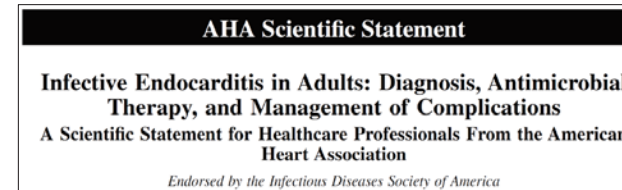
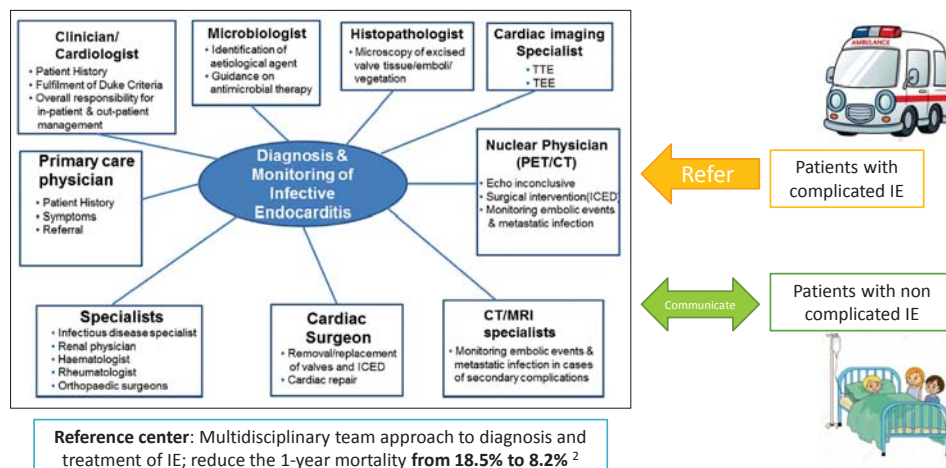
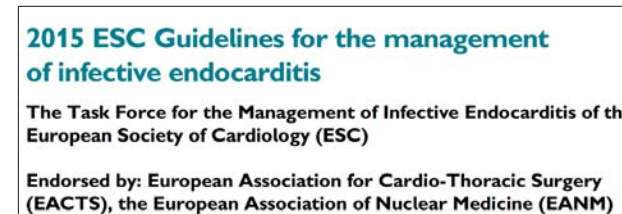


# Management of Native Valve Infective Endocarditis

## ESC 2015: Endocarditis team



2005 → AHA 2015  
Baddour LM, et al. Circulation. 2015;132(15):1435-86



2009 → ESC 2015  
Habib G, et al. Eur Heart J. 2015;36(44):3075-128

## Principles of antimicrobial therapy



- Goal of antibiotic treatment is to eradicate infection
- Bactericidal drug
- Combination intravenous therapy
- Required 4-6 weeks of treatment
- Therapeutic drug monitoring

- IE is a focal infection
  - high bacterial density -> inoculum effect
  - slow rate of bacterial growth within biofilms
  - low microorganism metabolic activity

# Empirical treatment of NVE

	AHA 2015	ESC 2015
Standard treatment	Acute (days) clinical presentations (BCNE) <ul style="list-style-type: none"> <li>Coverage for <i>S aureus</i>, <math>\beta</math>-hemolytic streptococci and aerobic Gram negative bacilli is reasonable (IIaC)</li> </ul> Subacute (weeks) presentation (BCNE) <ul style="list-style-type: none"> <li>Coverage of <i>S aureus</i>, VGS, HACEK and enterococci is reasonable (IIaC)</li> </ul>	Community acquire - acute clinical presentations <ul style="list-style-type: none"> <li>Ampicillin 12g/day IV in 4-6 doses (IB) <b>with</b> <ul style="list-style-type: none"> <li>Cloxacillin 12g/day IV in 4-6 doses</li> </ul> </li> <li>Gentamicin 3mg/kg/day IV or IM in 1 dose (IB)</li> </ul>
Penicillin-allergic patients		<ul style="list-style-type: none"> <li>Vancomycin 60mg/kg /day in 2-3 doses <b>with</b></li> <li>Gentamicin 3mg/kg/day IV or IM in 1 dose (IB)</li> </ul>

- BSAC 2012
  - Clinicians can await culture results if the patient is clinically stable
  - The use of gentamicin before availability of culture results is controversial
  - Local microbiological data
- ESC 2015: Cloxacillin/cefazolin administration is associated with lower mortality rates than other beta-lactams, including amoxicillin/clavulanic acid or ampicillin/sulbactam

# CLSI breakpoint for VGS & *S. gallolyticus*

Test/Report Group	Antimicrobial Agent	Disk Content	Zone Diameter Interpretive Criteria (nearest whole mm)			MIC Interpretive Criteria ( $\mu$ g/mL)			Comments
			S	I	R	S	I	R	
PENICILLINS									
A	Penicillin	—	—	—	—	$\leq 0.12$	0.25–2	$\geq 4$	(4) Viridans streptococci isolated from normally sterile body sites (eg, CSF, blood, bone) should be tested for penicillin susceptibility using an MIC method.
A	Ampicillin	—	—	—	—	$\leq 0.25$	0.5–4	$\geq 8$	

	AHA 2015	ESC 2015
Penicillin-susceptible	MIC < 0.12 mg/L	MIC < 0.125 mg/L
Relatively resistant to penicillin	MIC > 0.12 and < 0.5 mg/L	MIC 0.25 - 2 mg/L
Penicillin-resistant	MIC > 0.5 mg/L	MIC > 2 mg/L

## Therapy of NVE Caused by VGS & *S.gallolyticus*

	AHA 2015	ESC 2015	Comment
Penicillin-susceptible	MIC < 0.12 mg/L	MIC < 0.125 mg/L	
Standard treatment: 4-week duration	<ul style="list-style-type: none"> <li>Penicillin G 12-18 million U/day IV either in 4–6 doses or continuously (IIaB) or</li> <li>Ceftriaxone 2 g IV or IM in 1 dose (IIaB)</li> </ul>	<ul style="list-style-type: none"> <li>Penicillin G 12-18 million U/day IV either in 4–6 doses or continuously (IB) or</li> <li>Ampicillin 100 - 200mg/kg/day IV in 4–6 doses (IB) or</li> <li>Ceftriaxone 2 g IV or IM in 1 dose (IB)</li> </ul>	Preferred in patients >65 y or impaired renal function
Standard treatment: 2-week duration	<ul style="list-style-type: none"> <li>Penicillin G 12-18 million U/day IV either in 4–6 doses or continuously (IIaB) or</li> <li>Ceftriaxone 2 g IV or IM in 1 dose (IIaB) <b>with</b></li> <li>Gentamicin 3mg/kg/day IV or IM in 1 dose (IIaB)</li> </ul>	<ul style="list-style-type: none"> <li>Penicillin G 12-18 million U/day IV either in 4–6 doses or continuously (IB) or</li> <li>Ampicillin 100 - 200mg/kg/day IV in 4–6 doses (IB) or</li> <li>Ceftriaxone 2 g IV or IM in 1 dose (IB) <b>with</b></li> <li>Gentamicin 3mg/kg/IV or IM in 1 dose (IB)</li> </ul>	Only recommend in patients with <b>non-complicated IE</b> With normal renal function
Penicillin-allergic patients (4 weeks)	Vancomycin 30mg/kg /day in 2 doses (IIaB)	Vancomycin 30mg/kg /day in 2 doses (IC)	Consider penicillin desensitization

- 1) Vancomycin trough level 10-15 mg/L
  - 2) ESC: gentamicin trough level <1 mg/L and peak level = 10-12 mg/L (single daily dose)
- AHA: no optimal drug concentrations for single daily dosing

## Therapy of NVE Caused by VGS & *S.gallolyticus*

	AHA 2015	ESC 2015
Relatively resistant to penicillin	MIC > 0.12 and < 0.5 mg/L	MIC 0.25 - 2 mg/L
Standard treatment: 4-week duration	<ul style="list-style-type: none"> <li>Penicillin G 24 million U/day IV either in 4–6 doses or continuously (IIaB) <b>with</b></li> <li>Gentamicin 3mg/kg/day IV or IM in 1 dose for first 2 weeks (IIaB)</li> <li>Ceftriaxone may be a reasonable alternative treatment option for VGS isolates that are susceptible to ceftriaxone (IIbC)</li> </ul>	<ul style="list-style-type: none"> <li>Penicillin G 24 million U/day IV either in 4–6 doses or continuously (IB) or</li> <li>Ampicillin 200mg/kg/day IV in 4–6 doses (IB) or</li> <li>Ceftriaxone 2 g IV or IM in 1 dose (IB) <b>with</b></li> <li>Gentamicin 3mg/kg/day IV or IM in 1 dose for first 2 weeks (IB)</li> </ul>
Penicillin-allergic patients (4 weeks)	Vancomycin 30mg/kg /day in 2 doses (IIaB)	<ul style="list-style-type: none"> <li>Vancomycin 30mg/kg /day in 2 doses (IC) <b>with</b></li> <li>Gentamicin 3mg/kg/day IV or IM in 1 dose for first 2 weeks (IC)</li> </ul>
Penicillin-resistant	MIC > 0.5 mg/L	MIC > 2 mg/L
Treated as enterococcal IE (except double beta-lactam regimen)		

## Therapy of NVE Caused by *S. aureus*

	AHA 2015	ESC 2015	Comment
<b>Methicillin-susceptible staphylococci</b>			
Standard treatment	Cloxacillin 12 g/day IV in 4–6 doses for 6 weeks (IC)	Cloxacillin 12 g/day IV in 4–6 doses for 4–6 weeks (IB)	No aminoglycosides in staphylococcal NVE
Alternative treatment		<ul style="list-style-type: none"> <li>Sulfamethoxazole 4800 mg/day <b>with</b> trimethoprim 960 mg/day in 4–6 doses for IV 1 week then PO for 5 weeks (IIbC)</li> <li>with Clindamycin 1800 mg/day day in 3 doses for 1 week (IIbC)</li> </ul>	For <i>S. aureus</i>
Penicillin-allergic patients with non-anaphylactic reaction	Cefazolin 6 g/day in 3 doses for 6 weeks (IB)	<ul style="list-style-type: none"> <li>Cefazolin 6 g/day in 3 doses for 6 weeks</li> <li>Cefotaxime 6 g/day in 3 doses for 6 weeks</li> </ul>	Avoid cefazolin in CNS infection
<b>Methicillin-resistant staphylococci or Penicillin-allergic patients with anaphylactic reaction</b>			
Standard treatment	Vancomycin 30mg/kg /day 2 doses for 6 weeks (IC)	Vancomycin 30–60 mg/kg /day in 2–3 doses for 4–6 weeks (IB)	Consider penicillin desensitization
Alternative treatment	<ul style="list-style-type: none"> <li>Daptomycin ≥8mg/kg/day in 1 dose for 6 weeks (IIbB) consider in right sided IE</li> </ul>	<ul style="list-style-type: none"> <li>Daptomycin 10mg/kg/day in 1 dose for 4–6 weeks (IIbB)</li> <li>with Cloxacillin 2 g/4 hrs or Fosfomycin 2 g/6 hrs</li> </ul>	
		<ul style="list-style-type: none"> <li>Sulfamethoxazole /trimethoprim (IIbC) <b>with</b> Clindamycin (IIbC)</li> </ul>	For <i>S. aureus</i>

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Vancomycin trough level : ≥20 mg/L ( ESC ); 10–20 mg/L (AHA)

## Treatment of *Staphylococcus aureus* endocarditis with high doses of trimethoprim/sulfamethoxazole and clindamycin—Preliminary report



**Table 1**

Fatality rates of infective endocarditis (IE) in Aix-Marseille Université (Marseille, France) and cases of *Staphylococcus aureus* infections.

	2000–2006	2007–2008	2009–2011	2012
Cases	275	172	226	101
Deaths	26 (9%) <sup>†</sup>	21 (12%)	33 (15%) <sup>*,†</sup>	8 (8%) <sup>*</sup>
<i>S. aureus</i> IE	30 (11%) <sup>‡</sup>	18 (10%)	44 (19%)	33 (33%) <sup>‡</sup>

Significant difference ( $\chi^2$  P-value) between figures with the same symbol.

\* P=0.09.

† P=0.075.

‡ P<0.001.

Start April 2012  
TMP/SMX with clindamycin

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Casalta JP, et al. Int J Antimicrob Agents. 2013;42(2):190–1

## Enterococci

- E. faecalis* causes ≈97%; *E. faecium*, ≈1–2% of cases of enterococcal IE
- Treatment of enterococci need synergistic bactericidal combinations
- Resistant to multiple drugs
  - High-level aminoglycoside resistance (HLAR)
  - Aminoglycoside not synergistic with cell wall active agent
- Beta-lactams
  - Intrinsic resistant via PBP5 modification → *E. faecium*
  - Beta-lactamases (rare)
- Vancomycin

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## Therapy of NVE Caused by Enterococci

	AHA 2015	ESC 2015	Comment
<b>Penicillin and gentamicin-susceptible strain</b>			
Standard treatment	<ul style="list-style-type: none"> <li>Ampicillin 2 g IV every 4 h for 4–6 weeks (IIaB) or</li> <li>Penicillin G 18–30 million U/day IV in 6 doses for 4–6 weeks (IIaB)</li> </ul> <b>with</b> <ul style="list-style-type: none"> <li>Gentamicin 3mg/kg/day IV in 2–3 doses for 4–6 weeks (IIaB)</li> </ul>	<ul style="list-style-type: none"> <li>Ampicillin 200mg/kg/day IV in 4–6 doses for 4–6 weeks (IB)</li> </ul> <b>with</b> <ul style="list-style-type: none"> <li>Gentamicin 3mg/kg/day IV or IM in 1 doses for 2–6 weeks (IB) expert recommend 2 weeks (IIaB)</li> </ul>	6-weeks therapy recommended for NVE symptoms >3 months
Double beta-lactam	<ul style="list-style-type: none"> <li>Ampicillin 2 g IV every 4 h for 6 weeks (IIaB)</li> </ul> <b>with</b> <ul style="list-style-type: none"> <li>Ceftriaxone 2 g IV every 12 h for 6 weeks (IIaB)</li> </ul>	<ul style="list-style-type: none"> <li>Ampicillin 200mg/kg/day IV in 4–6 doses for 6 weeks (IB) or</li> </ul> <b>with</b> <ul style="list-style-type: none"> <li>Ceftriaxone 4 g IV or IM in 2 doses for 6 weeks (IB)</li> </ul>	For patients impaired renal function For <i>E. faecalis</i>
Penicillin-allergic patients	<ul style="list-style-type: none"> <li>Vancomycin 30 mg/kg /day in 2 doses for 6 weeks (IIaB)</li> </ul> <b>with</b> <ul style="list-style-type: none"> <li>Gentamicin 3mg/kg/day IV or IM in 3 doses for 6 weeks (IIaB)</li> </ul>	<ul style="list-style-type: none"> <li>Vancomycin 30 mg/kg /day in 2 doses for 6 weeks (IC)</li> </ul> <b>with</b> <ul style="list-style-type: none"> <li>Gentamicin 3mg/kg/day IV or IM in 1 doses for 6 weeks (IC)</li> </ul>	
<b>Penicillin -susceptible and aminoglycoside-resistant strain</b>			
Double beta-lactam	<ul style="list-style-type: none"> <li>Ampicillin <b>with</b> Ceftriaxone</li> </ul>	<ul style="list-style-type: none"> <li>Ampicillin <b>with</b> Ceftriaxone</li> </ul>	
Alternative treatment for streptomycin-susceptible	<ul style="list-style-type: none"> <li>Ampicillin or Penicillin <b>with</b> Streptomycin 15mg/kg/day IV in 2 doses for 4–6 weeks (IIaB)</li> </ul>	<ul style="list-style-type: none"> <li>Ampicillin <b>with</b> Streptomycin 15mg/kg/day in 2 doses for 2–6 weeks</li> </ul>	NVE with symptoms <3-months duration may be treated for 4 weeks

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## Therapy of NVE Caused by Enterococci

### Double beta-lactam

- An observational, nonrandomized, comparative multicenter cohort study was conducted at 17 Spanish and 1 Italian hospitals
- AC-treated patients had previous chronic renal failure than AG-treated patients (33% vs 16%,  $P = .004$ )

**Table 2. Treatment and In-Hospital Mortality According to Antimicrobial Combination in 246 Episodes of *Enterococcus faecalis* Infective Endocarditis Treated With Ampicillin Plus Ceftriaxone or Ampicillin Plus Gentamicin**

Variable	Ampicillin + Ceftriaxone (n = 159)	Ampicillin + Gentamicin (n = 87)	P Value
Failures			
Death during treatment	35 (22%)	18 (21%)	0.81
Death during 3-mo follow-up	13 (8%)	6 (7%)	0.72
Adverse effects requiring treatment withdrawal	2 (1%)	22 (25%)	<0.001
Treatment failure requiring change of antimicrobials	2 (1%)	2 (2%)	0.54
Relapse	3/124 (3%)	3/69 <sup>a</sup> (4%)	0.67
Drug stopped due to new renal failure	0	20 (23%)	<.001
Drug stopped due to vestibular toxicity	0	2 (2%)	.055



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Fernandez-Hidalgo N, et al. Clin Infect Dis. 2013;56(9):1261-8

	AHA 2015	ESC 2015
<b>Penicillin-resistant, vancomycin and gentamicin-susceptible strain</b>		
Beta-lactam-resistant due to beta-lactamase	<ul style="list-style-type: none"> <li>Ampicillin-sulbactam 3 g IV every 6 h for 6 weeks</li> <li>with</li> <li>Gentamicin 3mg/kg/day IV or IM in 3 doses for 6 weeks (IIaB)</li> </ul>	<ul style="list-style-type: none"> <li>Ampicillin-sulbactam or Amoxicillin-clavulanate</li> <li>with</li> <li>Gentamicin 3mg/kg/day IV or IM in 1 dose for 6 weeks (IC)</li> </ul>
Beta-lactam-resistant due to intrinsic resistant	<ul style="list-style-type: none"> <li>Vancomycin 30 mg/kg /day IV in 2 doses for 6 weeks (IIbC)</li> <li>with</li> <li>Gentamicin 3mg/kg/day IV or IM in 3 doses for 6 weeks</li> </ul>	<ul style="list-style-type: none"> <li>Vancomycin 30 mg/kg /day IV in 2 doses for 6 weeks (IC)</li> <li>with</li> <li>Gentamicin 3mg/kg/day IV or IM in 1 dose for 6 weeks (IC)</li> </ul>
<b>Penicillin, vancomycin and gentamicin-resistant strain</b>		
	<ul style="list-style-type: none"> <li>Daptomycin 10-12 mg/kg/day IV in 1 dose &gt; 6 weeks (IIbC)</li> </ul>	<ul style="list-style-type: none"> <li>Daptomycin 10mg/kg/day IV in 1 dose ≥ 8 weeks (IIaC)</li> <li>with</li> <li>Ampicillin 200mg/kg/day IV in 4-6 doses ≥ 8 weeks (IIaC)</li> </ul>
	<ul style="list-style-type: none"> <li>Linezolid 600 mg IV or PO in 2 doses for &gt; 6 weeks (IIbC)</li> </ul>	<ul style="list-style-type: none"> <li>Linezolid 600 mg IV or PO in 2 doses for ≥ 8 weeks (IIaC)</li> </ul>

1) Vancomycin trough level 10-15 mg/L (ESC); 10-20 mg/L (AHA)

2) ESC: gentamicin trough level <1 mg/L and peak level = 10-12 mg/L (single daily dose)

AHA: gentamicin trough level <1 mg/L and peak level = 3-4 mg/L (multiple daily doses)

3) AHA: streptomycin trough level <10 mg/L and peak level 20-35 mg/L



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### Duration of antimicrobial therapy

- Duration of ATB (AHA&ESC 2015)<sup>1,2</sup>
  - Blood cultures were initially positive
    - Count on the first day of blood cultures are negative
  - If operative tissue cultures are positive
    - An entire antimicrobial course is after valve surgery
  - If operative tissue cultures are negative
    - The remaining duration of antibiotics be given (including administration before surgery)
- ESC 2015: postoperative antibiotic regimen should be that recommended for NVE, not for PVE (ESC 2015)<sup>2</sup>
- Further research is needed to determine the switch to oral treatment and shorter course of antimicrobial therapy<sup>3</sup>



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1. Baddour LM, et al. Circulation. 2015;132(15):1435-86

2. Habib G, et al. Eur Heart J. 2015;36(44):3075-128

3. Cahill TJ, Baddour LM, Habib G, et al. JACC. 2017;69(3):325-44

### Surgery in NVE

- Surgery is undertaken in 40% of patients with infective endocarditis (ICE-PCS)<sup>1</sup>
- 24% of patients with left-sided IE and a guideline indication for intervention still do not undergo surgery (ICE-PCS)<sup>2</sup>
- Operations for active IE present high risk, with an overall in-hospital mortality of 20%<sup>3</sup>



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Short course of Infectious  
Diseases of the Year 2017

1. Murdoch DR, et al. Arch Intern Med. 2009;169(5):463-73

2. Chu VH, et al. Circulation. 2015;131(2):131-40

3. Cahill TJ, Baddour LM, Habib G, et al. JACC. 2017;69(3):325-44

Indications for surgery: Heart failure

AHA Guidelines 2015 (89)		Class, Level of Evidence	ESC Guidelines 2015 (68)		Class, Level of Evidence	Timing†
Early surgery	is indicated in patients with IE who present with valve dysfunction resulting in symptoms or signs of HF	I, B	Aortic or mitral NVE, or PVE with severe acute regurgitation, obstruction, or fistula causing refractory pulmonary edema or cardiogenic shock	I, B	Emergency	
Early surgery*	is indicated in patients with PVE with symptoms or signs of HF resulting from valve dehiscence, intracardiac fistula, or severe prosthetic valve dysfunction	I, B	Aortic or mitral NVE, or PVE with severe regurgitation or obstruction causing symptoms of HF, or echocardiographic signs of poor hemodynamic tolerance	I, B	Urgent	

**Early surgery** = during initial hospitalization and before completion of a full course of antibiotics

**Emergency surgery**= performed within 24 h  
**Urgent surgery** = within a few days  
**Elective surgery** = after at least 1 to 2 weeks of ATB

Indications for surgery: Uncontrolled infection

AHA Guidelines 2015 (89)	Class, Level of Evidence	ESC Guidelines 2015 (68)	Class, Level of Evidence	Timing†
Early surgery* is indicated in patients when IE is complicated by heart block, annular or aortic abscess, or destructive penetrating lesions	I, B	Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	I, B	Urgent
Early surgery* is reasonable for patients with relapsing PVE	IIa, C			
Early surgery* should be considered, particularly in patients with IE caused by fungi or highly resistant organisms (e.g., VRE, multidrug-resistant gram-negative bacilli)	I, B	Infection caused by fungi or multiresistant organisms	I, C	Urgent/elective
Early surgery* is indicated for evidence of persistent infection (manifested by persistent bacteremia or fever lasting >5-7 d, and provided that other sites of infection and fever have been excluded) after the start of appropriate antimicrobial therapy	I, B	Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	IIa, B	Urgent
		PVE caused by staphylococci or non-HACEK gram-negative bacteria	IIa, C	Urgent/elective

Indications for surgery: Prevention of embolism

Class, Level of Evidence	Class, Level of Evidence	Class, Level of Evidence	Class, Level of Evidence	Timing
<b>AHA Guidelines 2015 (89)</b>		<b>ESC Guidelines 2015 (68)</b>		
Early surgery* is reasonable in patients who present with recurrent emboli and persistent or enlarging vegetations despite appropriate antibiotic therapy	IIa, B	Aortic or mitral NVE, or PVE with persistent vegetations >10 mm after ≥1 embolic episode despite appropriate antibiotic therapy	I, B	Urgent
Early surgery* is reasonable in patients with severe valve regurgitation and mobile vegetations >10 mm	IIa, B	Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk	IIa, B	Urgent
Early surgery* may be considered in patients with mobile vegetations >10 mm, particularly when involving the anterior leaflet of the mitral valve and associated with other relative indications for surgery	IIb, C	Aortic or mitral NVE, or PVE with isolated very large vegetations (>30 mm)	IIa, B	Urgent
		Aortic or mitral NVE, or PVE with isolated large vegetations (>15 mm) and no other indication for surgery	IIb, C	Urgent

- The risk of embolism is highest during the first 2 weeks at diagnosis and decreases after the initiation of antibiotic therapy <sup>1</sup>
  - vegetation size (>10 mm), mitral valve, vegetation mobility, and *S. aureus* IE
- Early surgery reduced the composite endpoint of in-hospital death and embolic events within 6 weeks from 23% to 3% <sup>2</sup>
















## Stroke & IE

- In patients with major ischemic stroke or intracranial hemorrhage, it is reasonable to delay valve surgery for at least 4 weeks
- Risk of hemorrhagic transformation and hypotension during surgery
- Initiation of aspirin or other antiplatelet agents as adjunctive therapy in IE is not recommended
- Aspirin did not reduce the risk of embolic events and caused a nonsignificant trend toward increased incidence of bleeding

# Take home message

- IE criteria and new diagnostic tools should be used as a diagnostic guide rather than a replacement for clinical judgment
- Early management and a multidisciplinary approach improve the clinical outcome

**CENTRAL ILLUSTRATION** Infective Endocarditis: Preventive Strategies, Diagnosis, and Management

Preventive strategies	Improving diagnosis	Optimal management
 Reduce hospital acquired bacteremia  Good oral hygiene for at-risk groups  Antibiotic prophylaxis for high risk groups  In future, antibacterial coatings/materials	 High index of clinical suspicion in at-risk groups  Patient education  Early echocardiography  Adjunctive imaging if echocardiography non-diagnostic  Rapid microbiology results with antibacterial sensitivity	 Evaluation by an endocarditis team  Early risk stratification  Early transfer to center of expertise  Tailored antibiotic therapy  Early surgery for selected patients  Monitoring for complications

Cahill, T.J. et al. J Am Coll Cardiol. 2017;69(3):325-44.

Thank you 