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Topics for Discussion

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

Diagnosis of Endocarditis

Question #1

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Which one of the following statements is correct?

- 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

Question #1

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Which one of the following statements is correct?

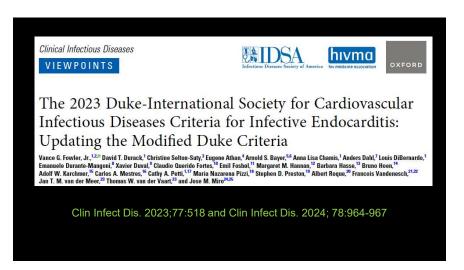
- 1. Staphylococcus aureus is the most common cause of bacterial endocarditis
- 2. Dental procedures carry a substantial risk for streptococcal endocarditis for patients with predisposing cardiac lesions
- 3. Three-quarters of patients with endocarditis have a known underlying cardiac predisposing condition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

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

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	



Weaknesses of "Old" Modified Duke Criteria

- Reduced sensitivity for diagnosis of PVE, CIEDrelated endocarditis, culture-negative endocarditis
- · Poorly validated in pediatric populations
- Newer imaging modalities and molecular diagnostics not included
- Uncertainty about "possible" cases

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2023 Duke-ISCVID Criteria for Diagnosis of Endocarditis

Definite pathologic diagnosis	Definite Clinical Diagnosis	Possible Clinical Diagnosis
Microorganisms identified on cardiac tissue, vegetation,	Two major criteria	Three minor criteria
graft, device	OR	OR
OR	Five minor criteria	One major plus one minor criteria
Vegetation, leaflet destruction, or adjacent	OR	
cardiac tissue showing inflammatory changes	One major plus three minor criteria	

Rejected endocarditis: criteria for definite or possible endocarditis are not met **OR** firm alternative diagnosis established OR lack of recurrence with < 4 days antibiotic therapy

2023 Duke-ISCVID Major Criteria			
Positive blood cultures	Imaging	Surgical	
Typical microorganisms* from 2 separate blood cultures OR Non-typical organisms in 3 or more separate blood cultures OR + PCR for Coxiella burnetti, Bartonella, T whipplei; Coxiella phase I IgG antibody titer >1:800, IFA IgG titer for Bartonella ≥1:800	+ ECHO/Cardiac CT 1) Vegetation, leaflet perforation, aneurysm, abscess, pseudo-aneurysm, fistula OR 2) New regurgitation c/w prior imaging OR 3) NEW PVE dehiscence + PET/CT PV, device, or graft	Evidence of IE by direct inspection at surgery	

Stapnylococcus aureus, vindans group streptococci, Streptococcus gailotyticus, TACLER species (Hemophilus species, Aggregatibacter, Cardiobacterium, Eikenella, Kingella), E. faecalis, S. lugdunensis, Granulicatella, Garnella, Abiotphia and in addition for PVE CoNS, C. acnes, Corynebacterium, Serratia

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2023 Duke-ISCVID Minor Criteria

- Predisposition: previous IE, PV, h/o valve repair, CHD, more than mild valve regurgitation or stenosis, CIED, hypertrophic cardiomyopathy, IVDU
- Fever, documented temperature >38.0°C (>100.4°F)
- Vascular phenomena: systemic arterial emboli, septic pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions, cerebral or splenic abscess
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor
- Positive blood cultures that do not meet major criteria, OR +PCR/NGS for typical organism from sterile body site
- + PET/CT of PV, graft, or device within 3 mo of implantation
- · New regurgitant murmur on exam and echocardiography unavailable

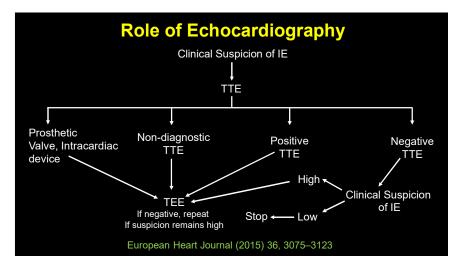
	2000 Criteria	2023 Criteria
% of all cases classified as possible	18-38	15-34
% of all possible cases that were true IE	41-52	30-36

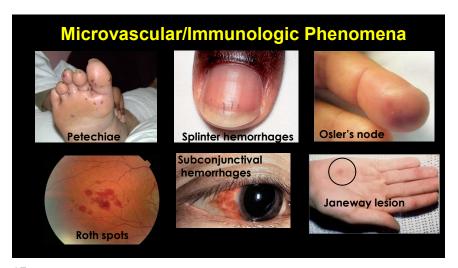
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erformance of New vs Old Duke Criteria			
Sensitivity			
True Positive Definition	2000 Criteria	2023 Criteria	
Definite	76	84	
Definite + Possible	93	99	
Specificity			
True Negative Definition	2000 Criteria	2023 Criteria	
Rejected	74	60	
Rejected + Possible	85	83	

Chambers, et al. Duke Infective Endocarditis Criteria 3.0 for the Clinician: Defining What Is Possible.

Clin Infect Dis. 2024, 78:964





Native Valve Endocarditis

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Question #2

A 63-year-old 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.

Question #2

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

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Regimen	Duration	Comments
MSSA		
Nafcillin or oxacillin	6 wk	2 wk uncomplicated R-sided IE (IDU)
Cefazolin	6 wk	Pen-allergic naf-intolerant patient
MRSA		
Vancomycin	6 wk	For MSSA if a beta-lactam cannot be used
Daptomycin	6 wk	10 mg/kg/day, vanco alternative

Question #3

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A 63-year-old 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 = $0.25~\mu g/ml$, ceftriaxone MIC = $0.25~\mu g/ml$.

Question #3

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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

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- 5. Ceftriaxone + gentamicin for 2 weeks then ceftriaxone for 2 weeks

Treatment of Viridans Group Strep 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 > $0.12 \mu g/ml$, < $0.5 \mu g/ml$
 - 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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Question #4

A 72-year-old 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: T 38.9°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 ampicillinsusceptible Enterococcus faecalis.

Question #4

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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

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Question #4

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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, <i>E. faecali</i> s only!	
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

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Empirical Therapy for Endocarditis While Awaiting Culture Results

- Vancomycin 60 mg/kg/d in divided doses + ceftriaxone 2 gm Q24h
- Severe penicillin allergy: Vancomycin + aztreonam 2 gm q8h

Oral Therapy of Endocarditis

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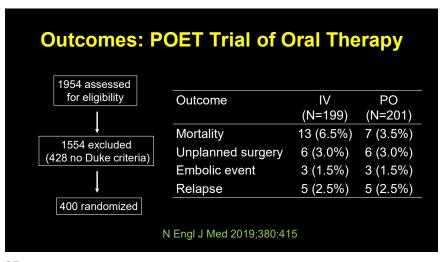
Principles Of Antimicrobial Therapy

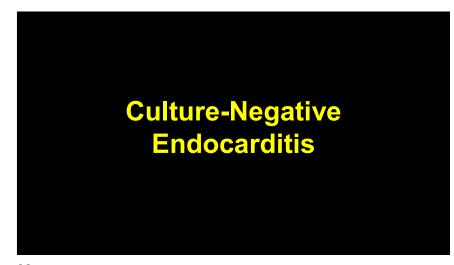
- The regimen should kill the pathogen
- A prolonged course of therapy (i.e., weeks not days)
- Intensive dosing to ensure adequate drug exposure
- Source control

POET Trial of Oral Therapy

- Noninferiority trial, 10% margin, left-sided endocarditis, IV vs partial oral
- Streptococci, Enterococcus faecalis, Staph. aureus (No MRSA), coag-negative staphylococci
- All patients given IV antibiotics for at least 10 days
- Primary outcome: composite of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse within 6 mo.

N Engl J Med 2019;380:415





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Question #5

A 37-year-old marginally housed male with a past history of injection drug use reports not feeling well for several weeks.

HPI: His reports intermittent fevers and thinks he has lost weight because clothes not longer fit him. He took a few doses of cephalexin given to him by a friend a couple of weeks ago which did not make much difference.

Exam: Tmax: 37.5°C/99.5°F; 2/6 systolic murmur on exam, otherwise WNL

Labs: CBC: mild normocytic anemia, hemoglobin 12 g/dL

UA: 50-100 red cells per high-power field

Serum creatinine: 3.6 mg/dL, high

C-reactive protein (CRP): 125 mg/L, high

C-ANCA (cytoplasmic antineutrophil antibody): positive

C3 complement: low

Blood cultures: negative at 96 hours

Question #5

What is the most likely diagnosis in this patient not feeling well for several weeks?

- 1. Granulomatosis with polyangiitis
- 2. Culture-negative endocarditis due to Staphylococcus aureus
- 3. Culture-negative endocarditis due to a viridans group streptococcal species
- 4. Culture-negative endocarditis due to Bartonella hensalae
- 5. Culture-negative endocarditis due to Tropheryma whipplei

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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)

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- · Not endocarditis
 - Libman-Sacks, myxoma, APLS, marantic

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Culture-Negative Scenarios

- Coxiella burnetii (Q fever): Direct or indirect animal contact, hepatosplenomegaly, abnormal or prosthetic valve.
 Doxycycline + hydroxychloroquine >1 yr.
- Bartonella: Homeless, indolent, valve normal or abnormal, louse vector. Rx: 6 wks doxycycline plus two wks gentamicin or plus 2 wks rifampin if valve resected (otherwise 3 months more of doxy)
- <u>Tropheryma whipplei</u>: Indolent, protracted course with arthralgias, diarrhea, malabsorption, weight loss, CNS involvement

Tools for Diagnosis of Culture-Negative Endocarditis

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

mNGS = metagenomic next generation sequencing

Prosthetic Valve and Device-Related Endocarditis

Question #6

72-year-old man s/p AV replacement with a bioprosthetic valve for bicuspid AV with insufficiency. He reports sore throat, cough, congestion, fever, chills, sweats and malaise for 3 days

- Exam: T 100.2° F, Pulse 85, BP 130/70mm Hg, RR 16
 - HEENT: oral cavity and tonsils red and swollen, no lymphadenopathy
 - Lungs: clear
 - Heart: no murmur
 - Skin: no rash
- · Rapid strep, rapid flu both negative

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Question #6

What is the best approach for managing this patient?

- 1. Obtain throat culture and prescribe Pen VK while awaiting
- 2. Obtain throat culture and give a script for Pen VK to be filled if culture is positive for GAS
- 3. Prescribe azithromycin for treatment of acute URI
- 4. Obtain blood cultures and await results
- 5. Obtain blood cultures and initiate therapy with vancomycin, gentamicin, and rifampin

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- 5. Obtain blood cultures and initiate therapy with vancomycin, gentamicin, and rifampin

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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 Karchmer and Chu, UpToDate, 2020

Diagnosis of PVE

- Duke criteria and TEE less sensitive for PVE compared to native valve endocarditis
- PET-CT (¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography) plus mod 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 nondiagnostic

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

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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 <u>≤</u> 0.12 μg/ml	Pen or ceftriaxone <u>+</u> gent OR Vancomycin	6 weeks (optional gent, 1 st 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

Observations studies question role of gentamicin and even rifampin

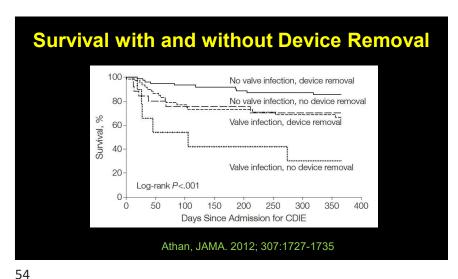
Cardiac Implantable Device Infections

(permanent pacemakers, defibrillators)

J Am Coll Cardiol 2008;49:1851; Circulation 2010;121:458; NEJM 2012;367:842; JAMA 2012;307:1727, Circulation 2024; 149:e201

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



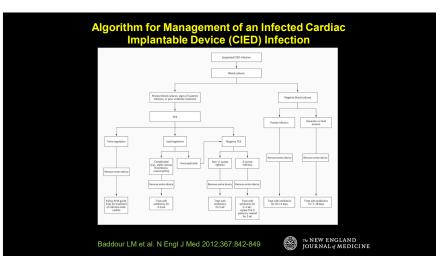
AHA Guidelines for Management of Cardiac Implantable Device Infections

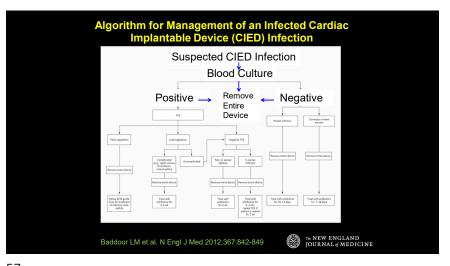
- · Blood cultures before antibiotics
 - If positive, then TEE

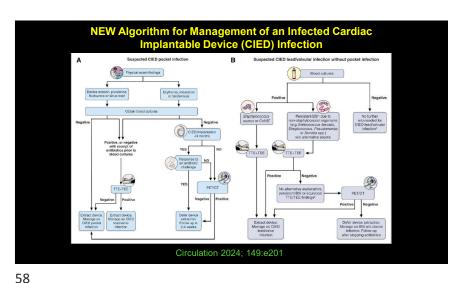
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- · Gram stain, culture of pocket tissue, lead tips
- Device removal for all infections and occult staphylococcal bacteremia (consider for bacteremia with other endocarditis-causing organisms)
- · Therapy (antibiotic based on susceptibility)
 - Pocket infection: 10-14 days
 - Bloodstream infection: > 14 days
 - Lead or valve vegetations/endocarditis: 4-6 weeks

Circulation 2010;121:458-77







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Can Defer CIED Extraction 2-4 Weeks If

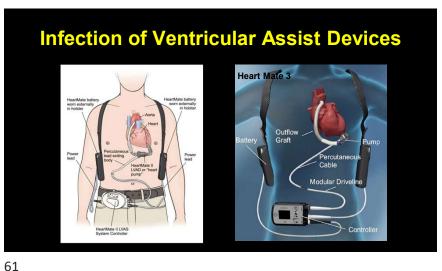
- Suspected pocket infection + negative blood cultures (before antibiotics) + implant < 3 mo + good response to oral antistaphylococcal antibiotic
- Suspected pocket infection + negative blood cultures (before antibiotics) + implant < 3 mo BUT response to antibiotics is suboptimal and PET/CT is negative

Circulation 2024; 149:e201

Can Defer CIED Extraction If

- Suspected CIED infection but NO signs of pocket infection + negative blood cultures
- Suspected CIED infection but NO signs of pocket infection + <u>positive blood cultures</u> + not S. aureus or CoNS, + clears in 72 hours if other organisms + alternative source
- Suspected CIED infection but NO signs of pocket infection + <u>persistently positive blood cultures</u> + no alternative source + TTE/TEE negative + PET/CT negative

Circulation 2024; 149:e201



Types of VAD Infections

- VAD-specific infections occurs only in LVAD patients
 - Pump pocket/cannula infections
 - Pocket infections
 - Driveline exit site infections (superficial or deep)
- VAD-related infections- risk of LVAD infection increased
 - Bloodstream infections (VAD-related, IV catheter/non-VAD related)
 - Endocarditis (pump or cannula, native valve)
 - Mediastinitis, sternal wound infections
- · Non-VAD infections

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Ann Cardiothorac Surg 2021;10:233; Clinical Transplantation 2019;33:e13552.

Microbiology of VAD-Specific Infections

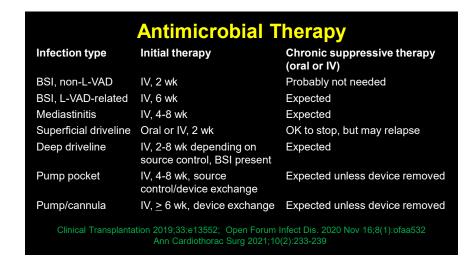
- S. aureus/coag-negative staphylococci
- · Pseudomonas aeruginosa
- Enteric Gram-negatives
- Enterococci
- Candida

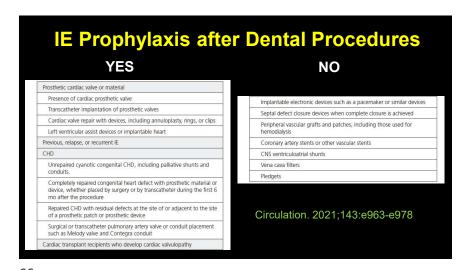
Clinical Transplantation 2019;33:e13552.

Management and Therapy

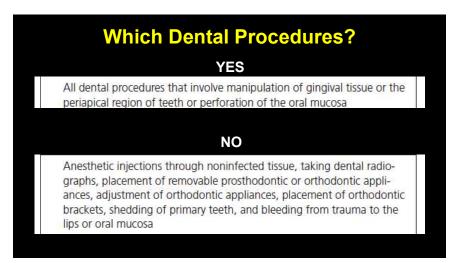
- · Initial empirical coverage for MRSA and Pseudomonas aeruginosa
- Pathogen-directed therapy when possible
- Chronic suppressive therapy to prevent relapse

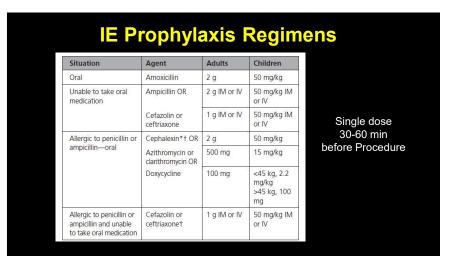
Clinical Transplantation 2019;33:e13552; Open Forum Infect Dis. 2020 Nov 16;8(1):ofaa532





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Main Take-home Points

- Duke-ISCVID criteria is a valuable tool for assessing the likelihood of endocarditis
- TTE is acceptable to rule out endocarditis if of high quality and in a low probability setting
- Use a tried-and-true regimen, avoid aminoglycoside combination therapy for NVE
- Think prior antibiotics and Bartonella in culture-negative endocarditis
- Any fever is a patient with a prosthetic valve is endocarditis until proven otherwise

Other Stuff

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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 is 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)

Am Heart J 2019:216:102-112

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

Fever During Therapy of Endocarditis

- Very common, lasts into the second week, a concern in PVE
- Cause (if one is found, 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, PET/CT, etc.