Update on valvular heart disease and endocarditis prophylaxis

Ann Bolger MD, FACC, FAHA
No conflicts to disclose
15.6 million people have RHD around the world. 300,000 of about 10 million individuals who acquire ARF every year go on to develop RHD, and 233,000 deaths annually are directly attributable to ARF or RHD.

- World Health Organization
The incidence of rheumatic fever

- Denmark
  - 1862: 250/100,000
  - 1962: 100/100,000
  - 1980: <2/100,000

- Developing Countries
  - 13.4/100,000 hospitalized children
  - 80–100/100,000 in school-age Pacific Islander children in New Zealand
  - 245–351/100,000 in Aboriginal children of central and northern Australia; community-based surveillance suggests that the true incidence exceeds 500 per 100,000

- Focal outbreaks in the US in 1980’s

Rheumatic Fever: Controversies and New Science

• Susceptibility
  Poverty
  Crowding
  Rheumatogenic strains of GAS (virulence factors)

• Diagnosis
  Jones Criteria
  More specific but less sensitive with each iteration

Geographical, genetic influences (HLA, B cell alloantigen) on incidence

Countries with endemic/epidemic ARF may need more sensitive criteria (WHO 2002)

What is the role of Echocardiography?
Jones versus WHO criteria for ARF

**Jones criteria (1992)**[15]

Two major or one major and two minor manifestations must be present, plus evidence of antecedent group A streptococcus infection

Chorea and indolent carditis do not require evidence of antecedent group A streptococcus infection

Recurrent episode requires only one major or several minor manifestations, plus evidence of antecedent group A streptococcus infection

**Major manifestations**

- Carditis
- Polyarthritis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

**Minor manifestations**

- Arthralgia
- Fever
- Raised erythrocyte sedimentation rate or C-reactive protein concentrations
- Prolonged PR interval on electrocardiogram

**Evidence of antecedent group A streptococcus infection**

- Positive throat culture or rapid antigen test for group A streptococcus
- Raised or rising streptococcal antibody titre

**WHO criteria (2002–03)**[8]

Chorea and indolent carditis do not require evidence of antecedent group A streptococcus infection

**First episode**

As per Jones criteria[15]

**Recurrent episode**

In a patient without established RHD: as per first episode

In a patient with established RHD: requires two minor manifestations, plus evidence of antecedent group A streptococcus infection. Evidence of antecedent group A streptococcus infection as per Jones criteria, but with addition of recent scarlet fever

Secondary Prevention of Rheumatic Fever

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prophylaxis Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic fever with carditis and residual heart disease</td>
<td>10 y or greater since last episode and at least until age 40 y; sometimes lifelong prophylaxis</td>
</tr>
<tr>
<td>Rheumatic fever with carditis but no residual heart disease</td>
<td>10 y or well into adulthood, whichever is longer</td>
</tr>
<tr>
<td>Rheumatic fever without carditis</td>
<td>5 y or until age 21 y, whichever is longer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G benzathine</td>
<td>1,200,000 U every 4 wk</td>
<td>Intramuscular</td>
</tr>
<tr>
<td></td>
<td>(every 3 wk for high-risk pts such as those with residual carditis)</td>
<td></td>
</tr>
<tr>
<td>Or</td>
<td>Penicillin V</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>250 mg twice daily</td>
<td></td>
</tr>
</tbody>
</table>
A different demographic

- The US population 65 and over will increase from 35 million in 2000 to 40 million in 2010 (a 15% increase) and then to 55 million in 2020 (a 36% increase for that decade)
- The Cardiovascular Health Study:
  
  5201 men and women older than 65 years

<table>
<thead>
<tr>
<th></th>
<th>65 to 75 years</th>
<th>75 to 85 years</th>
<th>&gt;85 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic Valve Sclerosis</td>
<td>20%</td>
<td>35%</td>
<td>48%</td>
</tr>
<tr>
<td>Aortic Valve Stenosis</td>
<td>1.30%</td>
<td>2.40%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Barasch E, Am J Cardiol. 2006 May 1;97(9):1281-6
Aortic valve sclerosis

- Sclerosis is associated with age, sex, hypertension, smoking, serum low-density lipoprotein and lipoprotein(a) levels, and diabetes mellitus
- Aortic sclerosis in subjects without known coronary disease is associated with adverse clinical outcomes
  - approximately 50% increased risk of myocardial infarction and cardiovascular death
  - The association persists even when age, sex, known cardiovascular disease, and cardiovascular risk factors are taken into account

Barasch E, Am J Cardiol. 2006 May 1;97(9):1281-6
Do statins retard aortic valve stenosis?

Several retrospective studies and one prospective trial show that patients receiving statins have slower progression of stenosis severity than do individuals not receiving them

• Cowell, N Eng J Med 352, 2005
  A randomized trial of patients with moderately severe disease
  – Average LDL 7.2 mmol/L
  – 165 people randomized to either placebo or atorvastatin (80 mg)
  – Average aortic valve area 1.01 cm²
  – After 25 months, no difference in rate of AS progression

• Moura JACC 49, 2007
  – 20 mg rosuvastatin to patients with an average LDL of 8.8 mmol/L
  – A second group with a lower average LDL (6.5 mmol/L) received no statin
  – Average valve area was 1.23 cm²
  – Statin administration slowed disease progression significantly

To be effective, statins may need to be given early, for mild disease, and may be most effective in patients with high LDL concentrations
Aortic Stenosis Severity

- Mild (area 1.5 cm², mean gradient less than 25 mm Hg, or jet velocity less than 3.0 m per second)
- Moderate (area 1.0 to 1.5 cm², mean gradient 25 to 40 mm Hg, or jet velocity 3.0 to 4.0 m per second)
- Severe (area less than 1.0 cm², mean gradient greater than 40 mm Hg, or jet velocity greater than 4.0 m per second)

Onset of Symptoms:
Mortality 25% per year

Percent Survival
Age, years

Average Survival (Years)

Ross Circulation 38, 1968
Symptoms in Aortic Stenosis

- 75% mortality within 3 years of symptoms
- 2% mortality per month
- Reports of sudden death within 3 months of symptom onset

Schwartz, Circulation 66, 1982
Asymptomatic AS

- Patients with an aortic valve area of less than 1.0 cm² who have a mean transvalvular gradient of more than 40 mmHg are judged to have severe aortic stenosis.
- The valve area at which individuals become symptomatic is quite variable.
- A valve area index of 0.45 cm²/m² could be helpful in deciding severity in some cases.

Pellika Circulation 111, 2005
Progression to Symptoms

• Progression is unpredictable, and can be as rapid as a gradient increase of 20 mmHg/year
• Neither AVA or peak velocity is an adequate discriminator of progression
• An annual increase of aortic valve jet velocity > 0.45 m/s predicts significantly worse outcome in terms of survival and need for valve replacement
• Progression can be even more rapid in people with severe renal failure

Otto Circulation 95, 1997
Exercise for Asymptomatic Aortic Stenosis

• Exercise testing can identify
  – a limited exercise capacity
  – abnormal blood pressure response
  – exercise-induced symptoms

• Exercise testing can predict development of symptoms
  – 117 patients manifesting symptoms, abnormal blood pressure (less than 20-mm Hg increase), or ST-segment abnormalities with exercise had a symptom-free survival at 2 years of only 19% compared with 85% among AS patients without those findings. Four patients died during the study (1.2% annual mortality rate); all had an aortic valve area less than 0.7 cm² and an abnormal exercise test.

  – In another series, exercise testing brought out symptoms in 29% of 118 “asymptomatic” AS subjects. Spontaneous symptoms developed in 51% of the patients with symptoms elicited on ETT over the next year, compared with only 11% of patients who had no symptoms.

Amato Heart 86, 2001
Das Eur Heart J 26, 2005
Exercise in Asymptomatic Aortic Stenosis

Exercise testing in adults with AS has poor diagnostic accuracy for evaluation of concurrent CAD.

An abnormal hemodynamic response (e.g., hypotension or failure to increase blood pressure with exercise) in a patient with severe AS is considered a poor prognostic finding.

Observations made during exercise may provide a basis for advice about physical activity.

**Exercise Testing**

**Class IIb**

1. Exercise testing in asymptomatic patients with AS may be considered to elicit exercise-induced symptoms and abnormal blood pressure responses. *(Level of Evidence: B)*

**Class III**

1. Exercise testing should not be performed in symptomatic patients with AS. *(Level of Evidence: B)*

*Bonow, ACC/AHA VHD Guidelines: 2008 Focused Update*
Hypertrophy in Aortic Stenosis

Adaptive pressure overload hypertrophy:
- Preserves ejection performance
- Impairs coronary blood-flow reserve
- Reduces diastolic function
- Associated with increased heart failure and mortality

Inappropriate hypertrophy:
- Particularly common in elderly patients, especially women
- Wall thickness is greater than necessary to counterbalance the high intracavitary pressures
- Results in low systolic wall stress and high ejection fraction
- Associated with high perioperative morbidity and mortality

Different gene expression patterns; distinct processes?

Kupari Eur Heart J 26, 2005
Contractile Deficit in LVH

Afterload excess and/or Contractile dysfunction

Mechanisms
• Intermittent ischemia
• Abnormal calcium handling
• Apoptosis
• Neurohormonal activation
• Hyperpolymerisation of the myocardial cytoskeleton
Low-Flow/Low-Gradient Aortic Stenosis

Muscle dysfunction that prevents the cardiac output from generating a mean gradient of more than 30 mm Hg indicates a poor prognosis.

Class IIa
1. Dobutamine stress echocardiography is reasonable to evaluate patients with low-flow/low-gradient AS and LV dysfunction. *(Level of Evidence: B)*

2. Cardiac catheterization for hemodynamic measurements with infusion of dobutamine can be useful for evaluation of patients with low-flow/low-gradient AS and LV dysfunction. *(Level of Evidence: C)*

Connolly Circulation 101, 2000
Bonow, ACC/AHA VHD Guidelines: 2008 Focused Update
Dobutamine for Low Gradient AS

- Increase in stroke volume > 20% during dobutamine infusion predicts less operative risk and improved long-term survival
- Quality of life of individuals without inotropic reserve who survive surgery could still be enhanced after successful aortic valve replacement
- Residual gradient after AVR has a negative effect on prognosis

Monin Circulation 108, 2003
Syncope in Aortic Stenosis

- Limited exercise-induced stroke volume increase cannot match decreased peripheral resistance
- High intraventricular pressures cause reflex depressor response (vasoplegic syncope)
- Ventricular arrhythmia (at risk for post op recurrence)
von Willebrand syndrome in Aortic Stenosis

• Impaired platelet function and decreased levels of von Willebrand factor in most patients with severe AS
• Associated with clinical bleeding, most often epistaxis or ecchymoses, in approximately 20% of patients.
• Severity of the coagulation abnormality correlates with the severity of AS
• Resolves after valve replacement, except when the prosthetic valve area is small for patient size (less than 0.8 cm² per m²)

AVR for Mild to Moderate AS

Average aortic valve gradient progression of 6.5 mmHg per year

Quere, Circulation 113, 2006
Percutaneous approaches to AS

• Balloon aortic valvotomy in adults
  – high recurrence rate (50% within 6 months)
  – absence of any mortality benefit (diffuse calcification)

• Stented valves
  – Balloon valvotomy first, then stented bioprosthetic valve deployed into the aortic annulus over a balloon. 
    Transapical
    • Thoracotomy without bypass
    Percutaneous
    • Anterograde via transseptal puncture
    • Retrograde across the native valves
Stented AVR

- Procedural success is closely linked to experience and is 90% in experienced centers.
- Valve function is good with a final valve area ranging from 1.5 to 1.8 cm².
- Feasibility of subsequent AVR unknown.
- Midterm clinical outcomes encouraging (up to 2 years).
- Long term durability and incidences of endocarditis or thromboembolic events are not yet established.

Complications

- 30 day mortality: 5 to 18%
- Acute myocardial infarction: 2–11%
- Mild-to-moderate aortic regurgitation: 50%
- Prosthesis embolization: 1%
- Vascular complications: 10 – 15
- Stroke: 3 to 9%
- Atrioventricular block: 4–8%
- Pacemaker implantation: 24%
Contraindications

- Aortic annulus <18 or >25 mm for balloon-expandable; <20 or >27 for self-expandable devices
- Bicuspid valves
- Asymmetric heavy valvular calcification
- Aortic root dimension >45 mm at the aorto-tubular junction
- Presence of apical LV thrombus
PREVENTION OF INFECTIVE ENDOCARDITIS: GUIDELINES FROM THE AMERICAN HEART ASSOCIATION

Mission of IE Prophylaxis:
target predictable bacteremias with organisms that can cause endocarditis in patients with more than baseline risk of infection

Does prophylaxis decrease bacteremia?
Does it prevent endocarditis?
Do the benefits of prophylaxis outweigh the risks?
Primary Regimens for Dental Procedures

1955  600,000 units of aqueous penicillin and 600,000 units of procaine penicillin in oil containing 2% aluminum monostearate administered intramuscularly 30 minutes before the operative procedure.

1960  Step I – Prophylaxis two days before surgery with 600,000 units of procaine penicillin intramuscularly on each day.

Step II – Day of surgery: 600,000 units procaine penicillin intramuscularly supplemented by 600,000 units of crystalline penicillin intramuscularly one hour before surgical procedure.

Step III – For two days after surgery: 600,000 units procaine penicillin intramuscularly each day.

1997  Amoxicillin two grams orally one hour before procedure.
IE is a rare disease
IE carries a high morbidity
Bacteremia with organisms known to cause IE occurs commonly in association with dental, GI, or GU procedures
There is a spectrum of underlying diseases
Prior indications for prophylaxis are common

Most IE cases are not associated with a history of an invasive procedure
There are significant costs and risks of overuse of antibiotics
Almost all supportive data comes from animal models with little semblance to human disease
Few data exist to show that current regimens are effective
### Endocarditis is a Rare Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate per 100,000 Patient Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Mitral valve prolapse</strong></td>
<td></td>
</tr>
<tr>
<td>No murmur</td>
<td>4.6</td>
</tr>
<tr>
<td>Murmur</td>
<td>52</td>
</tr>
<tr>
<td><strong>Congenital heart disease</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>20</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>180</td>
</tr>
<tr>
<td>VSD</td>
<td></td>
</tr>
<tr>
<td>Corrected</td>
<td>60</td>
</tr>
<tr>
<td>Uncorrected</td>
<td>220</td>
</tr>
<tr>
<td><strong>Rheumatic heart disease</strong></td>
<td>380-440</td>
</tr>
<tr>
<td><strong>Prosthetic valve</strong></td>
<td></td>
</tr>
<tr>
<td>Mechanical</td>
<td>308</td>
</tr>
<tr>
<td>Bioprosthesis</td>
<td>383</td>
</tr>
</tbody>
</table>

*Steckelberg IDCNA 7:9-19, 1993*
Definition of Patients at Risk, 1997 and 2007

• No Increased Risk:
  • Isolated Secundum ASD
  • ASD, VSD or PDA 6 months post-repair if no residua
  • Previous CABG, Cardiac Pacemaker or Implanted Defibrillator
  • MVP, Previous Kawasaki Disease, or Previous Rheumatic Fever if no insufficiency is present

• Highest Risk Category:
  • Prosthetic Cardiac Valves
  • Previous Bacterial Endocarditis
  • Complex Cyanotic Congenital Heart Disease, with surgically constructed systemic-pulmonary shunts or conduits
  • Transplant recipients with valvular insufficiency (added in 2007 guidelines)
Definition of Patients at Risk, 1997

Moderate Risk
Category:
- Most Other Congenital Cardiac Malformations
- Acquired Valvular Dysfunction
- Hypertrophic Cardiomyopathy
- Mitral Valve Prolapse with Insufficiency and/or Thickened Leaflets

MVP is the most common etiology requiring mitral valve replacement. MVP is the most common underlying cardiac condition in patients with IE.

Framingham Heart Study, Freed JACC 2002
Balancing Risks and Costs

The Risks of Endocarditis

**Patient Risks:**
- Risk of contracting the disease
- Risk of morbidity from the disease

**Procedure Risks:**
- Risk of causing bacteremia with organisms likely to cause endocarditis

The Costs of Prophylaxis

- Adverse antibiotic reactions
- Inconvenience
- Expense
- Microbial resistance
- False confidence?
Transient bacteremia is *common* with manipulation of the teeth and periodontal tissues

- Tooth extraction (10-100%)
- Periodontal surgery (36-88%)
- Scaling and root planing (8-80%)
- Teeth cleaning (up to 40%)
- Endodontic procedures (up to 20%)

Transient bacteremia is *common* during routine daily activities

- Tooth brushing and flossing (20-68%)
- Use of wooden toothpicks (20-40%)
- Water irrigation devices (7-50%)
- Chewing food (7-51%)

*Roberts GJ et al: Pediatr Cardiol 1997*


*Sconyers JR et al: J Dental Assn 1973;87:616*

What about...

**Magnitude of Bacteremia**
- The magnitude of bacteremia from a dental procedure is relatively low (< $10^4$ CFU/mL)
- Bacteremia from routine daily activities are of similar magnitude
- Experimental IE in animals require $10^6$-$10^8$ CFU/mL
- There are no data demonstrating a relationship between the magnitude of bacteremia and likelihood of IE in humans

**Oral Hygiene**
- In patients with poor oral hygiene, the frequency of positive blood cultures just prior to dental extraction may be similar to that following extraction
- Poor oral hygiene $\rightarrow$ increased risk of spontaneous bacteremia

**Bleeding**
- No data to support that visible bleeding during a dental procedure is a reliable predictor for bacteremia

References:
- Roberts GJ et al: Heart 2006;92:1274
- Roberts GJ Pediatr Cardiol. 1999;20:317
- Thayer W Hopkins Hospital Report. 1926;22:1
Do Antibiotics Reduce Bacteremia?

- Amoxicillin therapy causes significant reduction but does not eliminate bacteremia (Lockhart)

- Penicillin or ampicillin compared with placebo diminished the percentage of viridans group streptococci and anaerobes in culture, but no significant difference in the percentage of pts with positive cultures 10 minutes after tooth extraction (Hall)

- Cefaclor or erythromycin did not reduce post-procedure bacteremia compared with untreated controls (Hall)
2-Year Prospective Study in the Netherlands

427 pts with definite late prosthetic valve or native valve IE

→ 31 Excluded (non-oral bacteria)
→ 29 Excluded (procedure w/ low bacteremia risk)

89 pts with IE onset within 180 days of dental / medical procedure

→ 25 Native valve IE (not previously known) → no abx
→ 48 NVE (previously known) → 8 (17%) received abx
→ 16 prosthetic valve IE → 9 (56%) received abx

45 of 89 developed IE within 30 days
Use of prophylaxis might have prevented 23/ 427 (5.3%) of IE

van der Meer et al. Arch Intern Med 152, 1992
Population-Based Study in France (39 Million Adults in 1999)

• Estimated 2.7 million at-risk dental procedures done in 1999 in France on pts with preexisting cardiac condition (PCC)
  – 62% unprotected

• Estimated 1370 IE cases in 1 year (1 in 28,500 adults)
  – 714 (52%) in pts with PCC
    • 44 could have been related to at-risk dental procedures
    • 37 unprotected, 7 protected

• Prophylaxis reduced IE prevalence in pts with PCC from 1/46,000 to 1/149,000

➢ A huge number of doses of prophylaxis would be needed to prevent a small number of cases

Case-Control Study in Delaware valley

To evaluate dental prophylaxis and cardiac risk factors for community-acquired IE (N=273) vs controls matched for age, sex and residence

1. Risk factors for IE: mitral valve prolapse (OR 19.4), congenital heart disease (OR 6.7), rheumatic heart disease (OR 13.4), and previous cardiac valve surgery

2. Cases & Controls had similar exposures to dental work within 3 months. Only 6 cases and 2 controls received abx prophylaxis within 1 mo of study date

Results:

1. Dental treatment was not a risk factor for IE even in patients with valvular heart disease

2. Few cases of IE could be prevented with prophylaxis, even if it were 100% effective

IE Cases Possibly Related to “Unprotected” Procedures

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>2.7%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>5%</td>
</tr>
<tr>
<td>US</td>
<td>3%</td>
</tr>
</tbody>
</table>

---

Estimated Risk of IE From Dental Procedures

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>1 / 14 million</td>
</tr>
<tr>
<td>MVP</td>
<td>1 / 1.1 million</td>
</tr>
<tr>
<td>CHD</td>
<td>1 / 475,000</td>
</tr>
<tr>
<td>RHD</td>
<td>1 / 142,000</td>
</tr>
<tr>
<td>Prosthetic cardiac valve</td>
<td>1 / 114,000</td>
</tr>
<tr>
<td>Previous IE</td>
<td>1 / 95,000</td>
</tr>
</tbody>
</table>
The number of cases of IE that result from dental procedures is likely to be very small.

The number of cases that could be prevented by antibiotic prophylaxis, even if 100% effective, is small.

Effectiveness of prophylaxis is likely considerably less than 100%.

The risk of antibiotic-associated adverse events exceeds the benefit.

Maintenance of good oral health and hygiene may reduce the incidence of bacteremia.
2007 Recommendations: Dental Procedures

Antibiotic prophylaxis is recommended for patients deemed to be at HIGHEST RISK for IE morbidity who undergo any dental procedure that involves the gingival tissues or periapical region of a tooth and for those procedures that perforate the oral mucosa. While IE prophylaxis may be reasonable for these patients, its effectiveness is unknown (Class IIb, LOE C).
Implementing Guidelines against historical and individual practices

**Communication:**
- Are you serious?
- Why were you so wrong in the first place?
- Did your wrong ideas cost me money?
- You mean I could have DIED from that amoxicillin??
- I guess I’m not at risk for heart infections after all.
- So I’m at risk for heart infections, but there’s nothing I can do about it?

**Education**
- New look at the evidence
- Concern that antibiotics are becoming less useful because of overuse
- Other approaches to dealing with the risk of IE
  - Commitment to vigilance
  - Oral health

**Sources of Communication and Education**
- Primary care provider
- Dental practitioner
- American Heart Association
# Antibiotics to Prevent Valvular Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>Endocarditis</th>
<th>Rheumatic valvular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Rare</td>
<td>Overwhelming</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Unproven</td>
<td>Well established</td>
</tr>
<tr>
<td>Implementation of Guidelines in the US</td>
<td>&lt;30%</td>
<td>Unknown</td>
</tr>
</tbody>
</table>