Antibioprophylaxie de l’endocardite infectieuse
Un peu, beaucoup ou pas du tout ?

Bruno Hoen
Université des Antilles - CHU de Pointe-à-Pitre
Octobre 2016
Expert guidelines & consensus conferences

- USA (AHA):
- GB:
  - 2008 (NICE)
- Switzerland
  - 1984, 2000
- France (SPILF/AEPEI)
  - 1992, 2002
- Europe (ESC/ESCMID)
The number of procedures for which antibiotic prophylaxis was recommended had steadily increased over the past decades.

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

David T. Durack
Indications of prophylaxis

French 2002 guidelines

First step back in IE prophylaxis indications

Indications of prophylaxis

$t$
Prophylaxis of infective endocarditis
Revision of the march 1992 French consensus conference
French Recommendations 2002

Médecine et maladies infectieuses 2002;32: 551-586

Prophylaxis of infective endocarditis: French recommendations 2002
N Danchin, X Duval and C Leport

Heart 2005;91:715-718
doi:10.1136/hrt.2003.033183
April 2006: British guidelines

Second step back in IE prophylaxis indications

F. K. Gould\textsuperscript{1*}, T. S. J. Elliott\textsuperscript{2}, J. Foweraker\textsuperscript{3}, M. Fulford\textsuperscript{4}, J. D. Perry\textsuperscript{1}, G. J. Roberts\textsuperscript{5}, J. A. T. Sandoe\textsuperscript{6} and R. W. Watkin\textsuperscript{7}

\textsuperscript{1}Department of Microbiology, Freeman Hospital, Newcastle upon Tyne, UK; \textsuperscript{2}Department of Microbiology, Queen Elizabeth Hospital, Birmingham, UK; \textsuperscript{3}Department of Microbiology, Papworth Hospital, Cambridge, UK; \textsuperscript{4}Postgraduate Dental Department, University of Bristol, Bristol, UK; \textsuperscript{5}King’s College Dental Institute, London, UK; \textsuperscript{6}Department of Medical Microbiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK; \textsuperscript{7}Department of Cardiology, Queen Elizabeth Hospital, Birmingham, UK

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**High-risk cardiac factors requiring antibiotic prophylaxis**

- Previous infective endocarditis
- Cardiac valve replacement surgery, i.e. mechanical or biological prosthetic valves
- Surgically constructed systemic or pulmonary shunt or conduit

**Dental procedures requiring antibiotic prophylaxis**

- All dental procedures involving dento-gingival manipulation
<table>
<thead>
<tr>
<th>Procedures</th>
<th>Anecdotally associated with endocarditis?</th>
<th>% Bacteraemia</th>
<th>Requires IE prophylaxis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal varices—sclerotherapy</td>
<td>yes&lt;sup&gt;21,22&lt;/sup&gt;</td>
<td>10–50&lt;sup&gt;23,24&lt;/sup&gt;</td>
<td>yes</td>
</tr>
<tr>
<td>Oesophageal stricture dilatation</td>
<td>yes&lt;sup&gt;25&lt;/sup&gt;</td>
<td>21–54&lt;sup&gt;23,26–29&lt;/sup&gt;</td>
<td>yes</td>
</tr>
<tr>
<td>Oesophageal varices—Banding</td>
<td>no</td>
<td>6&lt;sup&gt;23&lt;/sup&gt;</td>
<td>no*</td>
</tr>
<tr>
<td>Oesophageal laser therapy</td>
<td>no</td>
<td>35&lt;sup&gt;23&lt;/sup&gt;</td>
<td>yes</td>
</tr>
<tr>
<td>Endoscopy—upper</td>
<td>yes&lt;sup&gt;30–33&lt;/sup&gt;</td>
<td>4&lt;sup&gt;23&lt;/sup&gt;</td>
<td>no*</td>
</tr>
<tr>
<td>Sigmoidoscopy/colonoscopy</td>
<td>yes&lt;sup&gt;34–37&lt;/sup&gt;</td>
<td>0–9&lt;sup&gt;23,26,38&lt;/sup&gt;</td>
<td>no*</td>
</tr>
<tr>
<td>ERCP</td>
<td>no&lt;sup&gt;39&lt;/sup&gt;</td>
<td>6–11&lt;sup&gt;23&lt;/sup&gt;</td>
<td>yes</td>
</tr>
<tr>
<td>Percutaneous endoscopic gastrostomy</td>
<td>no</td>
<td>0&lt;sup&gt;40&lt;/sup&gt;</td>
<td>no*</td>
</tr>
<tr>
<td>Echocardiography—transoesophageal</td>
<td>yes&lt;sup&gt;41&lt;/sup&gt;</td>
<td>1–13&lt;sup&gt;42,43&lt;/sup&gt;</td>
<td>no*</td>
</tr>
</tbody>
</table>
Troisième étape dans la réduction de la prophylaxie

Avril 2007: US guidelines

Indications de prophylaxie
Prevention of Infective Endocarditis. Guidelines From the American Heart Association. A Guideline From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group


_Circulation_ published online Apr 19, 2007;

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

<table>
<thead>
<tr>
<th>Reason</th>
</tr>
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<tbody>
<tr>
<td>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.</td>
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<tr>
<td>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.</td>
</tr>
<tr>
<td>The risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy.</td>
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<td>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.</td>
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Primary Reasons for Revision of the IE Prophylaxis Guidelines

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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.
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
Exit l'antibioprophylaxie
Le retour à la case départ ...
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
Juillet 2009 : clinical guidelines ESC/ESCMID

L'abandon de l'antibioprophylaxie n'est pas "raisonnable"

Confirmé en 2015
Antibiotic prophylaxis of IE: summary of evidence

- Animal experimentation 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.
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Effect of Bacterial Inoculum on Exp. IE Initiation

Number of CFU per valves

% infected valves

Time after inoculation

Inoculum 10⁶ CFU

Inoculum 10⁵ CFU

Inoculum 10⁴ CFU

P Moreillon – UNI Lausanne
Single-dose Amoxicillin Prophylaxis in Streptococcal IE

![Graph showing the effect of prophylaxis with different inoculum sizes.](image)

**It works !!!**

**P Moreillon – UNI Lausanne**
**Bacteremia Following iv Inoculation of Rats Receiving or not Amoxicillin Prophylaxis**

Inoculum = $10^6$ cfu of *S. intermedius* (tolerant to penicillin)

- **no prophylaxis**
- **40 mg/kg of amoxicillin**

![Graph showing bacteremia following iv inoculation of rats](image-url)
Experimental studies

Amoxicillin before vs. after bacterial challenge

Incidence of endocarditis in control rats (C) and in rats given amoxicillin 30 min before (A−30) or 30–240 min after (A+30–A+240) bacterial challenge with various inocula of *S. sanguis*. *P* values were calculated by $\chi^2$ analysis with Yates’s correction; asterisk indicates $P < .05$ compared with controls. There were no significant statistical differences between A−30, A+30, and A+120.
Experimental Endocarditis

- Inoculum
- Bacteremia
- Drug kinetics
- Resistance
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Bacteremia Associated With Toothbrushing and Dental Extraction

- Patients presented to urgent care service with the need for extraction of at least 1 erupted tooth
- Double-blind, placebo-controlled study
- Three randomization arms
  - Toothbrushing
  - Single-tooth extraction with amoxicillin prophylaxis
  - Single-tooth extraction with identical placebo

Lockhart et al., Circulation. 2008;117:3118-3125
Bacteremia Associated With Toothbrushing and Dental Extraction

- 600 patients screened, 290 randomized
  - 98 toothbrushing
  - 96 extraction+amox
  - 96 extraction+Pcb
- 98 bacteremia
  - 32 IE-causing bacteria
  - Similar magnitudes (4 log$_{10}$ CFU/ml) in all groups

Is antibiotic prophylaxis for dental extraction relevant?

Lockhart et al., Circulation. 2008;117:3118-3125
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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)

• No RCTs have been performed to date
• Main reasons:
  • 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 application – The APPROVED Clinical Trial – M.Thornhill, B. Prendergast, J. Nicholl et al
• 2012 NIH – The APPROVED Clinical Trial – M.Thornhill, B. Prendergast, J. Nicholl et al
Power calculations:

- Incidence of IE:
  - General population: ~2/100,000
  - Moderate risk population: ~20-30/100,000
  - High-risk population: ~300/100,000

- 12,000 high-risk patients would therefore only produce ~36 cases of IE

- <1/2 of IE cases caused by OVGS and therefore susceptible to AP = 18 cases

- When randomised = 9 cases on AP and 9 on placebo

- Assumes AP is 100% effective and none of the patients are edentulous
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)
The APPROVED clinical trial

- A proposal for a double blind placebo controlled trial of ‘Antibiotic Prophylaxis for the Prevention of Prosthetic Valve Endocarditis in Dentistry
- A UK wide collaborative study that would involve
  - All cardiothoracic centres in the UK
  - All primary and secondary care Dentists in the UK (CDOs)
  - Infectious Disease experts
  - Experts in Health Services Research, Health Economics and Clinical Trials Management.
- Grant application was submitted to:

NIHR Health Technology Assessment programme
National Institute for Health Research
**Antibiotic Prophylaxis Prevention of PROsthetic Valve Endocarditis in Dentistry**

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

**Prevalent Patient Identification**
100,000 prosthetic valve patients >18 yrs old from UK National Cardiac Surgical Database.
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**

40,000 patients

4,880 patients pa
124,000 person years of follow-up per group (AP vs 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).

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
NIHR – HTA

- Highly rated and recommended for funding
- Further funding assessment – estimated cost £12m (Euro 17m, US$ 19m)
- Too high a % of total NIHR research budget
  - Not justifiable for a relatively uncommon condition
  - Particularly in competition with much cheaper treatment RCTs for more common and equally serious diseases – cancer, diabetes, Alzheimer’s etc
- NIHR commented that an RCT for IE unlikely to be fundable – recommended observational studies
The APPROVED clinical trial

- Took the APPROVED clinical trial to NIH (USA)
- NIH R34 – Clinical Trial Planning Grant
- Very impressed with the study design
- NIH decided they could consider the RCT even though it was to be performed entirely outside the USA
  - Because the ethical/medico-legal concerns could be overcome in the UK
  - Because the NHS and National data systems made the study possible and cheaper in the UK (not possible in USA)
- Because of the size of funding likely to be required – NIH put together a consortium of NHLI, NIDCR, NIAID to consider and fund it
• **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)

- 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
How could a registry-based randomized trial be implemented for AP of IE? Situation in France (2)

- Preliminary analyses from this database
  - 70,000 patients with prosthetic valves (identified since 2005)
  - Over a two-year period:
    - 94,000 dental interventions
    - 450 IE following these interventions
  - Rate of AP in PV carriers in whom AP is recommended: 45%
Possible study designs

• In countries where AP is recommended
  • Intervention: Actions to enforce AP according to existing guidelines (objective: reach ≥80% AP coverage rate)
  • Control: no intervention (i.e. expected AP coverage rate < 50%)
  • Randomization: Dentist?
  • Type of dental intervention: only high-risk
  • Type of at-risk patients: only high-risk

• In countries where AP is not recommended (UK, Sweden)
  • Intervention: AP according to pre-2008 guidelines
  • Control: no change (i.e. no AP, wherever NICE guidelines are enforced)
  • Randomization: geographic?
  • Type of dental intervention: any?
  • Type of at-risk patients: any at-risk or only high-risk?
“Do what you can, with what you have, where you are.”
Theodore Roosevelt

• The randomized registry trial represents a disruptive technology that will transform existing standards, procedures, and cost structures
• Will it be given serious consideration as a way to resolve the recognized limitations of current clinical trial design?
• Today we can no longer afford to undertake randomized effectiveness trials that cost tens or hundreds of millions of dollars.
• But today we have registries and other powerful digital platforms
• Today we must design and conduct megatrials with what we have: bigger data and smaller budgets

Adapted from Lauer and D'Agostino, NEJM 2103;369:1579)
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Is antibiotic prophylaxis effective?
3 case-control studies

- **Imperiale, Am J Med 1990;88:131-6**
  - 8 cases, 24 controls, dental procedures
  - Ab in 1/8 Ca vs. 15/24 Co (p=0.025), OR=0.09 [0–0.99] – PE=91%

- **Van der Meer, Lancet 1992;339:135-9**
  - 48 cases, 200 controls, majority of dental procedures
  - Ab in 8/48 Ca vs. 28/200 Co (p=0.6) OR=0.51 [0.1–2.3] – PE=49% (dental, within 30 days)

- **Lacassin, Eur Heart J 1995;16:1968-74**
  - 18 cases, 22 controls, dental procedures, dental IE
  - Ab in 3/18 Ca vs. 6/22 Co (p=0.4) OR=0.54 [0.1-3.1] – PE=46%
Dental and cardiac risk factors for IE: a population-based, case-control study.

- **Methods**
  - 273 cases of community-acquired IE
  - 273 controls matched by age, sex, and neighborhood

- **Results**
  - Pre-existing cardiac disease:
    - OR = 16.7 (IC95 : 7.4 – 37.4)
  - Dental procedures within past 3 months:
    - OR = 0.8 (IC95 : 0.4 – 1.5)
  - Very few patients received antibiotic prophylaxis, in either group

- **Interpretations**
  - Few cases of IE could be prevented with prophylaxis even if 100% effective
  - Current policies for prophylaxis should be reconsidered.

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Procedure-induced Bacteremia

Transient bacteremia

Procedure

Years
Overall Transient Bacteremia

Procedure

Transient bacteremia

Years
Limited Effect of Antibiotic Prophylaxis

Transient bacteremia
Le concept de bactériémie cumulative modélisé chez le rat !

**S. gordonii**

**INOCULUM IDENTIQUE**

**Bolus**
1 ml en 1 min

**Perfusion continue**
0,0017 ml/min sur 10 h
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## 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, 2013²</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, 2015⁻⁵</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, 2015⁻³³ De Simone, 2012⁻³²</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, 2012⁻³⁵</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>
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<tr>
<td>Mackie, 2016⁻³⁴</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, 2015²</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>
Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of IE

Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of IE
Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of IE

Antibiotic Prophylaxis Prescribing Data

Number of Prescriptions of Amoxicillin 3g or Clindamycin 600mg

Average pre: 10,900
Reduction: 88%, p<0.001

Dayer M, Lancet 2015;395:1219
Incidence of Infective Endocarditis Cases (Spells) and Deaths / 10 Million / Month

Dayer M, Lancet 2015;395:1219
Incidence of Infective Endocarditis Cases (Spells) and Deaths / 10 Million / Month

Dayer M, Lancet 2015;395:1219
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
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
  - It is uncertain whether guideline changes had an impact on population incidence of IE
  - AP of IE has been –and still is– based on oral streptococcal IE models, while *S. aureus* has become the most frequent IE-causing pathogen
### 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 | Ila C         |
| **Procedure**            | Dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa                                                                                           | Ila 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</td>
<td>2 g p.o. or i.v.</td>
<td>50 mg/kg p.o. or i.v.</td>
</tr>
<tr>
<td></td>
<td>or Ampicillin (1)</td>
<td></td>
<td></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>

Recommended prophylaxis for dental procedures at risk

Single dose 30-60 minutes before procedure

[www.escardio.org](http://www.escardio.org)
Prévention de l'endocardite infectieuse
Actualisation 2011 des recommandations

Nom, prénom :

Cardiopathies à haut risque d'endocardite infectieuse :
- Prothèse valvulaire cardiaque ou anneau valvulaire
- Antécédent d'endocardite infectieuse
- Cardiopathie congénitale cyanogène

Remis par le Dr :

le : ........................................... à : ...........................................
tél. : ........................................... email : ...........................................

www.infectiologie.com
www.sfcardio.fr
www.adf.asso.fr

Association pour l'étude et la prévention de l'endocardite infectieuse

Fédération Française de Cardiologie
Prévention de l'endocardite infectieuse

Nom, prénom :

Vous présentez la cardiopathie suivante :

- Insuffisance aortique, insuffisance mitrale, rétrécissement aortique, bicuspidie aortique
- Cardiopathie congénitale non cyanogène
- Prolapsus valvulaire mitral avec insuffisance mitrale / épaissement
- Cardiomyopathie hypertrophique obstructive

Cette cardiopathie peut être associée à la survenue d'une endocardite infectieuse. Elle ne justifie toutefois pas l'administration préventive d'antibiotiques avant un soin dentaire.

Remis par le Dr :

le : à :
tél. : email :

www.infectiologie.com
www.adf.asso.fr
www.sfc cardio.fr
www.fedecardio.com

Association pour l'Étude et la Prévention de l'Endocardite Infectieuse
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*
Oral hygiene habits, oro-dental status and history of dental procedures in patients with definite infective endocarditis caused by oral streptococci: a case-control study

and the El-dents AEPEI study group

* these authors contributed equally to the study.
Oral hygiene and dental procedures

<table>
<thead>
<tr>
<th>Patient self-reported oral hygiene</th>
<th>Whole population</th>
<th>Case-patients</th>
<th>Control-patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tooth brushing frequency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than twice daily</td>
<td>274 (100%)</td>
<td>73 (26.6%)</td>
<td>201 (73.4%)</td>
</tr>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>More than twice daily</td>
<td>37 (13.6%)</td>
<td>9 (13.6%)</td>
<td>28 (14.0%)</td>
</tr>
<tr>
<td>Twice daily</td>
<td>88 (31.9%)</td>
<td>28 (38.4%)</td>
<td>60 (30.0%)</td>
</tr>
<tr>
<td>Once daily</td>
<td>67 (24.4%)</td>
<td>20 (27.1%)</td>
<td>47 (23.5%)</td>
</tr>
<tr>
<td>Less than once daily</td>
<td>22 (8.4%)</td>
<td>7 (9.6%)</td>
<td>15 (7.5%)</td>
</tr>
<tr>
<td><strong>Tooth brushing after meals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>More than twice daily</td>
<td>126 (46.3%)</td>
<td>30 (40%)</td>
<td>96 (47.8%)</td>
</tr>
<tr>
<td>Twice daily</td>
<td>88 (31.9%)</td>
<td>28 (38.4%)</td>
<td>60 (30.0%)</td>
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*p = 0.6780 0.0500*
Oral hygiene and dental procedures

<table>
<thead>
<tr>
<th></th>
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<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Tooth brushing frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than twice daily</td>
<td>37</td>
<td>16.2</td>
<td>9</td>
</tr>
<tr>
<td>Twice daily</td>
<td>88</td>
<td>38.6</td>
<td>28</td>
</tr>
<tr>
<td>Once daily</td>
<td>67</td>
<td>29.4</td>
<td>20</td>
</tr>
<tr>
<td>Less than once daily</td>
<td>22</td>
<td>9.6</td>
<td>7</td>
</tr>
<tr>
<td>Tooth brushing after meal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toothpicks use</td>
<td>67</td>
<td>29.6</td>
<td>24</td>
</tr>
<tr>
<td>Water pik use</td>
<td>10</td>
<td>4.4</td>
<td>5</td>
</tr>
<tr>
<td>Flossing</td>
<td>19</td>
<td>8.3</td>
<td>11</td>
</tr>
<tr>
<td>Interdental brush</td>
<td>24</td>
<td>10.7</td>
<td>9</td>
</tr>
</tbody>
</table>
Oral hygiene and dental procedures

<table>
<thead>
<tr>
<th></th>
<th>Whole population</th>
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<td>Flossing</td>
<td>19</td>
<td>8.3</td>
<td>11</td>
</tr>
<tr>
<td>Interdental brush</td>
<td>24</td>
<td>10.7</td>
<td>9</td>
</tr>
<tr>
<td>At least one of these behaviours</td>
<td>93</td>
<td>40.1</td>
<td>37</td>
</tr>
</tbody>
</table>
### 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</td>
<td>1</td>
<td></td>
<td>0.0005</td>
</tr>
<tr>
<td>and tooth brushing after meals</td>
<td>5.29</td>
<td>(2.00-14.02)</td>
<td></td>
</tr>
<tr>
<td>Without tooth brushing after meals</td>
<td>3.60</td>
<td>(1.35-9.57)</td>
<td></td>
</tr>
<tr>
<td>Interdental manipulations</td>
<td>6.40</td>
<td>(2.17-18.85)</td>
<td></td>
</tr>
<tr>
<td>and tooth brushing after meals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without tooth brushing after meals</td>
<td>3.49</td>
<td>(1.26-9.69)</td>
<td>0.0166</td>
</tr>
</tbody>
</table>
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