise, PVE	X	X	X
T. whipplei	Chronic illness		X	X
Brucella spp.	Travel	X		X
Bartonella spp.	Cats, homeless, lice	X	X	X
Mycoplasma		X		X
Q fever	Animal contact, lab	X	X	X
Yeast, molds	Immunocompromised	X		X

Prosthetic Valve and Device-Related Endocarditis

Diagnosis of PVE

- Duke criteria and TEE less sensitive for PVE compared to native valve endocarditis
- PET-CT (^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography) plus Duke criteria*
  - Increased sensitivity: 84% vs. 57%
  - Reduced specificity: 71% vs 96%
- Multislice/Cardiac CT angiography similar to TEE in sensitivity and specificity, but added anatomic detail, useful if TEE non-diagnostic

*J Am Coll Cardiol Img 2020;13:2605
Clin Infect Dis 2021; 72:1687; Journal of Cardiology 2019; 73:126

Microbiology of PVE

Organisms	2 mo. Post-op (%)	2-12 mo. Post-op (%)	> 12 mo Post-op (%)
S. aureus	30	13	22
Streptococci	2	13	30
Enterococci	8	11	11
HACEK	0	0	4
CoNS	28	36	12
Gram-neg bacilli	10	4	5
Fungi	9	8	1
Culture-negative	6	6	10

Adapted from Karcher and Chu, UpToDate, 2020

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Mycobacterium chimaera PVE

- Culture-negative endocarditis
- Indolent, may occurs years after cardiac surgery
- Due to contamination of heater-cooler units (Sorin Stockert 3T; LiveNova PLC, London, UK) connected to cardiac bypass machines

Antimicrobial Therapy of PVE

Organism	Regimen	Duration
S. aureus, CoNS	Naf (MS) or vanco (MR) + gent + rif (add later)	Gent x 2 wk, naf/vanco + rif x 6 weeks
Streptococci, MIC $\leq$ 0.12 μg/ml	Pen or ceftriaxone $\pm$ gent OR Vancomycin	6 weeks (optional gent, 1st 2 wk) 6 weeks
Streptococci, MIC > 0.12 μg/ml	Pen or ceftriaxone + gent OR Vancomycin	6 weeks 6 weeks
Enterococci	Same as for NVE	6 weeks

Transcatheter Aortic Valve Replacement

- Enterococci > S. aureus/CoNS > streptococci
- Risk of PVE for TAVR similar to surgical aortic valve replacement (SAVR)
- Sensitivity of TEE probably less in TAVR compared with SAVR
- Higher early and 1-year mortality with TAVR than SAVR, likely due to patient selection
- Antimicrobial therapy as for PVE

Clin Infect Dis 2021; 72:1687; PlosOne 2020;15: e0225077; Clin Microbiol Infect 2020;26:999

Cardiac Implantable Device Infections

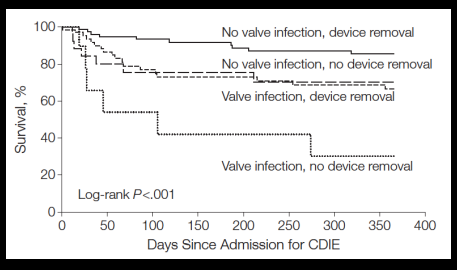
(permanent pacemakers, defibrillators)

J Am Coll Cardiol 2008;49:1851; Circulation 2010;121:458; NEJM 2012;367:842; JAMA 2012;307:1727

Cardiac Implantable Device Infection Types

- Pocket site/generator only : ~ 60%
  - Blood culture positive <50%
  - Pocket infection or generator/lead erosion
- Occult bacteremia/fungemia: ~7-30%
- Lead infection +/- endocarditis: ~10-25%
- PET-CT may detect localized infection if work-up is inconclusive

Survival with and without Device Removal



Athan, JAMA. 2012; 307:1727-1735

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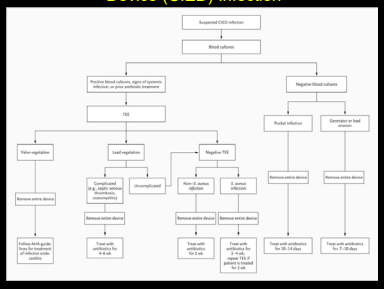
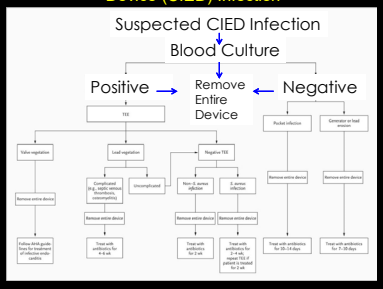
Algorithm for Management of an Infected Cardiac Implantable Device (CIED) Infection



Baddour LM et al. N Engl J Med 2012;367:842-849 The NEW ENGLAND JOURNAL of MEDICINE

Algorithm for Management of an Infected Cardiac Implantable Device (CIED) Infection



Baddour LM et al. N Engl J Med 2012;367:842-849 The NEW ENGLAND JOURNAL of MEDICINE

AHA Guidelines for Management of Cardiac Implantable Device Infections

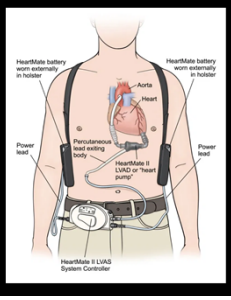
- Blood cultures before antibiotics
  - If positive, then TEE
- Gram stain, culture of pocket tissue, lead tips
- Device removal for all infections and occult staphylococcal bacteremia (conside for bacteremia with other endocarditis-causing organisms)
- Therapy (antibiotic based on susceptibility)
  - Pocket infection: 10-14 days
  - Bloodstream infection: ≥ 14 days
  - Lead or valve vegetations/endocarditis: 4-6 weeks

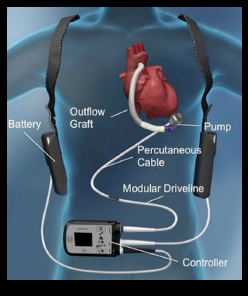
Circulation 2010;121:458-77

AHA Guidelines for Reimplantation

- Determine if reimplantation necessary
- New device on contralateral side
- ≥72h negative BC before reimplantation
- If IE: reimplant ≥ 14d after original removal
- Antibiotic prophylaxis: 1h before implantation, none thereafter

Infection of Ventricular Assist Devices





Types of VAD Infections

- VAD-specific infections
  - Pump pocket/cannula infections
  - Pocket infections
  - Driveline exit site infections (superficial or deep)
- VAD-related infections
  - Bloodstream infections (VAD-related, IV catheter/non-VAD related)
  - Endocarditis (pump or cannula, native valve)
  - Mediastinitis, sternal wound infections
- Non-VAD infections

Clinical Transplantation 2019;33:e13552.

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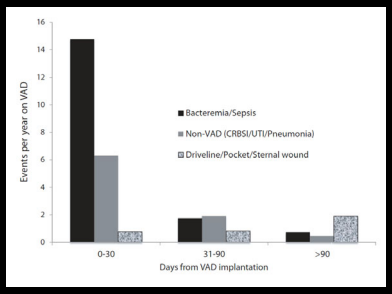
Timing and Types of Infections After VAD Implantation



Clinical Transplantation 2019;33:e13552.

Microbiology of VAD-Specific Infections

- S. aureus/coag-negative staphylococci
- Pseudomonas aeruginosa
- Enteric Gram-negatives
- Enterococci
- Candida

Clinical Transplantation 2019;33:e13552.

Antimicrobial Therapy

- Initial empirical coverage for MRSA and Pseudomonas aeruginosa
- Pathogen-directed therapy when possible
- Chronic suppressive therapy to prevent relapse

Clinical Transplantation 2019;33:e13552;
Open Forum Infect Dis. 2020 Nov 16;8(1):ofaa532

Antimicrobial Therapy

Infection type	Initial therapy	Chronic suppressive therapy (oral or IV)
BSI, non-L-VAD	IV, 2 wk	Probably not needed
BSI, L-VAD-related	IV, 6 wk	Expected
Mediastinitis	IV, 4-8 wk	Expected
Superficial driveline	Oral or IV, 2 wk	OK to stop, but may relapse
Deep driveline	IV, 2-8 wk depending on source control, BSI present	Expected
Pump pocket	IV, 4-8 wk, source control/device exchange	Expected unless device removed
Pump/cannula	IV, ≥ 6 wk, device exchange	Expected unless device removed

Clinical Transplantation 2019;33:e13552;
Open Forum Infect Dis. 2020 Nov 16;8(1):ofaa532

Other Management Issues

Surgical Management of NVE

- Optimal timing of surgery not known
- Early surgery
  - Heart failure due to valvular dysfunction, fistula, shunt
  - Uncontrolled infection
    - MDR, fungal pathogens, persistently pos. BC (5-7d)
    - Paravalvular complication (abscess, heart block, fistula)
  - Prevention of systemic embolization
    - Vegetation > 10 mm, one or more embolic events on therapy

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Fever during Therapy of Endocarditis

- Very common, lasts into the second week, a concern in PVE
- Cause (if one is found, when often it is not)
  - Abscess: valve ring or elsewhere
  - Septic pulmonary emboli, pleural effusion
  - Another infection (e.g., IV site, fungal superinfection)
  - Polymicrobial endocarditis
  - Drug fever
- Work-up:
  - Repeat blood cultures
  - Imaging studies: TEE, abdominal CT, MRI of the spine, etc

Valve Surgery with Stroke

- Stroke is an independent risk factor for post-op mortality
- Early surgery with stroke or subclinical cerebral emboli may be considered if intracranial hemorrhage excluded by imaging and neurological damage is not severe
- For patients with major stroke or hemorrhage, delay valve surgery 4 weeks (although more recent studies have called this into question)

Venn, Am Heart J 2019;216:102-112

Embolic Events in IE

- Systemic embolization in up to 50% and higher
- CNS accounts for 65%
- Highest rates in MV IE (anterior > posterior leaflet)
- 10-fold decrease in rate during first 2-3 weeks of antibiotic therapy
- ~3% of patients suffer a stroke after 1 week of therapy (benefit of early surgery correspondingly less)
- Value of CNS imaging all patients with IE unknown, may be considered as part of pre-op evaluation
- Systemic anticoagulation, antiplatelet therapy is contraindicated.

Anticoagulation

- Management is controversial
- Discontinue all forms of anticoagulation in patients with a mechanical PVE and a CNS embolic event for 2 weeks
  - Reinstitute heparin first then carefully transition to warfarin
- Aspirin or other antiplatelet agents as adjunctive therapy is not recommended
- Continuation of long-term antiplatelet therapy in IE with no bleeding complications may be considered
- Thrombolytic therapy not recommended

Pan-Scanning

- If done, perform prior to surgery
- No recommendations for routine evaluation of patients with IE for metastatic foci of infection
- Cerebrovascular imaging may be considered in all patients with L-sided IE

Thanks