Incidence of Infective Endocarditis Caused by Viridans Group Streptococci Before and After Publication of the 2007 American Heart Association’s Endocarditis Prevention Guidelines

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Background—The American Heart Association published updated guidelines for infective endocarditis (IE) prevention in 2007 that markedly restricted the use of antibiotic prophylaxis in certain at-risk patients undergoing dental and other invasive procedures. The incidence of IE caused by viridans group streptococci (VGS) in the United States after publication of the 2007 American Heart Association guidelines has not been reported.

Methods and Results—We performed a population-based review of all definite or possible cases of VGS-IE using the Rochester Epidemiology Project of Olmsted County, Minnesota. Patient demographics and microbiological data were collected for all VGS-IE cases diagnosed from January 1, 1999, through December 31, 2010. We also examined the Nationwide Inpatient Sample hospital discharge database to determine the number of VGS-IE cases included between 1999 and 2009. We identified 22 cases with VGS-IE in Olmsted County over the 12-year study period. Rates of incidence (per 100 000 person-years) during time intervals of 1999–2002, 2003–2006, and 2007–2010 were 3.19 (95% confidence interval, 1.20–5.17), 2.48 (95% confidence interval, 0.85–4.10), and 0.77 (95% confidence interval, 0.00–1.64), respectively (P=0.061 from Poisson regression). The number of hospital discharges with a VGS-IE diagnosis in the Nationwide Inpatient Sample database during 1999–2002, 2003–2006, and 2007–2009 ranged between 15 318 to 15 938, 16 214 to 17 433, and 14 728 to 15 479, respectively.

Conclusions—On the basis of data complete through 2010, there has been no perceivable increase in the incidence of VGS-IE in Olmsted County, Minnesota, since the publication of the 2007 American Heart Association endocarditis prevention guidelines. (Circulation. 2012;126:60-64.)

Key Words: endocarditis • guidelines • infective endocarditis • prevention • dental prophylaxis

Despite advances in medical, surgical, and critical care interventions, infective endocarditis (IE) remains a life-threatening illness.1 Therefore, implementation of effective prophylaxis measures is highly desirable. On the basis of the known risk of bacteremia during invasive procedures, the American Heart Association (AHA) has published formal recommendations for IE prophylaxis since 1955. Over the years, however, cumulative evidence has suggested that the risk of bacteremia during invasive dental procedures is not substantially greater than the risk during activities of daily life.2 On the basis of the availability of these and other more recently published data,3 the AHA made radical changes in their IE prevention guidelines in 2007 that recommended use of antibiotic prophylaxis for invasive dental procedures for only 4 groups of patients who would be at higher risk from complications and mortality if they developed endocarditis.4 Moreover, the 2007 guidelines no longer recommended antibiotics for IE prevention before invasive gastrointestinal and genitourinary procedures.4

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Because invasive dental procedures have been linked to IE caused by the viridans group of streptococci (VGS) in the
past, there has been a lingering concern among medical and dental healthcare providers that the decrease in the number of patients receiving antibiotic prophylaxis for invasive dental procedures might result in an increase in cases of VGS-IE. However, prophylaxis restrictions introduced in the updated guidelines on the incidence of IE caused by VGS in this country remain undefined.

We performed a temporal trend analysis of the incidence of IE caused by VGS in Olmsted County, Minnesota, from 1999 through 2010, which included an analysis of incidence both before and after publication of the 2007 AHA endocarditis prevention guidelines. We also evaluated the number of hospital discharges attributable to VGS-IE using the Nationwide Inpatient Sample (NIS) database between 1999 and 2009.

**Methods**

**Setting**

Olmsted County provides an exceptional opportunity to conduct population-based studies given its geographic isolation from other urban centers, as well as a unique medical records–linkage system that encompasses all residents of Olmsted County, regardless of their healthcare provider. Our group has previously performed 2 population-based analyses of IE in Olmsted County within the past decade that included cases between 1970 and 2006. During this time period, there were a total of 150 cases of IE, with an incidence of VGS-IE ranging from 1.7 to 3.5 cases per 100 000 person-years.

**Data Collection**

The Endocarditis Registry of the Division of Infectious Diseases at Mayo Clinic and the Rochester Epidemiology Project database were our primary resources for data collection and case ascertainment. The IE registry at Mayo Clinic is a prospectively maintained database of all IE cases since 1970. Patient medical records were retrieved through the Rochester Epidemiology Project database, which links and indexes diagnostic and procedure information from all sources of health care in Olmsted County into a single centralized system. All Olmsted County residents ≥18 years with definite or possible IE caused by VGS, as defined by the modified Duke criteria, between January 1, 1999, and December 31, 2010, were identified with this system. We obtained demographic, clinical, laboratory, and outcomes data from a detailed review of the complete medical records.

The NIS database has been described previously. The NIS is a stratified probability sample developed as part of the Healthcare Cost and Utilization Project funded by the Agency for Healthcare Research and Quality. The NIS contains data from ≈8 million hospital admissions each year. Discharge records were queried with use of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to determine the number of cases of VGS-IE that occurred between 1999 and 2009; the data for 2010 were not available. The following ICD-9-CM codes were used in combination to identify VGS-IE cases: Acute or subacute bacterial endocarditis, 421.0; streptococci unspecified, 041.00; and other streptococci, 041.09. We excluded the following ICD-9-CM diagnostic codes from our search: Staphylococcus group A, 041.01; streptococcus group B, 041.02; streptococcus group C, 041.03; enterococcus group D, 041.04; and streptococcus group G, 041.05.

We surveyed the local dental society membership regarding aspects of the 2007 AHA IE prevention guidelines changes. The following questions were included in a questionnaire: (1) Do you treat patients who live in Olmsted County? (2) Are you aware of the changes in the 2007 AHA/ADA endocarditis prophylaxis guidelines? (3) Did you revise your practice to include the 2007 guidelines? (4) Do you still use the guidelines that were available before 2007? If so, in whom? and (5) Do you think it is important to monitor the incidence of endocarditis caused by viridans group streptococci following publication of the 2007 guidelines?

The antimicrobial susceptibilities of all cases of VGS-IE between 1999 and 2010 in the Olmsted County database were recorded from in vitro susceptibility testing. Minimal inhibitory concentrations were determined by standard broth microdilution techniques and interpreted in accordance with Clinical and Laboratory Standards Institute breakpoints.

Site of infection acquisition was defined as described by Friedman et al. Patients were considered to have healthcare-associated infection if 1 of the following conditions was met before the development of signs or symptoms of IE: Received infusion therapy at home or self-administered intravenous medications in the last 30 days; attended a hospital or hemodialysis center or received intravenous chemotherapy in the last 30 days; was hospitalized in an acute care hospital for ≥2 days in the preceding 90 days; or resided in a nursing home or a long-term care facility.

Community acquisition of IE was defined by onset of signs and symptoms of IE in patients who did not fit the above criteria for a healthcare-associated infection. Nosocomial acquisition of IE was defined by onset of signs and symptoms of IE in patients who had been hospitalized for 48 hours or longer.

**Statistical Analysis**

Incident cases were residents of Olmsted County who first tested positive for VGS-IE in the 1999–2010 time frame. We calculated incidence rates as the number of VGS-IE cases per 100 000 person-years, assuming that the entire adult population was at risk. The denominators of age- and sex-specific person-years were derived from census figure and then directly adjusted to the white population in the United States in year 2000. Ninety-five percent confidence intervals (CIs) were estimated on the assumption that the incidence cases followed a Poisson distribution. Finally, a multivariable Poisson regression model was fit to the data to test for a temporal trend in the incidence of VGS-IE over the study time frame (time was grouped into three 4-year intervals and fit as a categorical variable), adjusted for age and sex. All analyses were performed with the SAS statistical software package (version 9.2, SAS Institute Inc, Cary, NC). P<0.05 was considered statistically significant.

**Results**

We identified 22 cases of VGS-IE in the Olmsted County adult population between the years 1999 and 2010. The age- and sex-adjusted incidence rates of VGS-IE in Olmsted County for 1999–2002, 2003–2006, and 2007–2010 were 3.19 (95% CI, 1.20–5.17), 2.48 (95% CI, 0.85–4.10), and 0.77 (95% CI, 0.00–1.64) per 100 000 person-years, respectively (Figure 1).

Only 3 (13.6%) of the 22 VGS-IE cases were identified between 2007 and 2010. Of these, 2 patients had not undergone any dental treatments within 6 months of admission. The remaining patient had a dental procedure 2 weeks before symptom onset and had taken clindamycin 600 mg by mouth 30 minutes before the dental procedure.

Penicillin susceptibility was screened among the strains of all 22 VGS-IE cases; 21 isolates (95.5%) were susceptible to penicillin, 1 isolate (4.5%) was intermediate susceptible, and none were resistant. Twenty-one of the 22 isolates were also screened for macrolide susceptibility; 15 (71.4%) were susceptible, whereas 6 (28.6%) were resistant. Clindamycin susceptibility testing was not performed.

IE cases were classified on the basis of site of infection acquisition. Using the definitions described above, 91% (20/22) were classified as community acquired and 9% (2/22) were healthcare associated; there were no cases that were
nosocomially acquired. The 2 strains of VGS that were classified as healthcare associated were both sensitive to penicillin.

Between 1999 and 2009, VGS-IE discharge data were accessible with the NIS database. The total number of VGS-IE cases from the NIS database, based on the ICD-9 codes listed in hospital discharges during 1999–2002, 2003–2006, and 2007–2009, ranged between 15,318 to 15,938, 16,214 to 17,433, and 14,728 to 15,479, respectively (Figure 2).

Discussion
To the best of our knowledge, this is the first population-based study in the United States to examine the incidence of VGS-IE in adults after the publication of the updated 2007 AHA IE prevention guidelines. Our investigation demonstrated no perceivable increase in incidence after publication of these guidelines.

Because there are no previously published prospective, randomized, placebo-controlled trials to evaluate either the risk of VGS-IE attributable to dental procedures or the efficacy of antibiotic prophylaxis in this setting, and because the likelihood of such trials being conducted is very low, population-based investigations are critical in the evaluation of IE prevention practices. Three other investigations support the present findings that the incidence of VGS-IE has not increased after publication of the 2007 AHA endocarditis prevention guidelines.9,13,14 This includes our evaluation of the NIS database from 1999 to 2009, which contained the total number of hospital discharges attributable to VGS-IE. The NIS is the largest all-payer inpatient care database in the United States and includes approximately a 20% stratified sample of US community hospitals.9 Discharge data in 1999 included 24 states, 984 hospitals, and 7,198,929 discharges, whereas in 2009, there were 44 states, 1050 hospitals and 7,810,762 discharges. Over the 11-year period, the number of states and total discharges increased, whereas the number of hospitals increased slightly. The number of hospital discharges attributable to VGS-IE remained stable between 1999 and 2009, despite increases in the number of states, hospitals, and total discharges that were surveyed.

The second investigation was a hospital-based survey13 that, in response to the publication of the updated 2007 AHA prophylaxis guidelines, examined the number of patients hospitalized at a university teaching hospital with a discharge diagnosis of acute or subacute bacterial endocarditis between May 2001 to April 2007 and May 2007 to January 2008. This preliminary survey revealed that the number of patients with IE over the 2 time periods had not changed substantially.

The third and most supportive study is from the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom, which also published guidelines that addressed antibiotic prophylaxis for IE in 2008.14 These guidelines recommended that antibiotic prophylaxis before dental procedures, solely to prevent IE, should not be administered to any group of patients, regardless of their anticipated risk of IE complications. This radical change in recommendations sparked immediate controversy and anecdotal claims of a possible increase in the number of cases of VGS-IE15,16 among clinicians in England.

Thornhill et al17 defined the impact of the NICE guidelines in the first 2 years after publication of these guidelines by quantifying the change in prescribing patterns of antibiotic prophylaxis before invasive dental procedures for patients at risk of IE and any concurrent change in the incidence of IE in the United Kingdom. Using the national database, they were able to survey the entire country regarding the practice of antibiotic prophylaxis for dental procedures. In their investigation, they identified patients who received a unique 3-g dose of amoxicillin before invasive dental procedures and compared that with denominator data of IE cases. Their analysis indicated a 78.6% reduction in the prescribing of antibiotic prophylaxis for dental procedures. In their investigation, they identified patients who received a unique 3-g dose of amoxicillin before invasive dental procedures and compared that with denominator data of IE cases. 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% These data support the recommendations published in the NICE guideline.17

To evaluate the antibiotic prescribing pattern for IE prophylaxis in Olmsted County, we performed an ancillary survey of the local dental society (90 members) and had a 41.1% response rate to a brief questionnaire. All respondents indicated that they were aware of the 2007 AHA IE prevention guidelines and had modified their respective practices to include the new recommendations for antibiotic prophylaxis. The results of our survey regarding awareness and implementation of the 2007 AHA guidelines among local dental practitioners are consistent with the trends noted by the American Dental Association (Peter Lockhart, American Dental Association, oral communication, 2011). The American Dental Association collected data from 901 respondents, which included its members and nonmembers, in a questionnaire regarding the 2007 AHA guidelines and found that self-reported awareness of the updated guidelines was almost universal (97.9%), and 77% of dental practitioners were either satisfied or very satisfied with the guidelines. Eighty percent of respondents reported a decrease in the number of patients who received antibiotic prophylaxis.

The incidence of VGS-IE in Olmsted County has been declining since its peak in 1985–1989.5,6 Factors responsible for this observation have been undefined to date. It is tempting to speculate that the decline in VGS-IE cases could be related to the overall decline in rheumatic carditis as a unique substrate for the development of IE caused by VGS. Studies18–20 from areas where rheumatic fever continues to be endemic and a prominent predisposing condition for the development of IE describe VGS as the predominant pathogens.

The present study has limitations. The adult population of Olmsted County is <150,000 people, which results in a small number of annual cases of VGS-IE. In addition, the time interval of our investigation after publication of the guidelines was relatively short. A delay between publication of the guidelines and implementation into clinical practice by healthcare professionals is characteristically seen with most guidelines; thus, it may take several years before the impact of these guidelines is evident. Nevertheless, we did not detect an increase in incidence of VGS IE during the 12-year study period. In addition, the racial homogeneity in Olmsted County (predominately white) may limit applicability of the study findings to more diverse populations. Furthermore, there are limited data available on compliance with the guidelines, and the risk profile of patients who receive prophylaxis is unknown (high versus low risk for complications).

The NIS contains discharge-level records, not patient-level records,9 and therefore, individual patients who are hospitalized multiple times in 1 year may be present in the NIS multiple times. In addition, diagnosis codes may not be accurate in defining disease syndromes.

Finally, self-reported data in response to a survey may not be a true reflection of actual practice behavior. Responders may be more likely than nonresponders to be aware of and follow the 2007 guidelines. For a more accurate estimation of adherence to new practice guidelines, patient records would need to be reviewed, and this was not performed in the present investigation.

Conclusions

Despite marked changes in IE prevention guidelines that were published by the AHA in 2007 that restricted antibiotic prophylaxis to 4 patient groups with a high risk of complications from IE, the findings of our population-based investigation from Olmsted County suggest that the incidence of VGS IE after publication of these guidelines did not increase. Continued monitoring of the incidence of VGS-IE over an extended period of time is mandatory, however, in both local and other populations to substantiate this preliminary finding.

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Disclosures

Dr Sohail has received compensation from TyRx, Inc. Dr Baddour receives royalty payments from UpToDate, Inc, payments for services as Editor-in-Chief for the Massachusetts Medical Society (Journal Watch Infectious Diseases), and coeditorship payments from the American College of Physicians (PIER [Physicians’ Information and Education Resource]). The other authors report no conflicts.

Dr DeSimone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Design and conduct of the study were by Drs DeSimone, Tleyjeh, Correa de Sa, Wilson, and Baddour. Acquisition of data was by Drs DeSimone, Stockelberg, Anavekar, Tleyjeh, Correa de Sa, and Baddour. Analysis and interpretation of data were performed by Drs DeSimone, Sohail, Tleyjeh, Correa de Sa, Wilson, and Baddour and Mr Lahr. Critical revisions of the manuscript for important intellectual content were performed by Drs DeSimone, Sohail, Tleyjeh, Correa de Sa, Stockelberg, Anavekar, Wilson, and Baddour and Mr Lahr. Drafting of the manuscript was done by Drs DeSimone, Sohail, Tleyjeh, Correa de Sa, and Baddour. Drs DeSimone and Baddour obtained funding for the present study. Administrative, technical, or material support was provided by Drs Wilson and Baddour. Study supervision was by Drs DeSimone, Stockelberg, Wilson, and Baddour. The Mayo Clinic Institutional Review Board approved this study (study ID: 10-007212).

References

Infective endocarditis (IE) is an uncommon but potentially lethal infection. Although there are no randomized trials to support its efficacy, antibiotic prophylaxis administered before certain dental procedures in patients with specific underlying cardiac conditions has been advocated since 1955 by the American Heart Association in IE prevention guidelines. The updated 2007 American Heart Association guidelines included a marked reduction in the cardiac conditions that warranted antibiotic prophylaxis for certain dental procedures. Despite these recommendations and the lack of evidence for antibiotic prophylaxis administration, there has been sustained concern among some healthcare personnel about an increase in IE cases caused by viridans group streptococci because of the limitation of antibiotic prophylaxis use. In response to these concerns, the current population-based survey was conducted to determine whether the incidence of viridans group streptococci–IE had increased in Olmsted County, Minnesota, since the publication of the 2007 American Heart Association IE prevention guidelines. Results demonstrated no observed increase in this population-based cohort. Moreover, data from a national inpatient database support this finding. Nevertheless, limitations of the study, including a small annual number of IE cases, mandate continued evaluation of incidence trends over an extended period of time, both locally and elsewhere, before concerns regarding increasing incidence of viridans group streptococci–IE related to changes in guidelines recommendations can be addressed fully.

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