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EDITORIAL COMMENT

Infective Endocarditis After Invasive Medical and Surgical Procedures*

Martin H. Thornhill, MBBS, BDS, PhD,[a] Mark J. Dayer, MBBS, PhD,[b] Thomas J. Cahill, MBBS, DPhil[c]

The incidence of infective endocarditis, a life-threatening disease characterized by a focus of infection within the heart, is rising (1-3). It is increasingly acquired in the health care setting, with at least 25% of cases occurring after a hospital or outpatient medical exposure (4). In parallel, nosocomial staphylococci have replaced oral streptococci as the most common causative pathogen. Despite advances in management, for example, dedicated infective endocarditis teams, multimodality imaging for identification of complications, and early definitive surgery for selected patients, in-hospital mortality remains approximately 20% (5-7).

Given the challenges of treating infective endocarditis, disease prevention is of fundamental importance. The development of strategies for prophylaxis of infective endocarditis has been frustrated, however, by a lack of high-quality evidence on specific triggers for the disease (8). The necessary precursor to formation of an infected vegetation is bacteremia (9). A range of invasive procedures, for example, dental extraction or colonoscopy, cause a subclinical, transient bacteremia (10,11). From the 1950s onwards, this led to the burgeoning use of antibiotic prophylaxis to reduce the incidence of bacteremia after dental and medical procedures. Indeed, prior to 2007, U.S. and European guidelines recommended antibiotic prophylaxis before a wide range of invasive medical procedures (**Table 1**) (12,13). However, a lack of definitive evidence for a link between these procedures and infective endocarditis, or for efficacy of antibiotic prophylaxis, have led to restriction in its use to high-risk patients undergoing invasive dental procedures in recent U.S. and European guidelines (5,6,14).

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In this issue of the *Journal,* an important study by Janszky et al. (15) reopens the debate on the role of invasive medical procedures as a trigger for infective endocarditis. Using the Swedish National Patient Register, the authors analyzed the frequency of invasive medical or surgical procedures in the 12-week period before a diagnosis of infective endocarditis, in comparison to an equivalent control period 1 year earlier. This "case-crossover" study is an established design for examining the effect of a putative transient risk factor. As each patient acts as their own control, it has the strength of controlling for other potential confounders that are stable over time. The authors identified a total of 7,013 cases of infective endocarditis from 1998 through 2011. Dental procedures were not analyzed, as the majority are not performed in hospital and were therefore not captured in the dataset.

The principal finding was that a long list of invasive medical procedures occurred more frequently in the 12 weeks preceding an infective endocarditis diagnosis than at other time points. Many of these procedures were among those previously recommended for antibiotic prophylaxis, but others were not (12,13). Several procedures that are known to cause bacteremia were associated with significant risk: these included cystoscopy (relative risk [RR]: 4.40; 95% confidence interval [CI]: 1.67 to 11.62), bronchoscopy (RR: 16.00; 95% CI: 2.12 to 120.65), chronic dialysis (RR: 3.64; 95% CI: 2.02 to 6.58), and

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From the [a]Department of Oral and Maxillofacial Medicine, Surgery & Pathology, University of Sheffield School of Clinical Dentistry, Sheffield, United Kingdom; [b]Department of Cardiology, Taunton and Somerset NHS Foundation Trust, Musgrove Park, Taunton, United Kingdom; and the [c]Oxford Heart Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom. Dr. Dayer has received speaker fees from Biotronik. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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TABLE 1 Historical and Current Recommendations for Use of Antibiotic Prophylaxis in Patients Undergoing Invasive Medical and Dental Procedures Alongside Risk Estimates for Post-Procedural Infective Endocarditis

	AHA 1997 (12)	ESC 2004 (13)	Current Recommendations AHA 2007 (14) ESC 2015 (6)	Janszky et al. 2018 (15) Outpatient	Janszky et al. 2018 (15) Inpatient
GI procedures					
Endoscopic esophageal procedures (including TEE)	✓	✓	–	2.60 (1.25–5.39)	3.60 (1.34–9.70)
Upper GI endoscopy with/without biopsy	Optional for HR	–	–	2.50 (1.59–3.94)	3.97 (2.68–5.88)
Lower GI endoscopy with/without biopsy	Optional for HR	–	–	2.89 (1.35–6.17)	2.82 (1.42–5.61)
Endoscopic retrograde cholangiopancreatography	✓	✓	–	2.60 (1.25–5.39)	3.60 (1.34–9.70)
GU procedures					
Endoscopic prostate procedures	✓	✓	–	–	–
Cystoscopy and endoscopic urological procedures	✓	✓	–	1.59 (0.98–2.58)	4.40 (1.67–11.62)
Obstetric and gynecological procedures					
Caesarian section	Optional for HR	If infection present	–	–	–
Vaginal delivery	Optional for HR	If infection present	–	–	–
Abortion/ D&C	If infection present	If infection present	–	1.49 (1.17–1.90)	3.00 (1.81–4.98)
Respiratory procedures					
Bronchoscopic procedures (especially rigid)	✓	✓	–	5.00 (1.10–22.82)	16.00 (2.12–120.65)
ENT procedures					
Tonsillectomy/adenoidectomy	✓	✓	–	1.49 (1.17–1.90)	2.33 (0.60–9.02)
Dental procedures					
Dental extractions	✓	✓	✓	–	–
Dental scaling/gingival procedures	✓	✓	✓	–	–
Endodontic procedures	✓	✓	✓	–	–

Values are relative risk (95% confidence interval). ✓ indicates recommended; – indicates not recommended. This table includes procedures for which antibiotic prophylaxis was previously recommended by the AHA or ESC and those for whom it is currently recommended. The risk of infective endocarditis after other invasive procedures was evaluated by Janszky et al. (15) and is shown in their paper.

AHA = American Heart Association; D&C = dilation and curettage; ENT = ear, nose, and throat; ESC = European Society of Cardiology; GI = gastrointestinal; GU = genitourinary; HR = high-risk patients; TEE = transesophageal echocardiogram.

colonoscopy (RR: 2.82; 95% CI: 1.42 to 5.61). Perhaps more surprisingly, there was also a significant association between relatively "sterile" interventions such as bone marrow puncture (RR: 4.67; 95% CI: 1.34 to 16.24) or transfusion (RR: 6.69; 95% CI: 4.43 to 10.11).

How should these data be interpreted? At face value, the implication is that virtually any inpatient or outpatient invasive procedure may be a trigger for subsequent infective endocarditis. Although this may be correct, some caution is required. First, observational data cannot establish causality. Despite the authors' efforts to avoid this, it is possible that some procedures were performed as part of the investigation of patients who were already experiencing infective endocarditis but prior to an established diagnosis. For example, anemia is a common presenting feature of infective endocarditis, and might lead to a blood transfusion and a bone marrow biopsy before the correct diagnosis is made. Alternatively, investigations may have been performed in patients as part of a work-up for cardiac surgery (e.g., coronary angiography) who went on to develop infective endocarditis as a post-operative complication. Invasive procedures could also be a surrogate marker of any acute illness, which might increase susceptibility to infective endocarditis but not be directly causative; patient-level data might refute these criticisms. Unfortunately, the study did not have access to information on the microbiology of cases: identifying flora from the oral cavity, gastrointestinal tract, skin, and so on after procedures associated with these sites would have provided further support for their role in causing infective endocarditis.

Despite these criticisms, this work is by far the largest study to address the link between invasive medical procedures and subsequent infective endocarditis. It is the highest-quality data available to support an association between invasive medical procedures and infective endocarditis, and it mirrors the findings of a recent case-crossover study suggesting a possible increase in risk after invasive dental procedures (16). Importantly, it will direct future research efforts toward clarifying precisely

which procedures are associated with highest risk, in an unbiased manner, and the mechanisms of health care-acquired infective endocarditis. Finally, although this is not a study of the role of antibiotic prophylaxis, the authors were able to estimate a number needed to prevent 1 case of endocarditis of 476, if prophylaxis was 100% effective. If the breadth of procedures associated with increased risk is confirmed by further studies, this will raise important questions for guideline committees about the benefits of recommending antibiotic prophylaxis prior to some of these procedures. However, broadening the scope of antibiotic prophylaxis to include all of these procedures is unlikely to be the solution. At least for those procedures where sterility should be easy to achieve and maintain, the solution is more likely to lay with improved sterile technique, infection control procedures and identifying systematic approaches for reducing health care-associated bacteremia rather than necessarily advocating antibiotic prophylaxis.

ADDRESS FOR CORRESPONDENCE: Dr. Martin H. Thornhill, Department of Oral and Maxillofacial Medicine, Surgery & Pathology, University of Sheffield School of Clinical Dentistry, Claremont Crescent, Sheffield S10 2TA, United Kingdom. E-mail: m.thornhill@sheffield.ac.uk. Twitter: @ShefDentistry.

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