Prévention de l'endocardite infectieuse : entre trop et trop peu ?

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Université de Lorraine - CHU de Nancy
17 septembre 2018
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
French 2002 guidelines

First step back in IE prophylaxis indications

Indications of prophylaxis

$t$
Short text*

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. Gould¹*, T. S. J. Elliott², J. Foweraker³, M. Fulford⁴, J. D. Perry¹, G. J. Roberts⁵, J. A. T. Sandoe⁶ and R. W. Watkin⁷

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

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
## BSAC guidelines 2006

<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(^{21,22})</td>
<td>10–50(^{23,24})</td>
<td>yes</td>
</tr>
<tr>
<td>Oesophageal stricture dilatation</td>
<td>yes(^{25})</td>
<td>21–54(^{23,26–29})</td>
<td>yes</td>
</tr>
<tr>
<td>Oesophageal varices–Banding</td>
<td>no</td>
<td>6(^{23})</td>
<td>no*</td>
</tr>
<tr>
<td>Oesophageal laser therapy</td>
<td>no</td>
<td>35(^{23})</td>
<td>yes</td>
</tr>
<tr>
<td>Endoscopy–upper</td>
<td>yes(^{30–33})</td>
<td>4(^{23})</td>
<td>no*</td>
</tr>
<tr>
<td>Sigmoidoscopy/colonoscopy</td>
<td>yes(^{34–37})</td>
<td>0–9(^{23,26,38})</td>
<td>no*</td>
</tr>
<tr>
<td>ERCP</td>
<td>no(^{39})</td>
<td>6–11(^{23})</td>
<td>yes</td>
</tr>
<tr>
<td>Percutaneous endoscopic gastrostomy</td>
<td>no</td>
<td>0(^{40})</td>
<td>no*</td>
</tr>
<tr>
<td>Echocardiography–transoesophageal</td>
<td>yes(^{41})</td>
<td>1–13(^{42,43})</td>
<td>no*</td>
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</tbody>
</table>
Troisième étape dans la réduction de la prophylaxie

Avril 2007: US guidelines
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

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<td>caused by a dental, GI tract, or GU tract procedure.</td>
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<tr>
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</tr>
<tr>
<td>procedure.</td>
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<td>benefit, if any, from prophylactic antibiotic therapy.</td>
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<td>Maintenance of optimal oral health and hygiene may reduce the</td>
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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.
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
Limit recommendations for IE prophylaxis only to those conditions associated with the highest risk of adverse outcome from IE

Antibiotic prophylaxis is recommended for all invasive dental procedures

Antibiotic prophylaxis is recommended for procedures on respiratory tract or infected skin, skin structures, or musculoskeletal tissue

Antibiotic prophylaxis solely to prevent IE is not recommended for GU or GI tract procedures

Wilson W, Circulation 2007
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
- 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.
July 2009: clinical guidelines ESC/ESCMID

It is not wise to give up antibiotic prophylaxis of IE

Confirmed en 2015
Controversy
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.
- 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.
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Effect of Bacterial Inoculum on Exp. IE Initiation

Number of CFU per valves vs. Time after inoculation

- Inoculum $10^6$ CFU
- Inoculum $10^5$ CFU
- Inoculum $10^4$ CFU

% infected valves

10 min 1 h 2 h 6 h 12 h

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

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
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

P Moreillon – UNI Lausanne
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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
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)

• 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 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
2006 NIH R21 RCT Planning grant

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
2006 NIH R21 RCT Planning grant

• Ethical/medico-legal issues randomising patients to placebo when AP is standard of care
• Moderate risk patients easier to recruit but because of lower risk of IE – much bigger numbers needed ~ 10 times more
• Cardiology units needed to identify and recruit high-risk patients
• But dentists also needed as they perform the procedures requiring AP cover
• Study is therefore very complex (expensive)
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).
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
**Antibiotic Prophylaxis Prevention of PROsthetic Valve Endocarditis in Dentistry**

**Incident Patient Identification**
12,000 new prosthetic valve patients pa >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**
The APPROVED clinical trial

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)

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)

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
The APPROVED clinical trial

• 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
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?
Many questions

• Is an international collaboration possible when countries do not use the same health insurance system databases?
  • Yes (see European study on impact of screening on prostate cancer mortality)
  • National data and analyses are pooled, which increased the strength of the results

• Which endpoint and which analysis strategy?
  • Incidence of IE
  • Intent-to-prevent and per-prophylaxis

• Duration of exposure time frame?

• Management of PV subjects who undergo repeat at-risk procedures?

• New ethical issues
  • How and when inform patients? And obtain informed consent?
  • Would an informed consent be necessary in any case?

• ....
“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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  - 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
Is antibiotic prophylaxis effective?
3 case-control studies

  - 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)

  - 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
Overall Transient Bacteremia
Limited Effect of Antibiotic Prophylaxis
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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  - 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
Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of IE

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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 (Superspells) and Deaths / 10 Million / Month

Dayer M, Lancet 2015;395:1219
By March 2013 this amounted to an extra:
• 35 IE cases/month

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)

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&lt;sup&gt;134&lt;/sup&gt;</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&lt;sup&gt;5&lt;/sup&gt;</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&lt;sup&gt;35&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Simone, 2015&lt;sup&gt;33&lt;/sup&gt;</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>DeSimone, 2012&lt;sup&gt;32&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duval, 2012&lt;sup&gt;135&lt;/sup&gt;</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&lt;sup&gt;34&lt;/sup&gt;</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&lt;sup&gt;2&lt;/sup&gt;</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
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
Pas trop enfumés ?
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 | 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 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>

[Recommended prophylaxis for dental procedures at risk](http://www.escardio.org)
IE prophylaxis cards (1)
IE prophylaxis cards (2)

PRÉVENTION DE L'ENDOCARDITE INFECTIEUSE
Actualisation 2011 des recommandations

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 / épaississement
- 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 :
ant à :
tél. :
email :

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

ASSOCIATION POUR L'ETUDE ET LA PREVENTION 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*
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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, 5, a Christophe Strady, 7 Edouard Euvrard, 8 Nelly Agrinier, 9 Daniel Thomas, 10 Bruno Hoen, 11, b and François Alla, 12, b; for the El-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 Épidémiologie 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
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>Tooth brushing frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than twice daily</td>
<td>37 (16.2%)</td>
<td>9 (13.6%)</td>
<td>28 (17.3%)</td>
</tr>
<tr>
<td>Twice daily</td>
<td>88 (38.6%)</td>
<td>28 (42.4%)</td>
<td>60 (37.0%)</td>
</tr>
<tr>
<td>Once daily</td>
<td>67 (29.4%)</td>
<td>20 (30.3%)</td>
<td>47 (29.0%)</td>
</tr>
<tr>
<td>Less than once daily</td>
<td>22 (9.6%)</td>
<td>7 (10.6%)</td>
<td>15 (9.3%)</td>
</tr>
<tr>
<td>Tooth brushing after meals</td>
<td>126 (53.6%)</td>
<td>30 (44.8%)</td>
<td>96 (57.1%)</td>
</tr>
</tbody>
</table>

*p-values: 0.6780, 0.0500
Oral hygiene and dental procedures

<table>
<thead>
<tr>
<th></th>
<th>Whole population</th>
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<th>Control-patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Tooth brushing frequency</td>
<td>274</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>More than twice daily</td>
<td>37</td>
<td>16.2</td>
<td>16</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>
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<td>22</td>
<td>9.6</td>
<td>7</td>
</tr>
<tr>
<td>Tooth brushing after meal</td>
<td>126</td>
<td>53.6</td>
<td>30</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>
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<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><strong>Age &lt; 65 years</strong></td>
<td>2.50</td>
<td>(1.25-5.00)</td>
<td>0.0095</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>2.25</td>
<td>(1.05-4.80)</td>
<td>0.0366</td>
</tr>
<tr>
<td><strong>Native valve diseases</strong></td>
<td>2.43</td>
<td>(1.17-5.05)</td>
<td>0.0411</td>
</tr>
<tr>
<td><strong>Pulpal necrosis</strong></td>
<td>3.36</td>
<td>(0.61-9.69)</td>
<td>NS</td>
</tr>
<tr>
<td>No interdental manipulations</td>
<td>1.00</td>
<td></td>
<td>0.0005</td>
</tr>
<tr>
<td>and tooth brushing after meals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Without tooth brushing after meals</strong></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><strong>Without tooth brushing after meals</strong></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>
</table>
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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