PREVENTING ENDOCARDITIS

Or…the dentists and dental hygienists are the good guys…

Internal Medicine Grand Rounds
April 4, 2008

Preventing Endocarditis

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INTRODUCTION

Case

- 72 yo male with MVP, chronic moderate-severe MR, borderline LV end-systolic diameter on echo (4.3 cm), asymptomatic
- Between scheduled serial echos, has dental work, receives Amoxicillin 2 gm 1 hr before
- 1-2 weeks after dental work, develops progressively worsening dyspnea, PND and new peripheral edema. Patient believes taking Amoxicillin is the cause.
- Pt admitted with new-onset CHF and atrial fibrillation. No evidence of endocarditis.
- Echo: increased LV dimensions, mildly decreased LV systolic function
- Underwent bioprosthetic MVR and Maze procedure → NSR, stabilization/improvement of LVSF, resolution of all symptoms
- On follow-up late April 2007, states 'my brother says they came out with new guidelines, and I understand I don't need those antibiotics before dental work anymore – the ones that caused my heart problem'
- Is he right?

HISTORICAL BACKGROUND

Infective Endocarditis and Dental Work

- Viridans group strep are common normal oral flora, and have been identified as cause >=50% community-acquired IE not associated with IVDA
- Osler, 1885: association between surgical bacteremia and IE
- 1935: Prevalence of bacteremia [Okell 1935]
    - 11% of persons with poor oral hygiene
    - 61% with dental extraction

Evolution of AHA Guidelines on Prophylaxis of IE

Year	Key Feature or Change [Wilson 2007]
1955	1st guideline. IM PCN 30 min before.
1957	In addition, PO PCN 4x/day for 2 days before and after
1960	Change to IM PCN once daily for 2 days before & after (plus IM PCN 1 hour before procedure)
1965	Omit Rx 2 days before. Address enterococcus after GI/GU.
1972	Updated details of IM PCN 1 hr before then once/d x 2 d
1977	Change post-Rx to PO PCN VK 500 q 6 hr x 8 doses. Pts and procedures divided into high vs. low risk → complex tables.
1984	Change to PO PCN VK 2 g1 hr before, 1 g 6 hrs after. Simpler lists of procedures IE prophylaxis is/is not recommended for.
1990	PO Amoxicillin 3 g 1 hr before, 1.5 gm 6 hrs after. More complete list of procedures.
1997	PO Amoxicillin 2 g 1 hr before. Cardiac conditions: high vs. med vs. low risk → IE prophylaxis only for high and med groups.

AHA Guidelines: Class, and Level of Evidence:

Classification of Recommendations

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

IIa. Weight of evidence/opinion is in favor of usefulness/efficacy
IIb. Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective, and in some cases may be harmful.

Level of Evidence

Level of Evidence A Data derived from multiple randomized clinical trials

Level of Evidence B Data derived from a single randomized trial, or non-randomized studies

Level of Evidence C Consensus opinion of experts

Guidelines through 1997 have been Class IIb, Level of Evidence C

Evolution of International Guidelines on IE Prevention

Various other bodies have also established guidelines for IE prevention over the years, including the European Society of Cardiology (ESC), the British Cardiac Society/Royal College of Physicians (BCS/RCP), and the Societe Francaise de Cardiologie (SFC) [Delahaye 2007]. Substantial harmony existed between the 1997 AHA guidelines and the guidelines issued by these societies in the early 2000's (2004 ESC, 2004 BCS/RCP) with respect to which cardiac conditions are associated with increased risk:

Table 1 Cardiac conditions associated with increased risk of infective endocarditis (universal to all guidelines)

High risk

- Prosthetic heart valves
- Uncorrected complex congenital cyanotic heart diseases
- Previous infective endocarditis
- Surgically constructed systemic or pulmonary conduits

Moderate risk

- Acquired valvular heart diseases
- Mitral valve prolapse with valvular regurgitation or severe valve thickening
- Non-cyanotic congenital heart diseases (except for secundum type ASD) including bicuspid aortic valves
- Hypertrophic cardiomyopathy

However, differences began to emerge regarding which patients should receive IE prophylaxis. The 2004 SFC guidelines limited IE prophylaxis only to high-risk groups [Delahaye 2007]. The BCS/RCP 2004 guidelines extended IE prophylaxis to procedures beyond that recommended for coverage by the AHA and other European groups, notably TEE, PTCA, coronary stenting, EGD without biopsy, cervical smears, and even acupuncture, body piercing and tattooing. This divergence helped prompt fresh calls for an international consensus on recommendations for IE antibiotic prophylaxis of IE.

Why revise AHA guidelines again?

Original Assumptions/Principles:

1. IE uncommon but life-threatening – prevention better than treatment
2. Certain cardiac conditions predispose to IE
3. Bacteremia with IE-causing organisms occurs commonly with dental, GI/GU procedures
4. Antimicrobial prophylaxis proven effective in lab animals for preventing experimental IE
5. Antimicrobial prophylaxis thought effective in humans for preventing IE due to dental/GI/GU procedures

The first 4 of these assumptions are still believed true, based on available evidence. However the 5th assumption has now been seriously challenged, with current consensus now holding that this assumption is most likely false. A preview summary of reasons is presented in the 2007 guidelines [Wilson 2007] in the table reproduced below. These assertions will be discussed sequentially in a later section.

TABLE 2. Primary Reasons for Revision of the IE Prophylaxis Guidelines

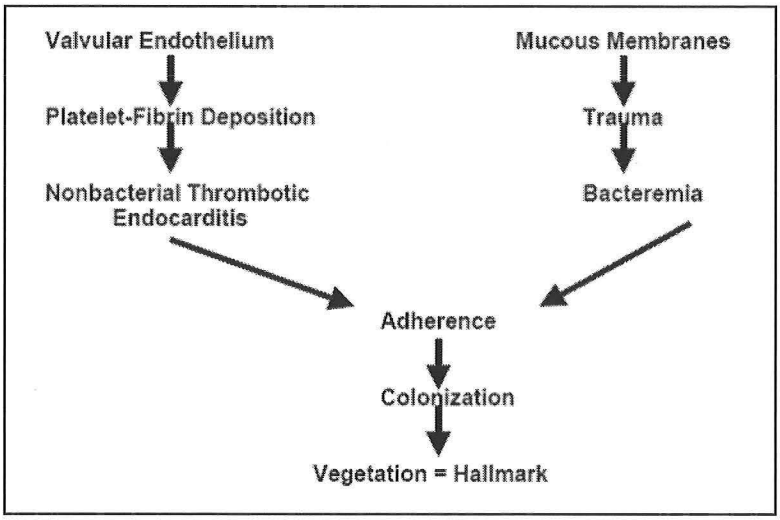
IE is much more likely to result from frequent exposure to random bacteremias associated with daily activities than from bacteremia caused by a dental, GI tract, or GU tract procedure.
Prophylaxis may prevent an exceedingly small number of cases of IE, if any, in individuals who undergo a dental, GI tract, or GU tract procedure.
The risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy.
Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of IE.

PATHOPHYSIOLOGY OF INFECTIVE ENDOCARDITIS

Mechanism

The development of IE is felt to require the combination of 2 chains of events: disruption of valvular endothelium leading to non-bacterial thrombotic endocarditis, with subsequent bacterial adherence/seeding during an episode of bacteremia. The final result is the hallmark of IE, a valvular vegetation.

1. Formation of NBTE
2. Transient Bacteremia
3. Bacterial Adherence
4. Proliferation of Bacteria Within a Vegetation



Prospects for Vaccine

Of interest, the need for bacterial adherence (and its correlation with the species of bacteria most commonly causing IE), has prompted investigation into agents or even vaccines that could disrupt bacterial adherence to NBTE, reducing the risk of IE. The general logic is:

- Bacteria produce factors that promote adherence → increase virulence
- Viridans strep → FimA protein (a lipoprotein receptor antigen I)
- Staph adhesins promote adhesion to medical devices as well as matrix proteins
- Strep and staph adhesins are immunogenic → Vaccine?

This work remains in an investigational stage [Wilson 2007].

ARGUMENTS FOR IE PROPHYLAXIS BEFORE DENTAL WORK

The rationale supporting several decades of AHA guidelines favoring antibiotic prophylaxis before dental work has gone as follows:

- Bacteremia causes IE
- Viridans strep normal oral flora
- Strep sensitive to ATB's used for prophylaxis
- Experimental animal evidence that prophylactic ATBs reduce risk of IE

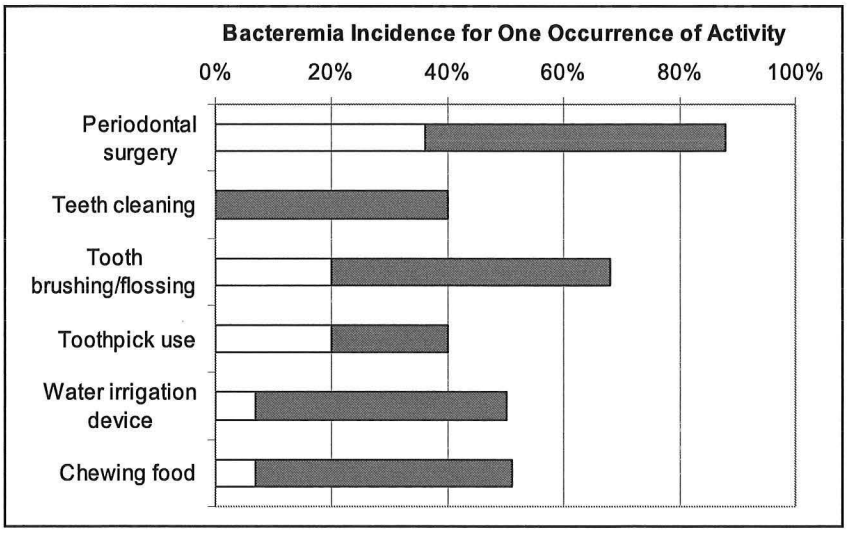
- Poorly documented case reports of IE after dental procedure
- Awareness of bacteremia with dental procedures
- Risk of ATB use low in 1 pt
- Morbidity and mortality from IE high

ARGUMENTS AGAINST IE PROPHYLAXIS BEFORE DENTAL WORK

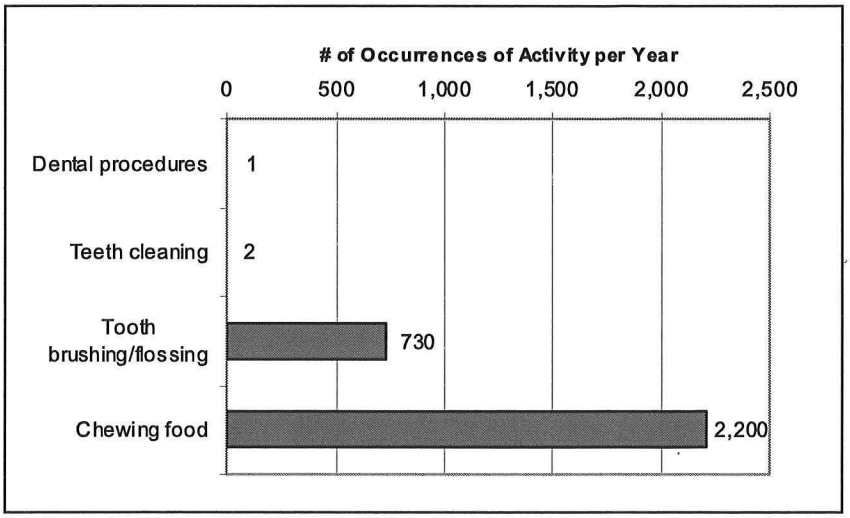
Despite the logic of the above chain of reasoning, no evidence exists that IE prophylaxis before dental work prevents IE in humans. Decades of following AHA guidelines seem to have had no impact on the frequency of IE. And a series of case-control studies and reviews have challenged the benefits of IE prophylaxis in humans.

Bacteremia from daily activities is much more common than bacteremia from dental work

Somewhat surprising is the frequency of bacteremia with common daily activities compared with dental work (shaded bars = reported incidence range).



The above is even more striking when considered in combination with frequency:



Combining (bacteremia/activity instance) * (# activities/year) leads mathematically to some eye-opening comparisons:

- Bacteremia exposure: ~ 5370 minutes of bacteremia/month from chewing food and tooth brushing/flossing vs. 6-30 minutes from one tooth extraction
- Relative exposure to bacteremia: Tooth brushing 2x/day for 1 yr vs. 1 tooth extraction/year = 154,000:1
- Cumulative bacteremia exposure during 1 year: All routine daily activities vs. 1 tooth extraction as high as ~ 5,600,000:1

Logically then, if antibiotics are to be administered prior to dental work because of the associated bacteremia and related risk, it would be inconsistent not to provide IE antibiotic prophylaxis daily.

Even if ATB prophylaxis were 100% effective, it would prevent a very few, if any, cases of IE

- Risk of IE in general population 1 case per 14 million dental procedures. In high-risk populations ~ 1 case per 100K-500K procedures

Risks of ATB prophylaxis are >= benefits, even if 100% effective

- Fatal anaphylaxis from dose of PCN estimated at 1 per 400K-600K
- For pts with prior PCN use, 2/3rds of PCN fatalities in pts with no known allergy

Resistance to antibiotics used for prophylaxis is steadily increasing

- Resistance to antibiotics used for prophylaxis increasing : 13-50% strep viridans now PCN-resistant.
- Single-dose antibiotic use thought to exert less selection pressure than full courses of treatment
- However repeat single-dose antibiotic use associated with increased resistance rates, which persist

Maintenance of optimal oral health may be more important for prevention of IE than antibiotic prophylaxis

Strom et al:

- Multi-center case-control study (54 Philly-area hospitals)
- IE no more likely in month following dental procedure than 2 months or 3 months after
- Control subjects without IE ***more*** likely to have undergone dental procedure than cases (P = 0.03)
- Conclusions:
  - Dental treatment NOT a risk factor for IE, even with valve disease
  - Few cases of IE preventable with prophylaxis EVEN IF it were 100% effective

WHICH CARDIAC PATIENTS SHOULD RECEIVE ANTIBIOTIC PROPHYLAXIS?

Prior AHA (and European) guidelines have taken the approach of classifying patients based on their life-time risk of developing infective endocarditis, and recommending antibiotic prophylaxis before dental work for the higher-risk groups. In the current guidelines, the focus has shifted to reserving prophylaxis for those at highest risk of adverse outcome if IE develops.

- Prior Guidelines:
  - Cardiac conditions with elevated lifetime ***risk of acquiring*** IE
- Current Guidelines
  - Cardiac conditions/patients with elevated ***risk of adverse outcome*** if IE occurs

Which cardiac conditions are associated with the highest lifetime risk of IE occurrence?

Lifetime risk of acquisition of IE (per 100K pt-yrs):

- MVP without MR murmur: 4.6
- MVP with MR murmur: 52
- VSD: 145
- Congenital aortic stenosis: 270
- RHD or prosthetic valve: 400
- Prior IE: 740
- Re-do valve replacement for IE: 2160

Which cardiac conditions are associated with the worst outcome if IE develops?

- Native valve viridans strep IE: mortality = 5%
- Prosthetic valve viridans strep IE: mortality >= 20%
- Recurrent IE: increased risk of CHF, need for surgery
- CHD studies underpowered to assess if an independent risk factor for morbidity, mortality. Complex cyanotic CHD and post-op palliative shunts/conduits appear high risk in retrospective studies
- IE in heart transplant recipients: increased morbidity/mortality

Cardiac conditions for which IE prophylaxis now recommended

Prosthetic cardiac valve
Previous IE
Congenital heart disease (CHD)*
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

†Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure.

Cardiac conditions for which IE prophylaxis no longer recommended

The guidelines say **patients who have taken prophylactic antibiotics routinely in the past but no longer need them** include people with:

- mitral valve prolapse
- rheumatic heart disease
- bicuspid valve disease
- calcified aortic stenosis
- congenital heart conditions such as ventricular septal defect and hypertrophic cardiomyopathy.

By comparison, the prior (1997) guidelines stated:

Endocarditis Prophylaxis Recommended (1997):

- ***High-Risk Category***
  - Prosthetic cardiac valves, including bioprosthetic and homograft valves
  - Previous bacterial endocarditis
  - Complex cyanotic congenital heart disease (e.g., single ventricle states, transposition of the great arteries, tetralogy of Fallot)
  - Surgically constructed systemic-pulmonary shunts or conduits
- ***Moderate-Risk Category***
  - Congenital cardiac malformations other than those listed in the high-risk and negligible-risk categories
  - Acquired valvular dysfunction (e.g., rheumatic heart disease)
  - Hypertrophic cardiomyopathy
  - Mitral valve prolapse with valvular regurgitation and/or thickened leaflets

Endocarditis Prophylaxis Not Recommended (1997):

- ***Negligible-risk category (no greater risk than the general population)***
  - Isolated secundum atrial septal defect
  - Surgical repair of atrial septal defect, ventricular septal defect or patent ductus arteriosus (without residua beyond six months)
  - Previous coronary artery bypass graft surgery
  - Mitral valve prolapse without valvular regurgitation or thickened leaflets1
  - Physiologic, functional or innocent heart murmur
  - Previous Kawasaki disease without valvular dysfunction
  - Previous rheumatic fever without valvular dysfunction
  - Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators

Thus the major practical change in patient selection from the 1997 to the 2007 Guidelines is omitting the 'Moderate-Risk Category' from IE prophylaxis.

FOR WHICH PROCEDURES SHOULD ANTIBIOTIC PROPHYLAXIS BE GIVEN?

Prior guidelines included extensive lists of procedures which should, and should not, receive prophylaxis. Some guideline versions included such phrases as 'dental work likely to cause bleeding' as inclusion criteria, which proved impractical to know ahead of time. In part in recognition of the minimal evidence to support such distinctions, and in part to simplify application of the guidelines, the recommendations for procedure coverage are now much more concise and straightforward.

Dental procedures

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa (but not routine analgesic injections through non-infected tissue).

GI/GU procedures (no)

- No prophylaxis, not even for high-risk patients
- If established GI/GU infection, reasonable to ensure patient's antibiotic coverage includes enterococcal coverage

Respiratory procedures

- Yes - invasive procedure involving incision or biopsy of respiratory mucosa
- No – routine bronchoscopy without biopsy

Skin/soft tissue/muscle

If surgery on infected tissue, yes, with antibiotic coverage for staph and strep species.

ANTIBIOTIC REGIMENS

Single-dose oral Amoxicillin remains the drug of choice in the AHA (and European) guidelines.

TABLE 5. Regimens for a Dental Procedure

		Regimen: Single Dose 30 to 60 min Before Procedure	
Situation	Agent	Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR		
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin*†	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV
	OR		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

IM indicates intramuscular; IV, intravenous.

*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

SPECIAL SITUATIONS

Certain special patient populations/situations are covered in the updated guidelines:

Already on antibiotics

For patients already on long-term antibiotic courses, the recommendation is to use an antibiotic from a different class for IE prophylaxis, rather than increase the dose of the existing antibiotic.

Cardiac surgery

- Careful pre-op dental evaluation (and treatment, if needed) is recommended before cardiac valve or congenital heart disease surgery, to reduce risk of late endocarditis from strep viridans
- Prosthetic valve surgery: peri-operative IE prophylaxis (Class I, LOE B)
    - Early prosthetic valve endocarditis (PVE) often staph aureus, coag-neg staph, or diphtheroids
    - Antibiotic choice depends on hospital's susceptibility patterns – primarily vs. staph
    - Initiate immediately before surgery, repeat during prolonged surgery, short post-op duration (no more than 48 hrs post-op)

CASE – REVISITED

- IE prophylaxis still recommended for this patient under the new guidelines(artificial heart valve)
- Points out common fallacy of reasoning that temporal sequence = cause→effect
    - IE prophylaxis before CHF: can't assume cause →effect (as patient assumed)
    - Dental work before IE: can't assume cause → effect

SUMMARY OF REVISED GUIDELINES

Primary prevention is maintenance of optimal oral health:

AHA Class & Level of Evidence: Class IIa, LOE B/C

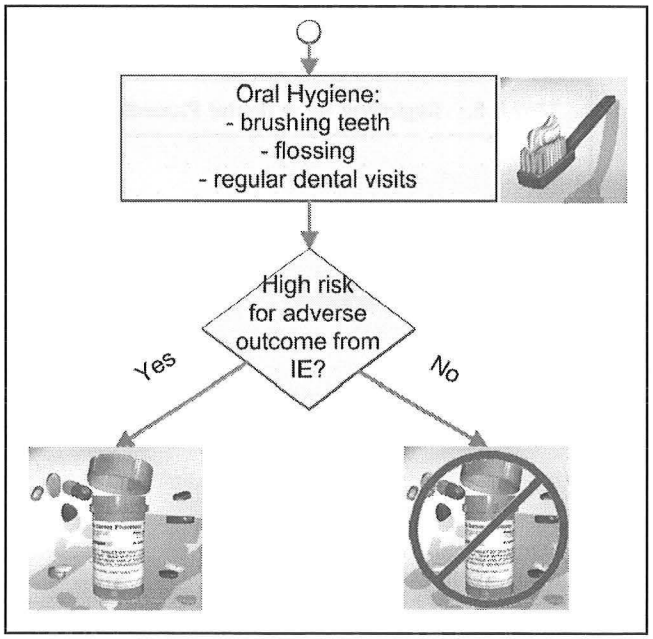
Only for:

High-risk for adverse outcome:

- artificial heart valves
- history of IE

plus:

- some congenital heart disease
- heart transplant with valve dz



GUIDELINES 1 YEAR LATER, & CONCLUSIONS

The AHA guidelines were first released online in April 2007, then published in Circulation in October 2007. The American Dental Association also published the guidelines in their journal in January 2008 (with an accompanying legal opinion).

Thus it still may be early to assess the effects of the substantial change in recommendations these guidelines entail. Several types of effects might be anticipated or of interest, although realistically most may be difficult to assess:

- Physician 'backlash'
- Patient resistance
- Decreased utilization of IE prophylaxis (e.g. # of Rx's written/filled)
- Change (increase or decrease) in rates of IE
- Change in rates of litigation related to IE
- Change in rate of rise of antibiotic resistance to antibiotics used for IE prophylaxis

I found no studies of these consequences thus far. Physicians have penned a handful of letters-to-the-editor and opinion columns, making the following points:

- The new guidelines are still just opinion (consensus) based, and have no randomized trial information to support them
- 'Lack of evidence of benefit' does NOT equal 'Evidence of lack of benefit'. That is:
- 'We do **not** know that IE prophylaxis is beneficial' does NOT equal 'We do know that IE prophylaxis is **not** beneficial'
- It's difficult to muster conviction when advising patients who've long been told they need prophylactic antibiotics that they no longer need them.

Perhaps the most personal statement is a recent opinion by a pediatric cardiologist:

> "This time I'm having a little trouble becoming enthusiastic about my repertoire of plausible explanations for why we are now doing things so differently. I've said, "The risks of IE with your specific heart defect during a dental visit may be smaller than previously thought, and the effectiveness of the antibiotic may be less than previously thought. You see, the risk of the antibiotic may be greater than the risk of getting IE. The AHA doesn't even recommend it anymore." My accompanying smile feels forced, as my mind is racing, "I sure hope that's right. What's right seems to change every few years. It's just the informed opinion of smart people. It's not like a double blind placebo-controlled study has been done. I know, and the AHA working group knows, some of these people are going to get IE. It may have nothing to do with any dentistry or surgery. They might have gotten IE even if they had received antibiotics on one of the older protocols. But the perspective of some patients and their parents will likely be different, largely because we've hammered them for years about the importance of antibiotic prophylaxis. When (not if, but when) one child gets IE after our about-face away from the time-honored antibiotics...can I call an expert panel to come explain that to them?" [Danford 2008]

Several authors are calling for the conduct of a more definitive clinical trial of IE prophylaxis. Difficulties in the past have included both ethical concerns and power limitations. Adequate power is made more difficult by:

- low incidence of IE
- variety of states to control for:

- type/severity of cardiac condition
- type of dental procedure
- dental disease state.

Nonetheless, at least one co-author of the new guidelines writes on-line that "A re-evaluation of the feasibility and ethical concerns regarding the performance of a randomized, placebo-controlled trial to determine the efficacy and safety of antibiotic administration for prevention of IE is underway." [Baddour, WWW]

If this comes to fruition, it offers fresh hope of clarifying this muddled area of practice, for the benefit of future guideline writers, physicians and patients.

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