Risk Factors for Infective Endocarditis

Oral Hygiene and Nondental Exposures

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Background—The risks of infective endocarditis (IE) associated with various conditions and procedures are poorly defined.

Methods and Results—This was a population-based case-control study conducted in 54 Philadelphia, Pa–area hospitals from 1988 to 1990. Community-acquired IE cases unassociated with intravenous drug use were compared with matched community residents. Subjects were interviewed for risk factors. Diagnoses were confirmed by expert review of medical record abstracts with risk factor data removed. Cases were more likely than controls to suffer from prior severe kidney disease (adjusted OR [95% CI]=16.9 [1.5 to 193], P=0.02) and diabetes mellitus (adjusted OR [95% CI]=2.7 [1.4 to 5.2], P=0.004). Cases infected with skin flora had received intravenous fluids more often (adjusted OR [95% CI]=6.7 [1.1 to 41], P=0.04) and had more often had a previous skin infection (adjusted OR [95% CI]=3.5 [0.7 to 17], P=0.11). No association was seen with pulmonary, gastrointestinal, cardiac, or genitourinary procedures or with surgery. Edentulous patients had a lower risk of IE from dental flora than patients who had teeth but did not floss. Daily flossing was associated with a borderline decreased IE risk.

Conclusions—Within the limits of the available sample size, the data showed that IE patients differ from people without IE with regard to certain important risk factors but not regarding recent procedures. (Circulation. 2000;102:2842-2848.)

Key Words: endocarditis ■ heart diseases ■ infection

Infective endocarditis (IE) is serious, albeit uncommon.1 Data supporting use of antibiotic prophylaxis derive primarily from anecdotal reports, studies of bacteremia after procedures, and animal models. However, there are few controlled (and no randomized) human studies of the effectiveness of antibiotic prophylaxis. Despite the absence of proof, expert groups, including the American Heart Association, issue guidelines periodically that specify antibiotic regimens for prophylaxis and its indications.2,3

Many IE risk factors have been postulated, but formal evaluation of these risks is lacking. In this study, we evaluated and quantified those risk factors identified as indications for antibiotic prophylaxis, as well as others found in the published literature. Our results regarding the risks associated with preexisting cardiac conditions and dental treatments have been presented previously4; this article presents results regarding other potential risk factors.

Methods

Selection of Study Subjects
We performed a case-control study in the 8 counties of the Philadelphia (Pa) Metropolitan Area and in New Castle County, Delaware.4 Active surveillance for IE was maintained in 54 hospitals from August 1988 through November 1990.4 Case ascertainment exceeded 90%.4

We obtained physician and patient consent and abstracted patients’ medical records onto structured forms to capture clinical and historical information. Potential cases were classified by 3 experts into 4 categories: definite, probable, and possible endocarditis, or probable noncase.4,5 Consultant judgments agreed well with previously published criteria.5–8

One community control subject was recruited for each case by use of a modification of the Waksberg random-digit-dialing method,9 matched for age (by 5-year strata), sex, and neighborhood (with area code, exchange, and initial digit of the case’s telephone number). Subjects younger than 18 years of age were excluded.

Data Collection
Information was abstracted from medical records and obtained from structured telephone interviews with controls and endocarditis cas-
es.4 All variables studied as risk factors and all subgroup analyses were planned a priori based on risk factors previously postulated in the literature, including socioeconomic factors (SES); history of living with pets or experiencing an animal bite, smoking, and menopausal status; history of kidney disease, diabetes mellitus, rheumatoid arthritis, other autoimmune disease, thyroid disease, alcoholism, cancer, stroke, ischemic heart disease (including myocardial infarction), cardiomyopathy, arrhythmia, heart operation, valvular heart disease, congenital heart disease, rheumatic fever, heart murmur, or other cardiac disease; oral hygienic practices (frequency of tooth brushing; frequency of routine dental care within the last year; use of a toothpick, Water Pik, or gum stimulator; use and frequency of flossing); and complete denture prostheses. Infections included pneumonia, conjunctivitis, and diarrhea, and skin, upper respiratory, urinary tract, and other infections. Procedures included pulmonary, gastrointestinal, cardiac, or genitourinary surgery and intravenous and nasal-oxygen therapies.

Medical records were requested to validate individual diagnoses and procedures, and >92% were received. Agreement between interviews and medical records exceeded 90%.4

Analysis
Organisms were specified by blood culture reports from the laboratories at the participating hospitals. Skin flora included Staphylococcus aureus, coagulase-negative staphylococci, group A and group B streptococci, and Erysipelothrix. Gastrointestinal organisms included Enterococcus, Streptococcus bovis, and Enterobacteriaceae. Dental flora included viridans streptococci, nutritionally variant streptococci, anaerobes, streptococcus unspecified, Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella, and Neisseria species. Cases related to intravenous drug use (IVDU) and nosocomial endocarditis were excluded.

We defined a variable called “cardiac valvular abnormality” as the presence of any of the following self-reported preexisting conditions: mitral valve prolapse, congenital heart disease; history of rheumatic fever with heart involvement, prosthetic heart valves, previous episode of endocarditis, and other valvular heart disease. Unless otherwise specified, analyses focused on infections and procedures experienced in the 3 months before the study date. Frequencies and cross-tabulations were produced that examined case-control status and potential risk factors. Conditional logistic regression, which controlled for the matching variables, was used to determine the independent effects of potential risk factors and possible interactions between them.10

Institutional Review Board approval was obtained at the University of Pennsylvania and at each participating hospital.

Results
As reported,4 416 potential IE cases were identified and recruited. Of the 379 judged to have definite, probable, or possible endocarditis, 287 (76%) were community-acquired non-IVDU; 273 (95%) completed the interview (238 with native valves and 35 with prosthetic valves) and are the focus of these analyses.

Cases and controls were similar with respect to age and sex (matching variables), race, education, occupation, and dental insurance (Table 1). However, cases were more likely to receive Department of Public Welfare, Medicaid, or Veterans Affairs benefits.

Host-Related Risk Factors
Cases were more likely than controls to suffer from self-reported prior severe kidney disease (adjusted OR=16.9 [95% CI 1.5 to 193], P=0.02). On the basis of medical record validation, it was determined that there were 8 cases with chronic renal failure (6 of whom were undergoing dialysis) included within those 15 cases and 1 control. Hemodialysis itself was associated with IE (8 cases [including 2 who did not report chronic renal failure and 3 who were infected with skin flora] and 0 controls; P=0.008). Kidney disease and hemodialysis could not be differentiated analytically to determine which was the independent risk factor because of their collinearity.

Cases were more likely than controls to report physician-diagnosed diabetes mellitus (adjusted OR=2.7 [95% CI 1.4 to 5.2], P=0.004; n=51 cases [20 infected with skin flora] and 29 controls). In cases infected with skin organisms (and their matched controls), the OR associated with diabetes was 3.6 (95% CI 1.4 to 8.9) (P=0.006) after adjustment for cardiac valvular abnormality (numbers too small to accommodate further adjustment).

Cases did not differ from controls in history of living with pets, animal bites, smoking, or menopausal status or in history of rheumatoid arthritis, other autoimmune disease, thyroid disease, alcoholism, cancer (overall or specific type), stroke, ischemic heart disease (including myocardial infarction), cardiomyopathy, arrhythmia, heart operation other than valve replacement, or cardiac disease other than prior history of endocarditis, valvular heart disease, congenital heart disease, rheumatic fever, or heart murmur (data not shown).

Prior Infection as a Risk Factor
An association between endocarditis and skin infections became nonsignificant with multivariate adjustment (Table 2). The elevated OR for skin infection disappeared after the analysis was restricted to subjects with cardiac valvular abnormalities (adjusted OR=0.41 [95% CI 0.04 to 4.66], P=0.5). However, when the analysis was restricted to cases who were infected with skin flora and their matched controls (Table 3), the OR for skin infections increased markedly to 6.0 (95% CI 1.3 to 27) (P=0.019). After adjustment for cardiac valvular abnormality and diabetes (numbers too small to accommodate further adjustment), the OR for cases infected with skin organisms was 3.5 (95% CI 0.7 to 17) (P=0.11). The OR for skin infection did not differ for those with and without cardiac valvular abnormality. A formal test of statistical interaction between skin infection and diabetes was attempted to assess whether the OR for skin infection was different with and without diabetes. The models did not converge, either for the analysis with all cases or for the more meaningful analysis of skin flora cases. Among the 51 cases and 29 controls with diabetes, all 6 who had prior skin infection were cases.

Urinary tract infection was not associated with IE. No cases had urinary tract infection caused by Enterococcus or Enterobacteriaceae.

Initially, pneumonia showed an increase among cases (OR=5.2, 95% CI=2.2 to 12.4; P<0.001), but nearly all pneumonias occurred in the month before the study date and appeared to be an early manifestation of endocarditis. Therefore, this association was considered uninterpretable.

The data were examined for associations within 1 year of the study date, but with the exception of “other infection”
(adjusted OR [95% CI]=6.5 [1.2 to 37], \(P=0.03\) at 1 year versus 1.2 [0.2 to 7.6], \(P=0.8\) at 3 months), none were found.

**Medical Procedures and Therapies**

Nasal-oxygen therapy and barium enema were associated with IE in unadjusted analyses, but only barium enema remained significant after multivariate adjustment (Table 4). Review of the records of cases who received barium enema indicated that in some instances, the procedure was performed as part of the workup for illness finally diagnosed as IE, or for a comorbidity. Accordingly, this cannot be interpreted as indicating a causal relationship between the procedure and IE. We attempted an
analysis for barium enema that was restricted to IE caused by gastrointestinal organisms, but only 3 of 38 cases with such organisms had undergone barium enema.

Administration of intravenous fluids was not associated with IE overall (Table 4), but when the analysis was restricted to cases infected with skin flora and their controls, the unadjusted OR increased markedly, from 1.8 (95% CI 0.9 to 3.8) \( (P=0.11) \) to 5.0 (95% CI 1.1 to 23) \( (P=0.04) \). After adjustment for cardiac valvular abnormality and diabetes (numbers were too small for further adjustment), OR was 6.7 (95% CI 1.1 to 41) \( (P=0.04) \) (Table 3). A test of interaction between cardiac abnormality and intravenous fluids in this subgroup could not be performed owing to small numbers; only 2 of the 12 skin flora cases with prior intravenous therapy had cardiac valve abnormalities.

Tests of interaction between procedures and antibiotic use provided no evidence that antibiotic use modified the risk associated with those procedures (all probability values for interactions were \( >0.19 \)); ie, there was no evidence to support the hypothesis that a risk posed by procedures was masked by the use of antibiotics.

Procedures or therapies performed within 1 year of the study date were not significantly associated with endocarditis.

### Oral Hygiene

No association was found between IE and frequency of routine dental care within the previous year, tooth brushing (use, frequency), or use of a toothpick, Water Pik, or gum stimulator. We found no association between IE and complete denture prostheses for edentulous mouths. Decreased risk was suggested with use of dental floss once a day or more compared with no use (OR=0.64 [95% CI 0.39 to 1.04; \( P=0.07 \)); adjustment for SES and host factors produced little

### Table 3: Skin and Dental Organism-Related Infections, Procedures, and Practices in Previous 3 Months in Cases and Community Controls, Delaware Valley, August 1988 to November 1990

<table>
<thead>
<tr>
<th>Cases with skin flora (( n=93 ))*</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>Unadjusted</th>
<th>Adjusted†</th>
<th>( P )†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin infection</td>
<td>13 14.0</td>
<td>3 3.2</td>
<td>6.00 (1.34–26.8)</td>
<td>3.51 (0.74–16.6)†</td>
<td>0.11†</td>
</tr>
<tr>
<td>Intravenous therapy</td>
<td>12 12.9</td>
<td>4 4.3</td>
<td>5.00 (1.10–22.8)</td>
<td>6.71 (1.09–41.2)†</td>
<td>0.040†</td>
</tr>
<tr>
<td>Cases with dental flora (( n=106 ))*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dentulous vs edentulous‡§</td>
<td>97 91.5</td>
<td>92 86.8</td>
<td>4.00 (1.13–14.2)</td>
<td>7.02 (1.25–39.6)</td>
<td>0.027</td>
</tr>
<tr>
<td>Flossing (among dentulous)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No flossing</td>
<td>51 48.1</td>
<td>48 45.3</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Floss (&lt;1/d)</td>
<td>25 23.6</td>
<td>18 17.0</td>
<td>0.95 (0.68–1.35)</td>
<td>0.60 (0.29–1.26)</td>
<td>0.17</td>
</tr>
<tr>
<td>Floss (\geq1/d)</td>
<td>21 19.8</td>
<td>26 24.5</td>
<td>0.91 (0.46–1.82)</td>
<td>0.36 (0.08–1.59)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*And their matched controls.
†Adjusted for cardiac valvular abnormality and diabetes. Numbers too small for further adjustment.
‡Five (4.7%) cases and 13 (12.3%) controls were edentulous.
§Four cases and 1 control had missing information for the teeth-flossing variable.
|Reference category.
‖Adjusted for SES, cardiac valvular abnormality, severe kidney disease, and diabetes mellitus.
change (OR=0.52 [95% CI 0.26 to 1.07], P=0.07). There was no evidence that this effect differed by presence of cardiac valvular abnormalities (P=0.49 for interaction) and no evidence of a risk in having teeth versus being edentulous (adjusted OR=1.07 [95% CI 0.53 to 2.14], P=0.9).

We repeated the oral hygiene analyses considering only cases infected with dental flora (106 cases and their matched controls) and observed an increased risk associated with having teeth compared with being edentulous: adjusted OR=7.02 (95% CI 1.25 to 39.6), P=0.03 (Table 3). Ninety-three percent of edentulous subjects had complete dental prostheses; edentulousness was associated with decreased risk (adjusted OR=0.11 [95% CI 0.02 to 0.71], P=0.02) compared with having teeth and not flossing.

**Discussion**

This large-scale, population-based case-control study was conducted to identify and quantify risk factors for IE, because the magnitude of these risks should be considered in the development of recommendations for antibiotic prophylaxis of this disease. We previously reported that cases were more likely than controls to suffer from cardiac valvular abnormalities but no more likely to have undergone dental procedures.4 In the present analysis, we found that cases were more likely to be of lower SES, to suffer from prior severe kidney disease or diabetes mellitus, and to have undergone barium enema (probably as a workup for an illness later diagnosed as endocarditis). Cases infected with skin flora were more likely to report having skin infections and to have received intravenous fluids. Cases did not differ from controls in many other ways, including exposure to various medical procedures. Whereas no association was found between IE and other dental care, flossing had a borderline association with decreased IE risk. Cases infected with dental flora were more likely to have teeth and less likely to floss daily.

Measures taken to ensure the validity of the results were considerable. We adjusted for known or suspected potential confounding, recognizing, however, that unknown confounding variables can never be excluded and that associations observed may not represent causal relationships. Particularly problematic were medical conditions such as pneumonia that are frequently early manifestations of IE, or procedures such as barium enema that are part of a diagnostic workup for an illness ultimately diagnosed as IE.

We protected against selection bias, a major concern for case-control studies, by using a population-based design, including random sampling of controls.

Considerable care was taken to ensure validity of IE diagnoses. Recognized authorities classified cases, guided by published criteria but masked to risk factors present before endocarditis onset; “best clinical judgment” was used after consideration of clinical, echocardiographic, and microbiological findings. Duke criteria for endocarditis did not exist when this study began. Key elements of these criteria were
being investigated by our study as risk factors, which precluded their use in our case definitions. However, all but 2 cases met Duke criteria for at least "possible" endocarditis. Details on the validity of study definitions have been published previously.5,6

We excluded cases associated with nosocomial endocarditis and IVDU but included prosthetic cardiac valve cases. Of 35 prosthetic valve cases, only 4 had undergone cardiac valve surgery within 1 year of the IE and therefore could possibly be considered nosocomial when a 1-year standard was used for post–cardiac valve surgery. All 4 cases were considered late endocarditis. Removal of these 4 IE cases does not change the results substantively.

A limitation when our negative results are interpreted is sample size, particularly for subgroup analyses. The study was designed to test hypotheses about the role of dental procedures.4 The sample size was chosen to detect associations with an OR of 2.0 for risk factors with a prevalence between 0.1 and 0.8. The best interpretation of our negative findings is that we did not detect many associations within the limits of our sample size, rather than a definitive claim that such associations are absent. When associations in subgroups were evaluated, the sample size was obviously smaller, which reduced the power substantially (eg, only 17 controls with known cardiac abnormalities were identified). However, because true biological associations in subgroups of cases would be expected to be much more specific, and therefore much larger, than associations with all cases (eg, skin infection as a risk factor for IE caused by skin organisms), the power for detecting these large, specific associations would be increased. Nevertheless, 95% CIs have been provided to ensure accurate interpretation about the precision with which we have measured associations with IE.

Caution is also prudent with regard to our positive findings. Given the large number of variables, some associations may have arisen by chance. However, the associations we found were based on variables defined before study inception as having a plausible biological basis.

IE risk factors can be classified as either host related or procedure related. Cardiac valvular abnormalities are well recognized as host-related risk factors.4,11 Other previously cited host-related risk factors include chronic alcoholism,12,13 meningitis,14,15 and diseases with accompanying disorders of immunity, such as systemic lupus erythematosus, diabetes, and inflammatory bowel disease.14–17 Contradictory reports of these, only diabetes was confirmed as a host-related risk factor, and chronic kidney disease was added, although we could not differentiate whether this was due to the underlying disease or to the procedures used to treat the disease.

Procedure-related risk factors are thought to be linked to endocarditis through induction of bacteremia and seeding of heart valves.5,18–20 and antibiotic prophylaxis is often considered in conjunction with procedures. The evidence associating many procedures with endocarditis is poor (animal data, case reports, case series, and assessments of bacteremia risk). Not until the studies from our group has it been known how many randomly chosen subjects in the general US population would be expected to have had similar dental4 or other procedures.

Our findings of increased risk from skin infection or intravenous therapy among those whose IE was caused by skin organisms are biologically plausible. Because skin infections cannot be anticipated in advance, antibiotic prophylaxis is not feasible. Rather, infections should be treated promptly. As to intravenous therapy, we could not differentiate whether the fluid itself or the intravenous line caused the associated IE, because they were inseparable in this type of data, but the clinical implications are the same for either source. IE associated with intravenous therapy constituted only 13% of the skin flora cases and 4% of cases overall; only 2 of these cases had preexisting cardiac valvular lesions, which makes the use of antibiotic prophylaxis highly problematic. Rather, intravascular devices should be cared for properly.

We found increased risk among dentulous cases infected with dental flora and reduced risk among those who floss daily, which suggests a benefit from oral hygienic practices, especially for those at high risk for IE. More than half of the 97 dentulous cases with dental flora had cardiac valvular abnormalities, 75% flossed irregularly or not at all, and 64% had not received dental treatment within the previous 3 months. These data suggest that patients with cardiac valvular abnormalities should be vigilant about oral hygiene.

In conclusion, IE patients differ from people without IE with regard to certain important risk factors but not concerning recent procedures. Definitive conclusions about the latter are limited by the available sample size, but these data quantify the range of possibilities. Given the infrequency of these procedures in the population and the low incidence of IE, more definitive studies of these procedures may be difficult.

Acknowledgments

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References

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