Antibiotic prophylaxis of infective endocarditis
What's up in 2018?

Bruno Hoen
Université des Antilles - CHU de Pointe-à-Pitre
13 juin 2018
Conflict of Interest disclosure

• I am passionately interested in the care of patients with infective endocarditis
• I cannot recall the last time I took antibiotics for myself
• I have nothing else to disclose
Expert guidelines & consensus conferences

- USA (AHA):

- GB:
  - 2008 (NICE)

- Switzerland
  - 1984, 2000

- France (SPILF/AEPEI)
  - 1992, 2002

- Europe (ESC/ESCMID)
• “There is *no proof* that prophylaxis with antibiotics is effective in persons...undergoing procedures associated with transient bacteremia.

• However, the use of prophylactic antibiotics appears to be a reasonable approach to the problem and the *consensus of opinion* strongly supports the use of antibiotics in this situation”

Hook and Kaye, 1962
The number of procedures for which antibiotic prophylaxis was recommended had steadily increased over the past decades.

Existing guidelines for IE prophylaxis in 2002

Antibiotic for prevention of endocarditis during dentistry: time to scale back?

David T. Durack
First step back in IE prophylaxis indications
April 2006: British guidelines

Second step back in IE prophylaxis indications
Troisième étape dans la réduction de la prophylaxie
Prevention of IE: Guidelines from the AHA

Cardiac conditions associated with the highest risk of adverse outcome from IE for which prophylaxis with dental procedures is 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)

Wilson W, Circulation. 2007
Thornhill et al. 2018, Ostergaard et al. 2018


OR of Developing IE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Thornhill</th>
<th>Ostergaard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous IE</td>
<td>266</td>
<td></td>
</tr>
<tr>
<td>Valve Replacement</td>
<td>65</td>
<td>70</td>
</tr>
<tr>
<td>Valve Repair</td>
<td>77</td>
<td>19</td>
</tr>
<tr>
<td>Cyanotic Congenital Heart Disease (CHD)</td>
<td>55</td>
<td>42</td>
</tr>
<tr>
<td>CHD Repaired with Shunt/Conduit</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Rheumatic Valve Disease</td>
<td>51</td>
<td>42</td>
</tr>
<tr>
<td>Non-rheumatic Valve Disease</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Prosthetic Heart/ICD</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>
Mars 2008 : UK NICE clinical guideline

Exit l'antibioprophylaxie
AP against IE is NOT RECOMMENDED!

www.nice.org.uk/CG064
Antibiotic prophylaxis against infective endocarditis is NOT RECOMMENDED

- for people undergoing dental procedures
- for people undergoing the following non-dental procedures:
  - upper and lower gastrointestinal tract
  - genitourinary tract; this includes urological, gynaecological and obstetric procedures, and childbirth
  - upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy
- Chlorhexidine mouthwash should not be offered as prophylaxis against infective endocarditis undergoing dental procedures
It is not wise to give up antibiotic prophylaxis of IE
WHAT IS THE EVIDENCE FOR AP?

In Humans and Animals
Antibiotic prophylaxis of IE: summary of evidence

- Animal experimentations showed that AP effectively prevents IE
- Human experimental trials showed that penicillin prophylaxis reduces the incidence of bacteremia after dental extraction
- No RCT was ever conducted to confirm the efficacy and assess the benefit:risk ratio of AP
- Human observational studies
  - The efficacy of AP has been challenged in case-control studies
  - Transient bacteremia is common with normal daily activities such as tooth brushing, flossing and chewing food, which may contribute to the risk of IE at least as much as dental procedures
  - The widespread antibiotic use has been recognized to contribute to the emergence of antibiotic resistance
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Experimental Endocarditis

- Inoculum
- Bacteremia
- Drug kinetics
- Resistance
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Controlled clinical trial: an "urgent" need

- 1976: Lancet editorial
  - Prophylaxis of bacterial endocarditis: faith, hope, and charitable interpretations

- 1992: Lancet editorial
  - Most experts groups have shied away from suggesting prospective controlled studies of the efficacy of chemoprophylaxis on the argument that it would require an impractically large population. Surely it is time for this negative view to be reassessed. The EC, with its 330 million inhabitants might take the matter in hands. The doctrine of faith, hope, and charity may be a philosophy for life: it is no basis for perpetuating costly and possibly ineffective medical practices

  - Prophylaxis for infective endocarditis: let’s end the debate
RCTs Of Antibiotic Prophylaxis (AP) to Prevent Infective Endocarditis (IE)

- Main reasons why no RCTs have been performed to date
  - Size, complexity and cost of a study
  - Ethical concerns – randomising patients to placebo or no AP

Attempts at performing an RCT
- 2006 NIH R21 – Clinical Trial Planning Grant – P. Lockhart et al
2011 NIHR HTA Grant Application

- We realised that the 2008 NICE guidance removed the ethical/medico-legal barriers to an RCT in the UK
- National data systems in the UK could help address size, complexity and cost issues
- We put together a multidisciplinary team of experts in IE and in complex clinical trial design (ScHARR and CTRU)
**Prevalent Patient Identification**
100,000 prosthetic valve patients >18 yrs old from UK National Cardiac Surgical Database.
Valve replaced >1 year earlier

**Incident Patient Identification**
12,000 new prosthetic valve patients pa >18 yrs old.
Valve replaced >1 year earlier

**Recruitment**
Through original surgical centre. Informed and consented by post. Edentulous patients excluded (20%). It is assumed that 50% of prevalent and 50% of incident cases will be recruited. Allergy history confirmed.

**Randomisation**
Patient provided with AP or PP supplies and study pack

**Antibiotic Prophylaxis (AP) Group**
- Single 2g oral dose amoxicillin
- Or if allergic to penicillin
- Single 600mg oral dose clindamycin

**Placebo Prophylaxis (PP) Group**
If an enrolled patient visits a dentist: 
Dentist identifies if an invasive dental procedure is needed

Patient takes AP or PP 30-60 mins before invasive dental procedure

Event and nature of invasive dental procedure reported by patient/dentist to study team

Patient monitored (via patient/HES) for
- Adverse drug event in 2 weeks post procedure
- Infective endocarditis (IE) hospital admission in 12 weeks post procedure

If IE develops, monitored for death, complications, outcome (via HES/ONS/Cardiac Centres)

Primary Analysis
Analysis of HES/ONS data for all patients for the entire study period:
- IE hospital admissions in study population per 1000 patient follow-up years
- Total mortality; IE related mortality
- Repeat valve replacements
- IE related treatment costs

124,000 person years of follow up per group (AP v PP) yielding ~372 cases of IE per group of which ~40% i.e. 149 cases of IE per group may be susceptible to AP (assuming 100% efficacy)
• **Assessment:** a good study design with high chance of delivering a clear outcome

• **Estimate:** 2 years - set up/approvals, publicise etc. 5 years data collection, 1 year analysis (Total 8 years)

• **NIH priced study at US$60m (Euro 53m, £38m) i.e. x3**

• **About to consider funding when 2012 ‘Fiscal Cliff’ financial crisis hit USA**

• **NIH required to stop all new funding**

• **2013 – NIH Funding freeze lifted**

• **Politically US$60m now considered too high a cost for any RCT – particularly when entirely outside USA**
How to assess the efficacy of antibiotic prophylaxis of IE in humans?
Searching for innovative designs

Contributors
François Alla, Xavier Duval, and Bruno Hoen
What about a randomized registry-based trial?

• It has already been done and (well) published
  • Screening and Prostate-Cancer Mortality in a Randomized European Study (N Engl J Med 2009;360:1320-8)
  • Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction (N Engl J Med 2013;369:1587-97)

• What is a registry-based randomized trial?
  • A registry-based trial is a RCT conducted within or with the help of a registry (the registry is used to identify patients and/or to replace the CRF and/or to carry out the follow-up)
  • Numerous advantages
    • a rigorous randomized experiment that can test a causal link between a treatment and an outcome
    • because inexpensive, investigators can enroll large numbers of patients
    • realworld population created from existing consecutively registry-enrolled patients, which makes it possible to assess effectiveness in addition to efficacy
How could a registry-based randomized trial be implemented for AP of IE?

- **Population (registry-based)**
  - Registries make it possible to identify (all) people with high-risk conditions (prosthetic valve, other...)

- **Randomization (not registry-based but cluster-based)**
  - Geographic area
  - Dentist's patients

- **Follow-up and Endpoint (registry-based)**
  - National hospital discharge diagnosis database
  - Advantage
    - virtually all IE cases are diagnosed and treated in hospitals
  - Drawbacks
    - Diagnosis of IE would not be expert-validated
    - Causative microorganism may not be reported
How could a registry-based randomized trial be implemented for AP of IE? Situation in France (1)

• The French National Health Insurance information system (SNIIRAM), anonymously collects all individual and health care claims reimbursed by the French National Health Insurance (covering the whole French population). It is linked/merged with the French Hospital Discharge database (PMSI), which contains discharge diagnoses (ICD-10 codes) and medical procedures for all patients admitted to hospital in France

• From this database it would be possible to
  • set up a cohort of patients with prosthetic valves
  • observe and define a target dental intervention during follow-up
  • whether or not antibiotic prophylaxis would be used for this target intervention (whatever the randomization arm),
  • Identify the occurrence of an IE and compare incidence of IE between groups
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Limited Effect of Antibiotic Prophylaxis

Transient bacteremia
Cumulative bacteremia and risk of IE in a rat model

S. gordonii

SAME INOCULUM

Bolus
1 ml / 1 min

Continuous infusion
0.0017 ml/min over 10 h

Inoculum: 10^6 CFU/ml

Bacteremia

Endocarditis

Cohort: 138,876 adults with PHV (285,034 person years)
- 69,303 (49.9%) underwent at least one dental procedure
- 396,615 dental procedures were performed
  - 103,463 (26.0%) were invasive and presented an indication for AP
  - which was performed in 52,280 (50.1%)
- With a median follow-up of 1.7 years, 267 people developed IE due to oral streptococci (93.7 per 100,000 person years)
- Compared with non-exposure periods, no statistically significant increased rate of oral streptococcal IE was observed
  - during the three months after an invasive dental procedure
  - after an invasive dental procedure without antibiotic prophylaxis
In the case crossover analysis, exposure to invasive dental procedures was more frequent during case periods than during matched control periods

– 5.1% v 3.2%

– odds ratio 1.66, 95% CI 1.05 – 2.63; P=0.03
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Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of IE

After NICE there was a significant increase in the number of IE cases/month above the previous trend (0.11 cases/10 million/month, CI 0.05-0.16, p<0.0001).

By March 2013 this amounted to an extra:
- 35 IE cases/month

Dayer M, Lancet 2015;395:1219
Time trend studies addressing the changing population incidence of infective endocarditis after guideline changed

<table>
<thead>
<tr>
<th>Paper</th>
<th>Study location</th>
<th>Population/diagnoses analyzed</th>
<th>Incidence change?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bikdeli, 2013</td>
<td>USA</td>
<td>All diagnoses of IE from Medicare Inpatient Standard Analytic Files</td>
<td>No evidence of an increase in adjusted rates of hospitalization or mortality after 2007 guideline change</td>
</tr>
<tr>
<td>Dayer, 2015</td>
<td>England, UK</td>
<td>All diagnoses of IE from NHS Hospital Episode Statistics</td>
<td>In the 2015 analysis there was an increase detected in the number of cases of IE above the projected historical trend (by 0.11 cases per 10 million people per month). Statistical analysis identified June 2008 as the change point (3 months after NICE guideline change).</td>
</tr>
<tr>
<td>Thornhill, 2011</td>
<td>England, UK</td>
<td>All diagnoses of IE from NHS Hospital Episode Statistics</td>
<td>In the 2015 analysis there was an increase detected in the number of cases of IE above the projected historical trend (by 0.11 cases per 10 million people per month). Statistical analysis identified June 2008 as the change point (3 months after NICE guideline change).</td>
</tr>
<tr>
<td>De Simone, 2015</td>
<td>Olmsted County, Minnesota, USA</td>
<td>Diagnoses of VGS IE from Rochester Epidemiology Project</td>
<td>No evidence of an increase in VGS IE</td>
</tr>
<tr>
<td>De Simone, 2012</td>
<td>Olmsted County, Minnesota, USA</td>
<td>Diagnoses of VGS IE from Rochester Epidemiology Project</td>
<td>No evidence of an increase in VGS IE</td>
</tr>
<tr>
<td>Duval, 2012</td>
<td>France – Greater Paris, Lorraine, and Rhône-Alpes</td>
<td>All diagnoses of IE and subgroups by specific organisms</td>
<td>No evidence of an increase in VGS IE</td>
</tr>
<tr>
<td>Mackie, 2016</td>
<td>Canada</td>
<td>Diagnoses of IE from Canadian Institute for Health Information Discharge Abstract Database</td>
<td>No significant change in the rate of increase in IE cases after publication of guideline change. Reducing incidence of VGS IE over time. Change point analysis did not identify guideline change as a significant inflection point.</td>
</tr>
<tr>
<td>Pant, 2015</td>
<td>USA</td>
<td>Diagnosis of IE using Nationwide Inpatient Sample</td>
<td>Significant increase in the rate of rise in strep IE after 2007 (change in the slope before and after = 1.37 95% CI 0.69 – 2.05, p = 0.002). No change point analysis.</td>
</tr>
</tbody>
</table>
Marriage Rate in New York and Murders by Blunt Object

R = 0.88
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What's up in 2018?
What to do?

Pro

- Costs of treating IE
- Consequences of developing IE

Con

- Cost of AP
- Antibiotic Resistance
- Side effects
Let's be pragmatic: AP for whom?

<table>
<thead>
<tr>
<th>Indication</th>
<th>ESC guidelines 2015</th>
<th>Class/Evidence</th>
</tr>
</thead>
</table>
| Patient population          | 1. Patients with any prosthetic valve, including a transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair.  
2. Patients with previous IE  
3. Patients with CHD, including  
a. Any type of cyanotic CHD  
b. Any type of CHD repaired with a prosthetic material, whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if residual shunt or valvular regurgitation remains | IIa C           |
| Procedure                   | Dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa                                                                                      | IIa C           |
Let's be pragmatic: what AP regimen?

**Recommended prophylaxis**

<table>
<thead>
<tr>
<th>Situation</th>
<th>Antibiotic</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>No allergy to Penicillin or Ampicillin</td>
<td>Amoxicillin or Ampicillin (1)</td>
<td>2 g p.o. or i.v.</td>
<td>50 mg/kg p.o. or i.v.</td>
</tr>
<tr>
<td>Allergy to Penicillin or Ampicillin</td>
<td>Clindamycin</td>
<td>600 mg p.o. or i.v.</td>
<td>20 mg/kg p.o. or i.v.</td>
</tr>
</tbody>
</table>
IE prophylaxis cards (1)
Prophylaxis of IE: beyond antibiotic prophylaxis

- **Oral hygiene**
- **Prevention of healthcare-associated IE**
  - Prevention of healthcare-acquired bacteremia. Reducing the rate of central line-associated bloodstream infections can be achieved by practice-changing interventions
  - Prevention of IE associated with cardiac implantable electronic devices
- **Innovative approaches**
  - Inhibition of bacterial adhesion to
    - living surfaces (endocardium)
    - inert surfaces (prostheses, endovascular/intracardiac devices)
  - **Vaccination**
    - *S. aureus, P. aeruginosa, S. agalactiae*
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Oral Streptococcal Endocarditis, Oral Hygiene Habits, and Recent Dental Procedures: A Case-Control Study

Xavier Duval,1 Sarah Millot,2 Catherine Chirouze,3,a Christine Selton-Suty,4,a Vanessa Moby,5,a Pierre Tattevin,6 Christophe Strady,7 Edouard Euvrard,8 Nelly Agrinier,9 Daniel Thomas,10 Bruno Hoen,11,b and François Alla12,b; for the EI-dents Association pour l'Etude et la Prévention de l'Endocardite Infectieuse (AEPEI) Study Group

1Inserm CIC-1425, AP-HP, Hôpital Universitaire Bichat; Inserm UMR-1137 IAME; Université Paris Diderot, UFR de Médecine-Bichat, and 2UMR 1149-Inserm, CRI, Université Paris Diderot, Faculté de médecine Bichat, Paris; 3UMR 6249 Laboratoire Chrono-environnement Université de Bourgogne Franche-Comté, Service de maladies infectieuses, CHRU Besançon; 4Centre Hospitalier Régional Universitaire, and 5Service Odontologie—Centre Hospitalier Régional Universitaire Nancy; 6Maladies Infectieuses et Réanimation Médicale, Centre Hospitalier Universitaire, Rennes; 7Cabinet d'Infectiologie, Clinique Saint André-Groupe Courlancy, Reims; 8Inserm, CIC-1431; Service de Stomatologie, Chirurgie Maxillofaciale et Odontologie Hospitalière, CHRU Besançon; 9Inserm, CIC-1433 Epidémiologie Clinique, Centre Hospitalier Régional Universitaire, Nancy; 10AP-HP, Hôpital Pitié-Salpêtrière, Département de Cardiologie, Paris; 11Université des Antilles et de la Guyane, Faculté de Médecine Hyacinthe Bastaraud, EA 4537; Centre Hospitalier Universitaire de Pointe-à-Pitre, Inserm CIC-1424, Service de Maladies Infectieuses et Tropicales, Dermatologie, Médecine Interne, Pointe-à-Pitre; and 12Université de Lorraine, Université Paris Descartes, Apemac, EA4360; Inserm, CIC-1433, Nancy, France
## Multivariate analysis

### Factor associated with oral streptococci IE

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 65 years</td>
<td>2.50</td>
<td>(1.25-5.00)</td>
<td>0.0095</td>
</tr>
<tr>
<td>Female</td>
<td>2.25</td>
<td>(1.05-4.80)</td>
<td>0.0366</td>
</tr>
<tr>
<td>Native valve diseases</td>
<td>2.43</td>
<td>(1.17-5.05)</td>
<td>0.0411</td>
</tr>
<tr>
<td>Pulpal necrosis</td>
<td>3.36</td>
<td>(0.61-9.69)</td>
<td>NS</td>
</tr>
<tr>
<td>No interdental manipulations and tooth brushing after meals</td>
<td>1</td>
<td></td>
<td>0.0005</td>
</tr>
<tr>
<td>Without tooth brushing after meals</td>
<td>5.29</td>
<td>(2.00-14.02)</td>
<td></td>
</tr>
<tr>
<td>Interdental manipulations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and tooth brushing after meals</td>
<td>3.60</td>
<td>(1.35-9.57)</td>
<td></td>
</tr>
<tr>
<td>Without tooth brushing after meals</td>
<td>6.40</td>
<td>(2.17-18.85)</td>
<td></td>
</tr>
<tr>
<td>Dental invasive procedures within the 3 preceding months</td>
<td>3.49</td>
<td>(1.26-9.69)</td>
<td>0.0166</td>
</tr>
</tbody>
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Prophylaxis of experimental IE with Antiplatelet and Antithrombin Agents (1)

- Rat model of experimental IE following prolonged low-grade bacteremia mimicking smoldering bacteremia in humans

ASA : aspirin, TCL ticlopidine, EPB : eptifibatide, ABC : abciximab

Veloso TR, J Infect Dis 2015;211:72–9
Prophylaxis of experimental IE with Antiplatelet and Antithrombin Agents (2)

DE : dabigatran etexilate, ACC : acenocoumarol

Veloso TR, J Infect Dis 2015;211:72–9
Thank you for your attention