Antibiotic Prophylaxis for Permanent Pacemaker Implantation

A Meta-Analysis

Antoine Da Costa, MD; Gilbert Kirkorian, MD; Michel Cucherat, MD; François Delahaye, MD; Philippe Chevalier, MD, PhD; Alexis Cerisier, MD; Karl Isaaz, MD; Paul Touboul, MD

Background—Infection remains a serious complication after permanent pacemaker implantation. Antibiotic prophylaxis is frequently prescribed at the time of insertion to reduce its incidence, although results of well-designed, controlled studies are lacking.

Methods and Results—We performed a meta-analysis of all available randomized trials to evaluate the effectiveness of antibiotic prophylaxis to reduce infection rates after permanent pacemaker implantation. Reports of trials were identified through a Medline, Embase, Current Contents, and an extensive bibliography search. Trials that met the following criteria were included: (1) prospective, randomized, controlled, open or blind trials; (2) patients assigned to a systemic antibiotic group or a control group; (3) end point events related to any infection after pacemaker implantation: wound infection, septicemia, pocket abscess, purulent secretion, right infective endocarditis, inflammatory signs, a positive culture, septic pulmonary embolism, or repeat operation for an infective complication. Seven trials met the inclusion criteria. They included 2023 patients with established permanent pacemaker implantation (new implants or replacements). The incidence of end point events in control groups ranged from 0% to 12%. The meta-analysis suggested a consistent protective effect of antibiotic pretreatment ($P = .0046$; common odds ratio: 0.256, 95% confidence interval: 0.10 to 0.656).

Conclusions—Results of the present meta-analysis suggest that systemic antibiotic prophylaxis significantly reduces the incidence of potentially serious infective complications after permanent pacemaker implantation. They support the use of prophylactic antibiotics at the time of pacemaker insertion to prevent short-term pocket infection, skin erosion or septicemia. (Circulation. 1998;97:1796-1801.)

Key Words: pacemakers ■ meta-analysis ■ prevention

Pacemaker pocket infection remains a serious, potentially life-threatening complication after permanent pacemaker implantation; rates varying between 0.5% and 5.1% have been reported in retrospective and prospective studies. Septicemia, endocarditis, or both have also been described in up to 0.5% of patients. In a recent study of 52 patients with pacemaker lead–related endocarditis, hospital mortality was 7.6% and overall mortality was 26.9% after a mean follow-up of 20 months. Many operators routinely prescribe an antibiotic prophylaxis at the time of implantation to prevent such complications, although there is no present evidence that this strategy is beneficial. Indeed, results of individual trials are not convincing and their results are controversial possibly because sample sizes were too small to allow conclusive answers. An appropriate double-blind randomized study is still needed. However, we believed that the time had come to review the present knowledge based on pertinent literature. We thus performed a meta-analysis of available randomized trials to try to evaluate the effectiveness of systemic antibiotic prophylaxis to reduce infection rates after pacemaker implantation.

Methods

We reviewed all published trials and searched all unpublished trials on antibiotic prophylaxis at the time of permanent pacemaker implantation to prevent secondary infections. The hypothesis tested was formulated before data were collected. Patients had to be adult to undergo either a new permanent pacing system implantation or a pulse generator or lead change. Trials that met the following criteria were included: (1) prospective, randomized, controlled, open, or blind trials; (2) patients assigned to a systemic antibiotic group or a control group; (3) end point events related to any infection after pacemaker implantation. Data from individual trials were extracted independently by three of us (A.D.C., G.K., F.D.) by using the following end points: all probable or documented infections after pacemaker implantation. In the event of any disagreement about the data extracted, a consensus was obtained among the three readers. Studies were identified by use of the National Library of Medicine Medline from January 1967 to June 1996, Embase (Excerpta Medica) from January 1974 to June 1996, and Current Contents from January

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Patients with overt wound infection at the site of temporary transvenous pacemaker were clearly stated as noneligible.11,15,16,18

Protocols
All procedures were undertaken in operating rooms, and skin was assiduously disinfected before surgery. In one study, both groups of patients received intrapocket antibiotic spray containing neomycin, bacitracin, and polymixin.17 In six studies, the timing of antibiotic administration was recommended within 2 hours preceding incision. In only one were antibiotics administered immediately after the procedure and then for 4 days.18 In six studies, duration of antibiotic administration after incision was variable, from 6 hours to 8 days.11–14,16–19 In the last study, antibiotic administration was done only before pacemaker implantation.15 No study has examined the efficacy of a prolonged antibiotic duration versus a short administration. The antibiotics used were penicillin M (flucloxacillin or cloxacillin) in five studies11–14,16,17,19 and cephalosporins in two studies: cefazedon and cefazolin, respectively.15,18 (Table 1).

End Points
In two studies, the end point was a repeat operation for an infective complication,13,17 repeat operation that could be performed either for septicemia, pocket abscess, or erosion of the pulse generator, or electrode through the skin in the study by Mounsey et al.13 Ramsdale et al17 considered the following criteria for the diagnosis of pocket infection: (1) an oral temperature ≥37.5°C at two consecutive measurements after the third postoperative day, (2) acute local inflammation associated or not associated with (3) the presence of pus in the generator pocket. Definition of infection was similar in the studies of Glièca et al18 and Muers et al.19 In the study of Lüninghake et al,15 the criteria have been systematically determined: local signs of inflammation around the pacemaker pocket and infection with proven infectious agent. In the remaining study, the criteria for local infection were presence of purulent substance and/or increased local temperature, redness, pain, and swelling.14

Length of Follow-up
Follow-up duration ranged from 1 month to 4 years; mean follow-up duration is known in only three studies and ranged from 14 to 23 months. The delay to infection is not clearly stated in two studies15,18; it ranged from 5 to 356 days in the other five studies.
Meta-Analysis
The incidence of end point events in control groups ranged from 0% to 12%. Results obtained from the different methods (see “Methods”) were similar; therefore only those obtained from the logarithm of the odds ratio method are presented with the corresponding 95% confidence intervals (CI). The meta-analysis suggested a consistent protective effect of antibiotic pretreatment ($P = .0046$; common odds ratio: 0.256, 95% CI: 0.10 to 0.656, Figure). No statistical heterogeneity was observed from the homo- geneity test that showed a value of $P = .36$ with a multiplicative model. The additive model was rejected because of significant heterogeneity. Overall mortality rate was not significantly different between the two groups (Table 2).

**Discussion**
Antibiotic prophylaxis is currently widely administered at the time of permanent pacemaker implantation. However, there is no convincing evidence of its usefulness. Its expected efficacy can be questioned, and a suitably powered clinical trial is still needed. Recent controversies have emphasized the need for a reappraisal of the current knowledge.28,29 Seven controlled, randomized studies have been identified. Despite their relatively limited quality, they represent the only pertinent data available on antibiotic prophylaxis. In four trials, antibiotic prophylaxis was effective to prevent pocket or lead infection.11–14,18,19 For Mounsey et al,12,13 erosion was the most common form of infection and never occurred after antibiotic prophylaxis. No efficacy could be observed in the three remaining studies because of the very low infection rates in the control and antibiotic groups.15–17 We thus performed a meta-analysis of these trials to better estimate the potential usefulness of antibiotic prophylaxis in this setting.11–19 We found that antibiotic administration at the time of pacemaker insertion significantly decreased the risk of pacemaker or lead infection when data were pooled. Most commonly, wound infection, inflammation, or skin erosion

**TABLE 1. Characteristics of the Studies Included in the Meta-Analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent/Dose/Regimen</th>
<th>Follow-up Mean (Range)</th>
<th>Blind or Open</th>
<th>No. of Patients Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muers et al (1981)</td>
<td>Flucloxacillin 1 g together with benzylpenicillin</td>
<td>23</td>
<td>Open</td>
<td>431</td>
</tr>
<tr>
<td>Jacobson et al11</td>
<td>Cloxacillin 2 g IV 1 hour before and 1 g IV every 6 hours for 2 days and by mouth for 8 days (1 g every 6 hours)</td>
<td>NA</td>
<td>Open</td>
<td>100</td>
</tr>
<tr>
<td>Bluhm et al (1983, 1984)</td>
<td>Cloxacillin 1 g together with amoxicillin 1 g IV 1 hour before and amoxicillin/flucloxacillin (Magnapen) by mouth 500 mg every 6 hours for 48 hours</td>
<td>NA</td>
<td>Open</td>
<td>500</td>
</tr>
<tr>
<td>Ramsdale et al (1984)</td>
<td>Flucloxacillin 2 g IV 1 hour before and flucloxacillin 1 g by mouth every 8 hours for 5 days</td>
<td>14</td>
<td>Blind</td>
<td>106</td>
</tr>
<tr>
<td>Glick et al (1987)</td>
<td>Cloxacillin 1 g together with benzylpenicillin</td>
<td>23</td>
<td>Open</td>
<td>431</td>
</tr>
<tr>
<td>Lüninghake et al15 (1993)</td>
<td>Cloxacillin 1 g IV every day for 5 days</td>
<td>14</td>
<td>Blind</td>
<td>106</td>
</tr>
<tr>
<td>Mounsey et al12,13 (1993, 1994)</td>
<td>Flucloxacillin 1 g IV before, and 500 mg by mouth every 6 hours for 48 hours</td>
<td>19</td>
<td>Open</td>
<td>473</td>
</tr>
</tbody>
</table>

**TABLE 2. Patient Characteristics**

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Age, y</th>
<th>Sex (%)</th>
<th>Antibiotic Group, No. of Patients</th>
<th>Control Group, No. of Patients</th>
<th>Infection (Antibiotic Group) No. of Patients</th>
<th>Infection (Control Group) No. of Patients</th>
<th>Death (Antibiotic Group) No. of Patients</th>
<th>Death (Control Group) No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muers et al</td>
<td>NA</td>
<td>NA</td>
<td>234</td>
<td>197</td>
<td>2</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Jacobson et al</td>
<td>73</td>
<td>51</td>
<td>50</td>
<td>50</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ramsdale et al</td>
<td>72</td>
<td>50</td>
<td>244</td>
<td>256</td>
<td>2</td>
<td>1</td>
<td>19</td>
<td>37</td>
</tr>
<tr>
<td>Bluhm et al</td>
<td>75</td>
<td>54</td>
<td>52</td>
<td>54</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Glick et al</td>
<td>66</td>
<td>66</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lüninghake et al</td>
<td>NA</td>
<td>NA</td>
<td>107</td>
<td>106</td>
<td>0</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mounsey et al</td>
<td>74</td>
<td>55</td>
<td>224</td>
<td>249</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1011</td>
<td>1012</td>
<td>5</td>
<td>37</td>
<td>20</td>
<td>17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NA indicates no data available.
were prevented. Uncertainty still remains as to whether antibiotics prevent septicemia or endocarditis, which can occur years after implantation.\textsuperscript{4,5} However, in a randomized, controlled study comparing mezlocillin-netilmicin combination with mezlocillin alone, De Lalla et al\textsuperscript{30} did not observe any pocket or lead infection in a series of 552 patients during a 29.2-month mean follow-up. These results are in agreement with randomized controlled trials that have shown that prophylactic antibiotics are effective in preventing surgical wound infections.\textsuperscript{31–33}

As in most meta-analyses, these results should be taken with care because antibiotic treatments, end points, and lengths of follow-up were not uniformly designed. However, the question was coherent among studies as to whether antibiotics protected against secondary infections. Because early infections appear to be acquired at the time of surgery\textsuperscript{6} and staphylococci are associated with the majority of pacemaker infections,\textsuperscript{34} antistaphylococcal antibiotics such as flucloxacillin or cloxacillin and cephalosporins were deemed the most appropriate in doses that give high serum and tissue levels during surgery and immediately afterward. In a study on surgical wound infection, Classen et al\textsuperscript{31} have shown that the risk of infection is best reduced when antibiotics were administered in the 2 hours before surgery, a recommendation that was followed in six of the seven studies of this meta-analysis. The difference in infection rates in the control groups between studies is puzzling. Good surgical conditions (operating room, experienced surgeons, careful skin preparation, local antibiotics) are probably a key to a low infection rate,\textsuperscript{17,20} but this factor cannot be clearly demonstrated from these seven trials that were done in experienced centers aware of these prerequisites.

Although pointing to pacemaker-related infection, end points could vary from one trial to the other. In one study the most common mode of presentation of pacemaker infection was erosion of either the pulse generator or the lead(s).\textsuperscript{12,13} Aggarwal et al\textsuperscript{28} have criticized such an end point, arguing that erosion might have been caused by mechanical factors. Although the origin of skin erosion has not been clearly established, it is generally believed that infection is secondary to a mechanical process.\textsuperscript{35,36} The results of Mounsey et al\textsuperscript{12,13} could lead to reevaluation of the responsibility of microorganisms in skin erosion because no patient had such a complication in their antibiotic prophylaxis group. In any case, consequences of the differences in the definition of end points across studies are limited because we used relative measures to assess effects of the treatment. This limitation was tested by the heterogeneity test, which failed to detect a difference in the size of effect between the trials.

In the seven trials analyzed in this study, efficacy of antibiotic prophylaxis was not evaluated long term, particularly after 2 years, and most patients probably have not been followed for >1 year. Results of the present meta-analysis thus apply to infections that occur within this delay. Endocarditis occurring late after implantation is a rare but serious life-threatening complication that often requires complex surgical procedures.\textsuperscript{4,5,37} Whether such a complication can be obviated by antibiotic prophylaxis at the time of implantation is unknown and requires further study. If confirmed, prevention of late infective complication suggested by De Lalla et al\textsuperscript{30} could be per se of high benefit.

**Limitations of Meta-Analyses**

Limitations of meta-analyses are well known.\textsuperscript{7,38,39} Comparative studies that have yielded conflicting results are difficult to evaluate because various factors other than antibiotics can influence sepsis rates, such as different techniques of operation, skin antisepsis, and antibiotic use (topical or systemic).\textsuperscript{28,29} As in any meta-analysis, critical attention must be paid to the quality of the primary trials. In terms of study design, all trials were prospective, controlled, and methodologically adequately randomized. However, only one was double blind. All used widely accepted and reasonable definitions of infection that were in agreement with infection criteria used by Choo et al\textsuperscript{40} in a landmark study. In only one study erosion of part of the pacing system through the skin was defined as an infec-
tion, but positive culture from the probable infected site was shown in all but two patients.\textsuperscript{13} Thus despite different clinical expressions, infection was demonstrated in the majority of end point events, giving validity and consistency to the results of this meta-analysis. Another unavoidable limitation of meta-analysis is that by relying on past information, it may reach conclusions that are correct but not relevant at the time of its publication because of technological or therapeutic progress. In our meta-analysis, despite additional, recent, improved techniques such as surgical and aseptic procedures, smaller pulse generators, and cephalic lead introduction, there was no difference in infection rates between recent and older reports.\textsuperscript{11–19} Last, individual patient data were not available for this meta-analysis because most studies were performed more than 10 years ago, thus precluding any subgroup (high-risk patients) analysis.

Clinical Implications

Despite these limitations, carefully designed meta-analyses can give a temporary overview on the present knowledge while awaiting the results of well-designed clinical trials. Infections after pacemaker insertion remain of major concern and can be life threatening or a source of undue morbidity.\textsuperscript{4,5} Besides, they increase the real cost of pacemaker implantation. Our conclusions are in strong favor of antibiotic prophylaxis in this circumstance, a finding that carries major clinical implications. Although questionable because of the lack of well-designed randomized studies, they support the use of antibiotic prophylaxis and suggest that it can decrease severe complications. Additionally, cost savings can be anticipated; they have been clearly demonstrated when antibiotic prophylaxis was used in similar situations such as closed fracture surgery.\textsuperscript{33}

Conclusions

Comparative studies on the merits of antibiotic prophylaxis have yielded inconclusive results. Results of the present meta-analysis suggest that systemic antibiotic prophylaxis significantly reduces the incidence of serious infective complications after permanent pacemaker implantation. They support the use of prophylactic antibiotics at the time of pacemaker insertion to prevent short-term pocket infection, skin erosion, or septicemia. Efficacy on late septicemia or pacemaker insertion to prevent short-term pocket infection, complications after permanent pacemaker implantation. They significantly reduces the incidence of serious infective complications after permanent pacemaker implantation. Our conclusions are in strong favor of antibiotic prophylaxis while awaiting the results of well-designed clinical trials.

Acknowledgment

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