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The evidence base for the efficacy of antibiotic prophylaxis in dental practice

Peter B. Lockhart, DDS; Bridget Loven, MLIS; Michael T. Brennan, DDS, MHS; Philip C. Fox, DDS

Approximately one-half of the 2 million cases of nosocomial infection that occur each year in the United States are associated with indwelling devices, and, in most cases, the cost of treating a device-related infection far exceeds the cost of initial placement.¹ These infections can result in prolonged antibiotic treatment, surgical removal or replacement of a device, disfigurement, disability, psychological trauma and death. Concern regarding the risk of cardiac infection resulting from bacteremia was raised as early as 1923, and in 1944 a relationship between bacteremia resulting from dental procedures and rheumatic heart disease was proposed.^{2,3} These observations led to formal recommendations by the American Heart Association (AHA) in 1955 for the use of prophylactic antibiotics before dental and other invasive medical procedures to prevent infective endocarditis (IE), and this has been a standard of care for more than 50 years in the United States.

There is evidence showing a benefit from primary antibiotic prophylaxis in the surgery literature—that is, the use of antibiotics at the time of device placement.^{4,5} However, there is increasing awareness of the lack of evidence supporting the practice of secondary prophylaxis—

ABSTRACT



Introduction. People with various medical conditions and devices are suggested candidates for receiving antibiotic prophylaxis before undergoing dental procedures. This practice is controversial, however, owing to the lack of proof of efficacy. The authors conducted a qualitative, systematic review to determine the level of evidence for this practice and whether antibiotic prophylaxis prevents distant site infections in these patients.

Methods. The authors selected eight groups of patients with specific medical conditions and devices who often are given antibiotic prophylaxis before undergoing invasive dental procedures. The conditions and devices were cardiac-native heart valve disease, prosthetic heart valves and pacemakers; hip, knee and shoulder prosthetic joints; renal dialysis shunts; cerebrospinal fluid shunts; vascular grafts; immunosuppression secondary to cancer and cancer chemotherapy; systemic lupus erythematosus; and insulin-dependent (type 1) diabetes mellitus. The authors thoroughly searched the literature for the years 1966 through 2005 for references indicating some level of support for this practice and graded each publication on the basis of level of evidence.

Results. The authors found formal recommendations in favor of antibiotic prophylaxis for only three of the eight medical conditions: native heart disease, prosthetic heart valves and prosthetic joints. They found no prospective randomized clinical trials and only one clinical study of antibiotic prophylaxis. Only one systematic review and two case series provided weak, if any, support for antibiotic prophylaxis in patients with cardiac conditions. The authors found little or no evidence to support this practice or to demonstrate that it prevents distant site infections for any of these eight groups of patients.

Conclusions. No definitive, scientific basis exists for the use of prophylactic antibiotics before dental procedures for these eight groups of patients.

Key Words. Antibiotic prophylaxis; bacteremia; amoxicillin; bloodborne pathogens; clinical protocols; dental care for chronically ill patients; endocarditis; bacterial endocarditis; heart murmur; heart valve diseases.

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Dr. Lockhart is the chairman, Department of Oral Medicine, Carolinas Medical Center, P.O. Box 32861, Charlotte, N.C. 28232-2861, e-mail "Peter.Lockhart@carolinashealthcare.org".

Ms. Loven is a biomedical information specialist, Regional Education & Outreach/Charlotte Area Health Education Center (AHEC), AHEC Library and Information Resource Center, Carolinas Medical Center, Charlotte, N.C.

Dr. Brennan is the oral medicine residency director, Department of Oral Medicine, Carolinas Medical Center, Charlotte, N.C.

Dr. Fox is the director of clinical research, Department of Oral Medicine, Carolinas Medical Center, Charlotte, N.C.

an effort to reduce a procedure-related bacteremia that could result in a distant site infection such as IE. Nevertheless, the frequency of infection with indwelling medical devices in general, and the devastating impact of an infection in a cardiac valve, prosthetic joint or vascular graft, are a driving force behind the use of prophylactic antibiotics.

Since the 1950s, antibiotic prophylaxis increasingly has been recommended for a variety of noncardiac medical conditions and devices as well (Box 1).⁶⁻¹⁰ A wide diversity

of opinion exists concerning patients who should receive antibiotic prophylaxis before undergoing dental procedures, and this leads to the perceived need on the part of dentists to contact physicians for advice on management. Our research group conducted a survey of infectious diseases (ID) specialists on this issue and found wide differences of opinion.¹¹ In response to a variety of clinical scenarios, a range of 14 and 91 percent responded they “usually” or “always” would recommend use of prophylactic antibiotics before dental procedures for some of these groups of patients. Interestingly, 24 percent volunteered that they did so for medicolegal rather than scientific reasons. Anecdotal evidence suggests that many—if not most—nephrologists, transplant surgeons, cardiologists and other specialists want their patients to receive antibiotic prophylaxis for all invasive dental procedures to prevent distant site infection of organs, tissues or prosthetic materials. Given the controversy and the problems associated with this practice, we sought to review the available evidence regarding the use of prophylactic antibiotics in dental practice.

METHODS

We selected eight medical conditions and devices for this systematic review based on their prevalence in dental practice, the frequency of mention in the dental literature and the results of our survey of ID specialists.¹¹⁻¹⁸ The eight conditions and devices are

BOX 1

Proposed medical conditions and devices associated with risk of infection resulting from dental procedures.

CARDIAC AND PULMONARY CONDITIONS/DEVICES

Native heart valve disease
Prosthetic heart valve
Pacemaker
Stents
Implantable defibrillator
Pulmonary arteriovenous malformation⁹

PROSTHETIC JOINTS

SHUNTS

Cerebrospinal fluid
Renal dialysis (hemo- and peritoneal)

SOLID ORGAN TRANSPLANTS

STEM CELL AND BONE MARROW TRANSPLANTS

VASCULAR GRAFTS AND SHUNTS^{12,3}

IMMUNOSUPPRESSION

Drugs (such as cancer chemotherapy, high-dose steroids)
Disease (such as cancer, HIV)
Insulin-dependent (type 1) diabetes mellitus

ASPLENISM

SYSTEMIC LUPUS ERYTHEMATOSUS

IMPLANTS (NONDENTAL)^{7,8}

HEAD AND NECK RADIOTHERAPY

INDWELLING CATHETERS

DEBILITATION

AUTOIMMUNE DISEASES (SUCH AS ARTHRITIS)

SICKLE CELL ANEMIA¹⁰

- cardiac: native heart valve disease, prosthetic heart valves and pacemakers;
- hip, knee and shoulder prosthetic joints;
- renal dialysis shunts;
- cerebrospinal fluid (CSF) shunts;
- vascular grafts;
- immunosuppression secondary to cancer and cancer chemotherapy;
- systemic lupus erythematosus (SLE);
- insulin-dependent (type 1) diabetes mellitus.

Given the lack of clinical trials or original studies for comparison, a quantitative systematic review (that is, a meta-analysis conducted with statistical methods) cannot be done to determine the strength of the evidence and to assess recommendations based on that evidence. We therefore chose the strategy of using a systematic review, in which the literature is summarized but not statistically combined.¹⁹

In November 2003, we conducted a preliminary MEDLINE search for articles published between

ABBREVIATION KEY. AAOS: American Association of Orthopaedic Surgeons. ACC: American College of Cardiology. ADA: American Dental Association. AHA: American Heart Association. AV: Arteriovenous. CSF: Cerebrospinal fluid. ID: Infectious diseases. IE: Infective endocarditis. GI: Gastrointestinal. PD: Peritoneal dialysis. SLE: Systemic lupus erythematosus. TEE: Transesophageal echocardiography. VC: Ventriculocardiac. VGS: Viridans group streptococci. VP: Ventriculoperitoneal.

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1996 and 2003 on the topic of dental antimicrobial prophylaxis. In November 2005, we conducted an extensive MEDLINE search of the literature for all journal articles from 1966 through 2005 relating to dental antimicrobial prophylaxis. We eliminated letters to the editor and case reports. From the nearly 4,000 citations retrieved, we selected only those that dealt with one or more of the eight medical conditions and devices listed above. (**Editor's note:** Readers interested in additional information regarding the search strategies used in the authors' literature review may access it via the Supplemental Data link in the online version of the article on the JADA Web site [<http://jada.ada.org>].)

In 2004, we chose the collection of a major health sciences library serving both a dental school and a medical school, as well as an affiliated academic health care system, in which to look for medical and dental textbooks mentioning dental antimicrobial prophylaxis. We searched for references to dental antimicrobial prophylaxis in major textbooks in the fields of cardiology, thoracic surgery, orthopedic surgery, nephrology, neurology and neurosurgery, vascular surgery, oncology, immunology, rheumatology, hematology, endocrinology, ID, maxillofacial surgery and dentistry published between 1998 and 2004. Finally, we searched for American and international professional, government research and voluntary health care organization Web sites pertaining to these eight medical conditions and devices (Box 2). We focused our search on refereed journal articles and textbook chapters, but used all references with some level of support related to the practice of antibiotic prophylaxis. Two of the authors (P.B.L. and M.T.B.) reviewed all articles identified by our search criteria and assigned these source documents to one of seven categories:

- prospective clinical studies or systematic literature reviews;
- observational studies, case reports and series, or surveys;
- expert opinions or narrative literature reviews;
- cost or decision utility analyses;
- textbook chapters;
- professional association publications, official recommendations, and scientific and advisory statements.

The decision as to the category into which a given reference fell was straightforward for virtually all of these references. After reviewing the literature for each medical condition and device, the

same two investigators graded the strength of the evidence for the efficacy of antibiotic prophylaxis in preventing distant site infections. The basis for their grades was classification of recommendations and levels of evidence from the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines Writing Committee (Box 3, page 462).²⁰

RESULTS

The two authors categorized all references with some level of support for antibiotic prophylaxis into one of the seven types of literature, and they had no disagreement concerning these categorizations (Table, page 463). What follows is a review of the literature and the level of evidence supporting the use of antibiotic prophylaxis for each of these eight medical conditions and devices.

Cardiac: native heart valve disease and prosthetic heart valves. *Background and demographics.* Formal recommendations from the AHA concerning antibiotic prophylaxis for patients who have cardiac conditions and are undergoing invasive procedures go back more than 50 years, and virtually all professional association guidelines, textbooks and journal articles quote these recommendations.²¹⁻²⁴ Dental procedures always have been the central focus of the issue of antibiotic prophylaxis, but there never has been a prospective clinical trial for efficacy. These recommendations came into being and have been sustained for several reasons:

- the focal infection theory, which was particularly popular in North America in the first one-third of the 20th century²⁵;
- the almost universal mortality resulting from IE in the preantibiotic era;
- early animal studies attempting to replicate IE in humans;
- the high incidence of viridans group streptococci (VGS) as a cause of IE and the high frequency of VGS bacteremia after dental office procedures;
- hundreds of poorly documented case reports implicating dental procedures, none of which demonstrate a causal relationship;
- an exaggerated temporal relationship between an invasive procedure and the onset of symptoms of IE.

It is estimated that about 85,000 mechanical heart valves are placed annually in the United States and that about 3,400 (4 percent) will become infected, at an average cost of about

BOX 2

Web sites searched for recommendations regarding antibiotic prophylaxis.

CARDIAC CONDITIONS AND DEVICES

American College of Cardiology:

"www.acc.org"

American Heart Association (AHA):

"www.americanheart.org"

European Society of Cardiology:

"www.esacardio.org"

National Heart, Lung, and Blood Institute:

"www.nhlbi.nih.gov"

World Heart Federation:

"www.worldheart.org"

PROSTHETIC JOINTS

American Academy of Orthopaedic Surgeons:

"www.aaos.org"

RENAL DIALYSIS SHUNTS

American Nephrology Nurses Association:

"www.annanurse.org"

American Society of Nephrology:

"www.asn-online.org"

American Society of Pediatric Nephrology:

"www.aspneph.com"

Association for Professionals in Infection Control and Epidemiology:

"www.apic.org"

Hypertension, Dialysis and Clinical Nephrology:

"www.hdcn.com"

International Society of Nephrology:

"www.nature.com/isn/index.html"

International Society for Peritoneal Dialysis:

"www.ispd.org"

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative:

"www.kidney.org/professionals/kdoqi/index.cfm"

National Institute of Diabetes and Digestive and Kidney Diseases:

"www2.niddk.nih.gov"

National Kidney Foundation:

"www.kidney.org"

Renal Physicians Association:

"www.renalmd.org"

CEREBROSPINAL FLUID SHUNTS

American Academy of Neurology:

"www.aan.com/professionals/"

American Association of Neurological Surgeons:

"www.aans.org"

Hydrocephalus Association:

"www.hydroassoc.org"

National Institute of Neurological Disorders and Stroke:

"www.ninds.nih.gov"

VASCULAR GRAFTS

VascularWeb (comprising the Society for Vascular Surgery, Society for Clinical Vascular Surgery, Peripheral Vascular Surgery Society and others):

"www.vascularweb.org"

IMMUNOSUPPRESSION SECONDARY TO CANCER AND CANCER CHEMOTHERAPY

American Cancer Society:

"www.cancer.org"

American Society of Clinical Oncology:

"www.asco.org"

National Cancer Institute:

"www.cancer.gov"

National Heart, Lung and Blood Institute:

"www.nhlbi.nih.gov/index.htm"

SYSTEMIC LUPUS ERYTHEMATOSUS

American College of Rheumatology:

"www.rheumatology.org"

Lupus Foundation of America:

"www.lupus.org"

National Institute of Arthritis and Musculoskeletal and Skin Diseases:

"www.niams.nih.gov"

INSULIN-DEPENDENT DIABETES MELLITUS

American Association of Clinical Endocrinologists:

"www.aace.com"

American Diabetes Association:

"www.diabetes.org"

National Diabetes Information Clearinghouse, a service of the National Institute of Diabetes and Digestive and Kidney Diseases:

"diabetes.niddk.nih.gov"

GENERAL

National Guideline Clearinghouse:

"www.guideline.gov"

American Dental Association:

"www.ada.org"

National Institute of Dental and Craniofacial Research:

"www.nidcr.nih.gov"

Centers for Disease Control and Prevention:

"www.cdc.gov"

\$50,000 per occurrence.¹ Although the prognosis for patients with IE has improved dramatically in the antibiotic era, it is associated with a high morbidity and mortality for some cardiac patients.²⁶

Evidence for prophylaxis. The early focus of journal articles and textbook chapters on dental office procedures as a cause of IE continues today, both with and without an emphasis on dental disease and poor oral hygiene.²⁷⁻³⁰ There have been conflicting results from efforts to assess the evidence that dental extractions can cause IE, that

prophylaxis is cost-effective³¹ and that antibiotics are effective in preventing IE. Epidemiologic and cost-benefit analysis evidence is mounting to suggest that this practice should be eliminated, except perhaps for a select group of patients with cardiac conditions who are felt to be at greatest risk of experiencing a bad outcome from IE.³² Some retrospective studies suggest that prophylaxis provides some benefit, but they are of small size, often with inadequate clinical data and methodology.³³ There were no randomized studies and only one case-controlled study, which

BOX 3

Classification of recommendations and levels of evidence.*

CLASSIFICATION OF RECOMMENDATIONS

Class I	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness or efficacy of a procedure or treatment
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
IIb	Usefulness/efficacy is less well-established by evidence/opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful or effective, and in some cases may be harmful

LEVEL OF EVIDENCE

A	Data derived from multiple randomized clinical trials
B	Data derived from a single randomized trial or from nonrandomized studies
C	Only consensus opinion of experts, case studies or standard of care

* Adapted from the American College of Cardiology Foundation and American Heart Association Task Force on Practice Guidelines.²⁰

included patients who had had a dental procedure as long as 180 days before the onset of symptoms of IE.³⁴ These studies, including a Cochrane systematic review of 980 references, suggest that antibiotic prophylaxis, even if clinically effective, would prevent only a small minority of cases of IE.^{30,34-36}

Although formal guidelines exist, so do controversy and confusion concerning this practice. For example, some dentists use antibiotic prophylaxis for all patients with a heart murmur of any type.³⁷ However, though considered to be at higher risk, many patients with prosthetic heart valves do not receive prophylactic antibiotics before undergoing highly invasive dental procedures.³⁷⁻⁴³ The confusion on this issue is reflected in cardiology textbooks, which give a variety of opinions—some of which suggest a greater threat from poor oral hygiene than from dental procedures.⁴³⁻⁵⁵ Some references suggest that all patients be evaluated for dental disease before undergoing elective valve replacement,⁵⁶ though data on cost-effectiveness are lacking, owing in part to the rarity of endocarditis.

Classification of recommendation and level of evidence. Native heart valve disease—Class III; Level C. Prosthetic heart valve (that is, higher risk group as classified by the AHA)—Class IIb; Level C.

Cardiac pacemakers. *Background and demographics.* Cardiac pacemakers were first implanted in patients in the late 1950s, and about 500,000 people in the United States and more than 3.2 million people worldwide have these devices.⁵⁷ About 300,000 pacemaker-defibrillators are placed in the United States

each year as well. Upward of 20 percent of patients develop pacemaker infections, with a cost of about \$35,000 per occurrence.¹ These infections tend to occur soon after placement, primarily in the pacemaker generator pocket. However, they must be differentiated from pacemaker endocarditis, which involves the pacemaker tip, endocardial

tissue or valve adjacent to the electrode and which occurs in 0.13 to 19.9 percent of patients.⁵⁸

Evidence for prophylaxis. Retrospective reviews of pacemaker endocarditis indicate that upward of 92 percent of the pathogens are *Staphylococcus aureus* and *Staphylococcus epidermidis*, and the remainder are gram-negative bacilli.^{58,59} These microbiological data strongly suggest that receipt of antibiotic prophylaxis before dental procedures is of little or no value, given the extremely low volume of staphylococci in the oral cavity.⁶⁰⁻⁶² The AHA recommends against antibiotic prophylaxis, even in the presence of immunosuppression,^{21,24} and the majority of the literature sources agree with the AHA recommendations for both patients with cardiac pacemakers and those with internal cardiac defibrillators.^{56,63} However, some case reports and textbooks continue to promote the need for antibiotic prophylaxis in certain situations,^{64,65} while others reject the AHA recommendations and advocate for antibiotic prophylaxis for all transvenous implants (Table).⁶⁶⁻⁶⁹ Therefore, this practice continues, as evidenced by surveys suggesting that upward of 8 percent of dentists in the United Kingdom and 17 percent of ID consultants in the United States favor prophylaxis for a variety of dental procedures.^{11,70-73}

Classification of recommendation and level of evidence. Class III; Level C.

Orthopedic prosthetic joints. *Background and demographics.* It is estimated that 600,000 joint prostheses are placed in the United States each year and that about 12,000 (2 percent) of those become infected, resulting in a cost of about \$30,000 per occurrence.^{1,74} Prosthetic joints are infected in one of four ways: by contamination at

TABLE

Literature supporting antibiotic prophylaxis for dental procedures.

MEDICAL DEVICE OR CONDITION	REFERENCES, BY TYPE OF LITERATURE					
	Prospective Clinical Study or Systematic Literature Review	Observational Study, Case Report and Series, or Survey	Expert Opinion or Narrative Literature Review	Cost or Decision Utility Analysis	Textbook Chapter	Professional Association Publication, Official Recommendation, Scientific and Advisory Statement
Cardiac Conditions and Devices Native heart valve disease, prosthetic heart valve Cardiac pacemaker	35	11,27,33,34	14,89	—	28,30,44,56,123,188,198	21-23,115
		11,57,58,64	15	—	56,65-69,123	21,24,115
Prosthetic Joints: Hip, Knee, Shoulder	—	11,79,83,92,93,95-98,100,110,121,122,281	14,74,78,80,86,111-113,127,282	87,105,108	4,56,106,116,117,123-125,126,138,244	77,81,114,115,118,119
Dialysis Renal Dialysis Catheters and Prosthetic Shunts Peritoneal Dialysis	—	11	12-14,18,107,134,135,140,146,187,192	—	145,159,162	16,17,24,115
		145-147			66,131,136-139,189,218	24
Shunts Cerebrospinal fluid Ventriculoperitoneal Ventriculocardiac	158	11,163	18 13,135 14	—	159,162,164	11,16,24,163 24
		11,174	15,18,177,178	—	56,167,175,176	24,115
Vascular Grafts: Abdominal and Thoracic Aorta; Iliac, Femoral and Popliteal Arteries	—	11,174	15,18,177,178	—	56,167,175,176	24,115
Immunosuppression Secondary to Cancer and Cancer Chemotherapy	—	11,186,194	13,14,18,177,187,192	—	66,136,138,139,188-190,195,196	24,115,118,185,193
Systemic Lupus Erythematosus	—	11,206,208		—	66,198,200,209-212	—
Insulin-Dependent Diabetes Mellitus	—	11	14,18,57,214,215	—	66,123,138,189,190,217,218	118,216

the time of surgery, by spread from an adjacent area, hematogenously or by reactivation of an infection from a previous joint infection. With the exception of cardiac conditions, more has been written about joint replacement than any other proposed indication for prophylaxis, dating back at least to the early 1970s.

Evidence for prophylaxis. Early recommendations called for antibiotic coverage of all patients with prosthetic joints before dental procedures. Some of the emphasis came from studies in which a huge (> 1 × 10⁹) inoculum of *S. aureus* was

injected into rabbits, and from case reports that claimed a relationship, often in spite of a late onset of infection (more than six months after the procedure).⁷⁵ Surveys suggest that the majority of orthopedic surgeons favor prophylaxis, in spite of the lack of scientific evidence, though all of these reports precede the formal association recommendations in 1997.^{21,76-80} Other surveys show a wide diversity of opinion among physicians and dentists.^{11,70,81-83} Some authors conclude that the cost to the health care system, the risk of a life-threatening reaction to antibiotics and other fac-

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tors far outweigh the risk of joint infection.⁸⁴⁻⁹⁰

It has been proposed that oral bacteria cause between 6 and 13 percent of cases of prosthetic joint infections, but closer analysis of the many reported cases suggests that joint infections rarely arise from an oral site. We could not find a well-documented case of a joint infection associated with a dental office procedure, but case reports, case series and retrospective studies continue to appear reporting joint infections arising from oral flora.^{74,91-99} Some case reports attempt to link joint infections and dental procedures on the basis of the bacterial family (for example, *Streptococcus viridans*) but not a specific species, and the authors focus on the mouth when there are other likely sources.^{96,97,100} It is well-established that the majority of late joint infections are caused by *S. epidermidis* or *S. aureus*,^{91,101,102} which make up only approximately 0.005 percent of the oral flora.^{60,61} Overall, aerobic gram-positive cocci accounted for 74 percent of joint infections, gram-negative bacilli for 14 percent and anaerobes for 8 percent—few of which suggest an oral source.¹⁰² In addition, most of these case reports lack the temporal relationship of the accepted time frame between a dental procedure and the onset of symptoms of a joint infection.

In a series of controlled epidemiologic studies of a cohort of 39,000 implants, the overall incidence of large-joint implant infections due to viridans streptococci was 0.06 cases per 1,000 joint-years.¹⁰³ The authors point out that this low incidence is similar to the rate of viridans group endocarditis in the general population, or in patients with mitral valve prolapse and no heart murmur, for whom the AHA does not recommend antibiotics.¹⁰⁴

Some groups conclude that morbidity, mortality and cost calculations justify prophylaxis for dental procedures, at least in the first year after placement, for “high-risk” patients or both.^{15,92,105-107} The methodology for these studies requires several assumptions, including risk projections for incidence of joint infection resulting from a dental procedure, which the authors point out might not be valid and might result in contradictory findings.^{87,108} Some articles and textbook chapters conclude that prophylaxis is not justifiable except for high-risk patients, patients with a systemic condition that would predispose to joint infection and the presence of “dental sepsis.”^{94,5,74,88,108-113}

In 1997, the American Dental Association

(ADA) and American Association of Orthopaedic Surgeons (AAOS) agreed on a formal advisory statement that attempted to define specific orthopedic populations and specific dental procedures that put patients at risk, in an effort to reduce the unnecessary exposure of patients to antibiotics.⁷⁷ This report recommended that patients within two years of joint replacement and those with malignancy, insulin-dependent diabetes, previous joint infection, malnourishment, hemophilia, rheumatoid arthritis, SLE, or disease or drug-induced immunosuppression be considered for prophylaxis. Borrowing from the AHA recommendations, the organizations also made an attempt to define the dental procedures that put patients at risk. These recommendations were reviewed in 2003, and an attempt was made to clarify the patients at risk of developing infections associated with dental procedures.¹¹⁴

Most book chapters since 1997 reiterate or emphasize the ADA/AAOS recommendations,^{56,115-118} but some point out the lack of scientific evidence for prophylaxis and the risk of a life-threatening reaction to antibiotics.^{85,106,119,120} Furthermore, case reports exist of infections arising in hip prostheses after dental procedures despite antibiotic prophylaxis.^{121,122} Other authors appear to ignore these guidelines and recommend antibiotic prophylaxis for all patients with joint replacements, often relying on opinion papers.¹²³⁻¹²⁷ Therefore, the issue of the efficacy of prophylaxis has never been resolved satisfactorily, and the potential for dental procedures to seed prosthetic joints continues to create controversy.⁵⁶

Given the lack of evidence that dental procedures cause infections in prosthetic joints, the rationale for antibiotic coverage often stems from the frequency and cost of these infections (as instigated by other causes) and their devastating impact on the patient.⁴ It is clear that the frequent occurrence of bacteremia arising from common daily activities (such as toothbrushing) far exceeds that of dental procedures, and this strongly suggests that even if the mouth does serve as a rare source of the bacteria infecting a joint, the likelihood of its arising during a dental procedure is remote.

Classification of recommendation and level of evidence. Class III; Level C.

Renal dialysis shunts. *Background and demographics.* Of the more than 375,000 people with end-stage renal disease in the United States, more than 275,000 are receiving dialysis for

chronic renal failure.¹²⁸ Vascular access sites include grafts of synthetic materials (such as silastic versus polytetrafluoroethylene), native (autogenous) arteriovenous (AV) fistulas, or cuffed or noncuffed catheters.¹²⁹ Grafts usually are placed below the skin in the antecubital fossa and are punctured two to three times per week to gain access for dialysis. Repetitive needle punctures can result in shunt infection from skin flora, predominantly *S. aureus* (53 percent) and coagulase-negative staphylococci (20 percent).²⁴ In one study, gram-positive bacteria were found in 52 to 62 percent of patients with infected permanent catheters, with the remainder split between gram-negative and polymicrobial bacteria.¹²⁹ Dialysis-related catheter infections are an important cause of morbidity and mortality and of hospital admissions, often despite aggressive antibiotic therapy.¹³⁰⁻¹³² Upward of 22 percent of AV shunts become infected (3.2 per 100 patient-months), resulting in the need for systemic antibiotics and possible removal of the shunt.^{129,131} IE is a devastating complication of vascular access infections, 60 percent of which are caused by *S. aureus*. Mortality can be as high as 30 percent, and 25 percent of cases require heart valve replacement.¹³³

Evidence for prophylaxis. The support for antibiotic prophylaxis for renal dialysis shunts comes largely from textbook chapters, professional association publications and the literature in the form of opinion-based journal articles (Table). Some authors in the dental literature have supported antibiotic prophylaxis on the basis of a proposed risk of shunt infection,^{18,66,134-140} and others have done so out of a greater concern for prevention of IE, given the higher incidence of native heart valve disease in this patient population.^{12,66,141,142} There are AHA guidelines for nonvalvular cardiovascular devices, but they do not mention the need for antibiotic prophylaxis for hemodialysis shunts.²⁴

Peritoneal dialysis (PD) catheters are also at risk of infection (1.1-1.3 episodes/patient/year); the leading complication is peritonitis, which can result in hospitalization and death.^{143,144} However, PD catheters are considered to be at much lower risk of infection associated with invasive dental procedures than are hemodialysis shunts.¹⁴⁵⁻¹⁴⁷ Most publications concerning antibiotic prophylaxis either do not mention PD catheters or a risk resulting from dental procedures or they recommend against prophylaxis.¹⁴ However, some

authors recommend prophylaxis for these patients on the basis of a few case reports of peritonitis, in spite of the fact that the bacteria cultured from these infections have little or no specificity for the oral cavity in the vast majority of cases (such as *S. aureus* and *S. epidermidis*, pseudomonas and other gastrointestinal [GI] species) and that the dental condition and/or procedure was not well-documented.^{134,145-149}

Guidelines for PD were first published in 1983 and were updated in 2005 with a stronger emphasis on prevention of infection.¹⁴⁴ These guidelines suggest that “invasive procedures may infrequently cause peritonitis in PD patients,” and suggest that “a single dose of amoxicillin (2 g) 2 hours before extensive dental procedures,” but point out that “there are no studies to support this approach.” Therefore, owing to the lack of scientific evidence, the literature continues to show a wide range of opinion on prophylaxis.

Classification of recommendation and level of evidence. Class III; Level C.

CSF shunts. Background and demographics. It is estimated that more than 45,000 prosthetic ventriculocardiac (VC) and ventriculoperitoneal (VP) CSF shunts are placed in the United States each year.^{1,150} CSF shunt infections occur in 5 to 40 percent of patients at a cost of about \$50,000 per occurrence, with a mortality upward of 40 percent.¹ These patients are at increased risk of experiencing problems such as intellectual and neurological impairment.^{1,56,151-153} Approximately 70 percent of shunt infections appear within two months of placement, and 86 percent appear within six months.^{151,154} Most infections occur in the first four weeks after placement and are thought to occur at the time of surgery, given that about 40 percent involve *S. epidermidis* or *S. aureus*.^{155,156} Gram-negative bacteria are the next most frequent pathogens, accounting for 6 to 25 percent of cases, and are associated with a higher mortality.^{154,157} Other sources are hematogenous seeding, retrograde infection from the distal end of the shunt and wound infection.

Evidence for prophylaxis. The only clinical study we could find for any of the eight conditions in this systematic review was a prospective study of 14 children with VP shunts who had dental cleaning procedures without antibiotic prophylaxis, none of whom developed infection.¹⁵⁸ Given its nonrandomized nature and small size, this study provides no support for or rationale against prophylaxis. The argument for antibiotic prophylaxis

laxis before dental procedures is based on the incidence of shunt infections in general and their potentially devastating consequences, rather than on scientific data regarding efficacy.^{11,159} Most textbook chapters either point out the lack of data to support prophylaxis¹⁶⁰ or do not address the issue at all, since a hematogenous seeding of the central nervous system is rare, and the microbial cultures and timing of these infections strongly suggest a nonoral source.^{56,151,161} Other textbooks, surveys, pilot studies and oral health care guidelines point out the lack of scientific data but nevertheless suggest that antibiotic prophylaxis may be of benefit for invasive dental procedures (Table).^{135,158,162-164} There are AHA guidelines for nonvalvular cardiovascular devices, but they do not recommend antibiotic prophylaxis for VC shunts.²⁴

Classification of recommendation and level of evidence. Class III; Level C.

Vascular grafts. *Background and demographics.* It is estimated that more than 450,000 vascular grafts are placed in the United States each year, about 16,000 of which (average, 4 percent; range, 0.4-8 percent) become infected, resulting in a cost of about \$40,000 per occurrence.^{1,165,166} Infection of a vascular graft is a potentially disastrous situation, especially when it involves the suture lines, and it usually necessitates removal of the graft.^{167,168} These infections are difficult to manage and can result in loss of limb or organ dysfunction, and they carry a mortality rate of 90 percent for aortic grafts.^{1,56,166,169-171} Bacterial seeding of a graft site via a hematogenous route is an uncommon event, and given that most infections occur in the first two months after placement, they are thought to occur during the intra- or perioperative period of graft placement in the majority of cases. Although there has been considerable progress in the development of artificial graft materials since their introduction more than 50 years ago, the ideal material still is being sought. There are ongoing efforts to design an antibiotic-embedded graft that is infection-resistant.

Evidence for prophylaxis. The majority of bacteria cultured from these grafts are *S. epidermis* or *S. aureus* or gram-negative bacteria common to the GI tract, but they rarely are oral flora.^{169,170,172} Support for antibiotic prophylaxis for these patients comes from textbook chapters, case reports and review articles, which make at least a soft recommendation for prophylaxis primarily on

the basis of morbidity and mortality associated with graft infections. There is an assumption that bacteremia associated with dental procedures may account for some late infections.^{56,115,173-177}

Other texts and narrative review papers take a stronger stand and recommend that patients be warned about the possibility of graft infection resulting from a bacteremia, and about the importance of antibiotic prophylaxis.^{167,176,178} In a survey of ID specialists, 35 percent indicated that they either always or usually recommended prophylaxis for patients with vascular grafts.¹¹ Other authors have suggested that there is no indication for antibiotic prophylaxis.¹⁰⁹ Immunosuppression, diabetes and chronic renal disease are felt to be contributing factors, but the AHA guidelines for nonvalvular cardiovascular devices do not recommend antibiotic prophylaxis for peripheral vascular shunts.²⁴

Classification of recommendation and level of evidence. Class III; Level C.

Immunosuppression secondary to cancer and cancer chemotherapy. *Background and demographics.* Approximately 1,400,000 people are diagnosed annually with cancer in the United States. Many of these patients will receive some form of cancer chemotherapy, and many of them will have clinically significant neutropenia, raising a concern regarding bacteremia resulting from invasive dental procedures.¹⁷⁹ In addition, some cancer patients are immunocompromised by virtue of their disease (for example, leukemia). VGS are a major concern in immunosuppressed, neutropenic patients with cancer, causing upward of 61 percent of documented bacteremia and resulting in a mortality rate of 6 percent to 30 percent.¹⁸⁰ Escande and Herbrecht¹⁸¹ reviewed the cases of 390 patients with hematologic and solid-tumor cancers and found 477 strains of bacteria during 410 bacteremic episodes, 18 of which were "oral streptococci." In addition to GI and skin sources, oropharyngeal mucositis and gingivitis are major risk factors for streptococcal bacteremia,^{182,183} since the most common bacteria cultured are *Streptococcus mitis*, *Streptococcus sanguis II* and *Streptococcus oralis*.¹⁸⁴ Given that more than one-half of neutropenic cancer patients become febrile and have an identified locus of infection and more than 20 percent have bacteremia, there is understandable concern about invasive dental procedures for these patients.¹⁸⁵

Evidence for prophylaxis. Some opinion papers, textbook chapters, review articles and profes-

sional associations have suggested that patients with immunosuppression undergoing invasive dental procedures be covered with antibiotics,^{18,115,118,139,186-193} and surveys have shown that this is a common clinical practice (Table).^{11,70} Various levels of neutropenia are proposed as thresholds below which prophylactic antibiotics should be used.^{66,136,185,194-196} A 2003 AHA scientific statement on nonvalvular cardiovascular device-related infections states that “immunosuppression is not an independent risk factor for nonvalvular device infections” and that immunocompromised hosts with these devices “should receive ... antibiotic prophylaxis as advocated for immunocompetent hosts.”²⁴

The National Cancer Institute Web site suggests that patients with indwelling venous access lines and neutrophil counts between 1,000 and 2,000 cubic millimeters receive the AHA-recommended regimen for antibiotics, with consideration given to a more aggressive antibiotic therapy in the presence of infection.¹⁹⁷ This source also has a specific recommendation for patients with less than 1,000 neutrophils. One source takes an extreme view and states that “patients with low granulocyte counts should only be treated on an emergency basis,”¹⁷⁷ and another offers the opinion that dental bacteremia can result in “overwhelming septicemia ... and the spread and severity of the infection can potentially be rapid and life-threatening.”¹⁴ Although we could find no well-documented case to support this level of concern, bacteria cultured from the blood of febrile, neutropenic patients strongly supports the mouth as a common source of bacteremia. Some articles and official guidelines do not make a specific recommendation in favor of antibiotics in the dental office setting, but do describe oral conditions and neutropenic states that raise concern.¹⁸⁵ Some book chapters do not address this subject at all. This is a difficult issue to resolve because of the poorly defined shift in the bacterial flora of the mouth and GI tract resulting from a variety of causes such as the decreased number and functionality of white cells, use of antibiotics and overall debilitation. It therefore is difficult to determine the likelihood that invasive dental procedures would cause morbidity or mortality.

Classification of recommendation and level of evidence. Class IIb; Level C.

SLE. Background and demographics. More than 50 percent of patients with SLE have car-

diac involvement, in particular vegetations associated with Libman-Sacks endocarditis.^{198,199} Although the mechanism for formation of these vegetations is unclear, a combination of immune complexes, complement activation and other inflammatory reactions, fibrosis, scarring and calcification likely are involved.^{200,201} Valvular disease and vegetations may be related to the duration, activity or severity of SLE and thus fluctuate over time, but valvular disease is associated with increased morbidity and mortality.²⁰² The most common valvular problem is mitral valve insufficiency, to the extent that it often requires prosthetic replacement.²⁰²⁻²⁰⁵ Retrospective cohort analyses of patients with SLE suggest a prevalence of IE of 0.4 to 4 percent.²⁰⁶⁻²⁰⁸

Evidence for prophylaxis. The primary concern for bacteremia in patients with SLE is the issue of the potentially increased risk of developing IE as a result of undergoing dental procedures. Miller and colleagues²⁰⁸ analyzed transesophageal echocardiography (TEE) data for 275 patients and found a prevalence of 3.3 to 4.4 percent of patients at risk of developing IE and, therefore, requiring antibiotic prophylaxis according to the AHA recommendations. However, it is unclear if this is an underestimate, since only 8 percent of patients in this study had undergone TEE. Some textbook chapters make some degree of recommendation for antibiotic coverage for dental procedures for people with SLE, largely on the basis of the increased incidence of native cardiac valve disease in this population (Table).^{66,197,200,209-212} The Lupus Foundation of America Web site points out the increased risk of infection for patients with lupus, especially those taking immunosuppressive drugs, and suggests that people at high risk of developing infection “often benefit from taking antibiotics before dental treatment or surgical procedures,” though there is no reference for this statement.²¹³

Classification of recommendation and level of evidence. Class III; Level C.

Insulin-dependent diabetes. Evidence for prophylaxis. Some articles and opinion papers suggest that patients with unstable, insulin-dependent diabetes should receive coverage with prophylactic antibiotics for invasive dental procedures,²¹⁴⁻²¹⁶ and some book chapters and specialty guidelines suggest prophylaxis in the presence of oral infection (Table).^{18,115,118,123,138,189,190,216-218} The specific concern regarding distant site infection is not clear, but patients with diabetes are

more susceptible to developing endocarditis if they have an identifiable source of infection.²¹⁹

Classification of recommendation and level of evidence. Class III; Level C.

GENERAL CONSIDERATIONS

Although there are many references containing opinions as to the desirability of antibiotic prophylaxis for patients with these eight conditions or devices, our systematic review of the literature and other sources confirms the viewpoint that there is limited, if any definitive, scientific support for the practice in general. We found only one clinical study,¹⁵⁸ one systematic review³⁵ and two case studies that addressed any of the eight conditions of interest. The rationale for antibiotic prophylaxis can be different for each medical condition or device, but support for this practice ranges from case reports and other anecdotal sources to formal recommendations and advisory statements. The wide diversity of opinion for all of these patients reflects the lack of science and formal, evidence-based recommendations except for cardiac disease, cardiac and some noncardiac devices,²¹⁻²⁴ and prosthetic joints.⁷⁷ This has resulted in a general acceptance of the AHA recommendation for amoxicillin, though there are many antibiotics and combinations of antibiotics that might be recommended by individual clinicians for these medical conditions. The 2003 AHA Scientific Statement on Nonvalvular Cardiovascular Device-Related Infections “does not recommend antibiotic prophylaxis after device placement for patients who undergo dental ... procedures” but indicated that “prophylaxis is recommended for ... incision and drainage of infection at other sites.”²⁴ Nevertheless, the use of the AHA recommendation for amoxicillin is the standard for most, if not all, of these patient groups, on the basis of the frequency with which only the AHA guidelines are mentioned in the references we reviewed.

There are various grading systems for classifying and making recommendations regarding clinical management issues according to levels of evidence.^{16,220} Using the method of the ACC/AHA Task Force on Practice Guidelines, we conclude that all of the conditions covered in this review would be given a recommendation classification of III, with an evidence level of C, with the exception of severely immunosuppressed patients receiving chemotherapy and the higher-risk patients with cardiac conditions for whom a Class IIb-Level C

classification might be more appropriate. Our decision to give cardiac conditions a recommendation classification of IIb reflects the concern on the part of some experts that patients in the highest risk category (for example, those with a prosthetic valve or a history of IE) might benefit from prophylaxis. The lack of any randomized controlled trials to assess the efficacy of antibiotic prophylaxis in these eight patient groups necessitated a qualitative rather than a quantitative systematic review. Until such trials are undertaken, recommendations will continue to be based on consensus opinion of experts on the basis of studies with a low level of evidence.

The general lack of consensus on the necessity for antibiotic prophylaxis for these patients also is documented by the subspecialty literature. Interestingly, there was no mention of antibiotic prophylaxis in many journal articles and textbooks, suggesting a lack of concern on the part of some specialty groups. For example, there was little or no discussion of prophylaxis for the following medical devices and conditions in standard textbooks and other literature: native heart valve disease,²²¹⁻²²³ pacemakers,^{42,224-231} prosthetic joints,²³²⁻²³⁴ dialysis catheters and prosthetic shunts,²³⁵⁻²⁴⁰ VP and VC shunts,²⁴¹⁻²⁵² peripheral vascular grafts,²⁵³⁻²⁵⁶ neutropenia secondary to cancer chemotherapy,²⁵⁷⁻²⁶⁵ SLE²⁶⁶⁻²⁷¹ and insulin-dependent diabetes mellitus.²⁷²⁻²⁸⁰ Furthermore, while a Web site might address antibiotic prophylaxis for a given device or condition in the general sense, it might not mention it for the dental practice setting (Box 2).

In cases in which hematogenous spread of bacteria has been shown to be the cause of an infected medical device or other distant site, the origin invariably is an established infection in a site other than the oral cavity. Even in the rare case in which the mouth is found to be the source, the greatest likelihood is that the causative bacteria gained entrance to the circulation from a routine daily activity (for example, chewing food or toothbrushing) rather than during a dental office procedure. However, it is the latter that is given greater significance in the literature.^{75,100,281,282} On critical review, most of these cases are of questionable validity owing to the reporting of bacteria that are uncommon or rare inhabitants of the oral cavity, or the reporting of a bacterial family or genus rather than a specific species.^{60-62,283}

The pathophysiology of infections that involve

devices such as catheters and shunts includes the adherence of bacteria (for example, coagulase-negative staphylococci) to foreign materials by production of biofilms. This makes them particularly difficult to treat, because biofilms provide protection from the immune system by impairing phagocytosis and killing bacteria.²⁸⁴⁻²⁸⁹ In addition to an inhibition of immune response activity, the slow growth of bacteria and poor antibiotic penetration of biofilms creates a situation such that infections can only be eradicated by removal of the device.^{1,284,285}

CONCLUSION

Antibiotic prophylaxis for the eight medical conditions and devices we examined is highly controversial, and what drives the use of this practice is long-standing dogma and habit, medicolegal concerns and the potentially devastating consequences of infection in some of these patients. In addition to the lack of evidence of the efficacy of this practice, there is the problem of identifying patients at risk and defining the dental office procedures that increase this risk.²⁹⁰ Prospective, randomized, placebo-controlled clinical trials are needed for a definitive decision as to which patients and dental procedures represent a significantly increased risk of distant site infection. The acquisition of such data has been hampered by concerns over the ethics, size, logistics and cost of such studies. Nevertheless, the weight of evidence suggests that the practice should be stopped in most, if not all, of these eight patient groups.

Given the widespread use of antibiotics for so many patients, official recommendations from national committees representing authoritative professional groups are needed for some of these conditions. This would help decrease any negative impact of this practice, including development of resistant strains, medicolegal problems for clinicians, allergic reactions to antibiotics and cost to the health care system. In the meantime, a better understanding of the pathogenesis of these infections, including the host immune response to bacteremia, along with prospective clinical trials will allow for more evidence-based decisions on the continuation of this practice for different patient groups. Until then, the focus should be on rigorous oral hygiene as a strategy to decrease chronic oral bacteremia. ■

Readers interested in additional information regarding the search strategies used in the authors' literature review may access it via the Supplemental Data link in the online version of this article on the

JADA Web site ("<http://jada.ada.org>").

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