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

Running title: DeSimone et al.; Incidence of VGS endocarditis

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Abstract:

Background - The American Heart Association (AHA) 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 due to viridans group streptococci (VGS) in the United States following publication of the 2007 AHA 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 microbiologic data were collected for all VGS-IE cases diagnosed from January 1, 1999 through December 31, 2010. We also examined the Nationwide Inpatient Sample (NIS) 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 [CI], 1.20-5.17), 2.48 (95% CI, 0.85-4.10), and 0.77 (95% CI, 0.00-1.64), respectively (p-value=0.061 from Poisson regression). The number of hospital discharges with a VGS-IE diagnosis in the NIS database during 1999-2002, 2003-2006, and 2007-2009 ranged between 15,318-15,938, 16,214-17,433, and 14,728-15,479, respectively.

Conclusions - Based on data complete through 2010, there has been no perceivable increase in incidence of VGS-IE in Olmsted County, MN following publication of the 2007 AHA Endocarditis prevention guidelines.

Key words: endocarditis, guidelines, infective endocarditis, prevention, dental prophylaxis
Introduction

Despite advances in medical, surgical, and critical care interventions, infective endocarditis (IE) remains a life-threatening illness. Therefore, implementation of effective prophylaxis measures is highly desirable. Based on 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. Based on availability of these and other more recently published data, the AHA made radical changes in their IE prevention guidelines in 2007 that recommended use of antibiotic prophylaxis for invasive dental procedures to only four groups of patients who would be at higher risk from complications and mortality if they developed endocarditis.

Moreover, the 2007 guidelines no longer recommended antibiotics for IE prevention before invasive gastrointestinal and genitourinary procedures.

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

We performed a temporal trend analysis of the incidence of IE due to VGS in Olmsted County, MN, between 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 due to VGS-IE using the Nationwide Inpatient Sample (NIS).
database between 1999 and 2009.

Methods

Setting

Olmsted County, Minnesota, 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 two population-based analyses of IE in Olmsted County within the past decade that included cases between 1970 and 2006\textsuperscript{5,6}. During this time period, there was 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\textsuperscript{5,6}.

Data Collection

The Endocarditis Registry of the Division of Infectious Diseases at Mayo Clinic and the Rochester Epidemiology Project (REP) 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\textsuperscript{5}. Patient medical records were retrieved through the REP database, which links and indexes diagnostic and procedure information from all sources of health care in Olmsted County into a single centralized system\textsuperscript{5}. All Olmsted County residents 18 years or older 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 using this system\textsuperscript{6,7}. We obtained demographic, clinical, laboratory, and outcomes data from a detailed review of the complete medical records.
The NIS database has been previously described\(^8\). The NIS is a stratified probability sample developed as part of the Healthcare Cost and Utilization Project (HCUP) funded by the Agency for Healthcare Research and Quality (AHRQ). The NIS contains data from approximately eight million hospital admissions each year\(^9\). Discharge records were queried using ICD-9-CM codes to determine the number of cases of VGS-IE that occurred between 1999 and 2009; the data for 2010 is not currently available. The following ICD-9-CM codes were used in combination to identify VGS-IE cases: acute or sub-acute 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: streptococcus group A: 041.01; streptococcus group B: 041.02; streptococcus group C: 041.03; enterococcus group D: 041.04; 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 due to viridans group streptococci following publication of the 2007 guidelines.

The antimicrobial susceptibilities of all cases of VGS-IE between 1999 and 2010 in Olmsted County database were recorded from in-vitro susceptibility testing. Minimal inhibitory concentrations (MICs) were determined by standard broth microdilution techniques and interpreted in accordance with Clinical and Laboratory Standards Institute (CLSI) breakpoints\(^{10,11}\).
Site of infection acquisition of was defined as described by Friedman et al\(^\text{12}\). Patients were considered to have health care-associated infection if one of the following conditions were 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 or more days in the preceding 90 days; or resided in a nursing home or a long-term care facility\(^\text{6,11}\). 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 health-care associated infection\(^\text{12}\). 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 \(^\text{6}\).

**Statistical Analysis**

Incident cases were residents of Olmsted County, Minnesota that 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 figures and then directly adjusted to the Caucasian population in the United States in year 2000. Ninety-five percent confidence intervals were estimated assuming 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 carried out using the SAS statistical software package (Version 9.2, SAS Institute Inc., Cary, NC). A p-value < .05 was considered statistically significant.
Results

We identified 22 cases of VGS-IE in Olmsted County adult population between the years 1999 and 2010. The age- and sex-adjusted incidence rates of VGS-IE in Olmsted County, MN, for 1999-2002, 2003-2006, 2007-2010, was 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 three of the 22 (13.6%) VGS-IE cases were identified between 2007 and 2010. Of these, two patients had not undergone any dental treatments within six months of admission. The remaining patient had a dental procedure two weeks prior to symptom onset, and had taken clindamycin 600 mg by mouth 30 minutes prior to the dental procedure.

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

IE cases were classified based on site of infection acquisition. Using the definitions described above, 91% (20/22) were classified as community-acquired, 9% (2/22) were health care-associated; and there were no cases that were nosocomially acquired. The two 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 15,318-15,938, 16,214-17,433, and 14,728-15,479, respectively (Figure 2).
Discussion

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

Because there are no previously published prospective, randomized, placebo-controlled trials to evaluate either the risk of VGS-IE due to dental procedures or the efficacy of antibiotic prophylaxis in this setting, and the likelihood of such trials being conducted is very low, population-based investigations are critical in evaluating IE prevention practices.

Three other investigations support our findings that the incidence of VGS-IE has not increased following publication of the 2007 AHA endocarditis prevention guidelines. This includes our evaluation of the NIS database from 1999 to 2009 that contained the total number of hospital discharges due to VGS-IE. The NIS is the largest all-payer inpatient care database in the United States that includes approximately a 20% stratified sample of U.S. community hospitals. Discharge data in 1999 included 24 states, 984 hospitals, and 7,198,929 discharges, while in 2009, there are 44 states, 1,050 hospitals and 7,810,762 discharges. Over the 11-year period, the number of states and total discharges increased, while the number of hospitals slightly increased. The number of hospital discharges due 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 is a hospital-based survey 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 two 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 that also published guidelines that addressed antibiotic prophylaxis for IE in 2008\textsuperscript{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-IE\textsuperscript{15,16} among clinicians in England.

Thornhill et al\textsuperscript{17} defined the impact of the NICE guidelines in the first two 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 gram dose of amoxicillin prior to invasive dental procedures and compared that to denominator data of IE cases. Their analysis indicated a 78.6\% reduction in prescribing of antibiotic prophylaxis after the introduction of the NICE guidelines. Yet, they did not detect a significant increase in the number of IE cases above the long-term baseline trend during their study period. There was no significant increase in the rate of IE-related in-hospital mortality or increase in the number of IE cases due to streptococci of oral origin. The estimated annual percentage change in the number of oral streptococcal IE cases from January 2000 to March 2008 was 8.41\% (95\% CI, 6.66\%-10.19\%); the estimated change after the new guidelines was 10.38\% (95\% CI, 2.93\%-18.36\%);
(P=0.66). Twelve-months prior to the NICE guidelines, dentists accounted for 91.9% of prescriptions for antibiotic prophylaxis, while 14-25 months after the introduction of the guidelines, the number of prescriptions written by dentists significantly decreased by 79.9%. These data support the recommendations published in the NICE guideline17.

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 (ADA; Peter Lockhart, personal communication). The ADA collected data from 901 respondents, which included its members and non-members 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 1985-19895,6. 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 due to 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.

Our 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 following 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 Caucasian) may limit applicability of the study findings to more diverse populations. Furthermore, there are limited data on compliance with the guidelines available and the risk profile of patients who receive prophylaxis is unknown (high-risk vs. low-risk for complications).

The NIS contains discharge-level records, not patient-level records\(^9\), therefore individual patients who are hospitalized multiple times in one 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 that the non-responders 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 our investigation.

**Conclusions**

Despite marked changes in IE prevention guidelines that were published by the AHA in 2007 that restricted antibiotic prophylaxis to four patient groups with a high-risk of complications from IE, the findings of our population-based investigation from Olmsted County, Minnesota suggest that the incidence of VGS IE following 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.

Acknowledgments: Author contributions: 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: DeSimone, Tleyjeh, Correa de Sa, Baddour. Acquisition of data: DeSimone, Steckelberg, Anavekar, Tleyjeh, Correa de Sa, Baddour. Analysis and interpretation of data: DeSimone, Sohail, Tleyjeh, Correa de Sa, Lahr, Wilson, Baddour. Critical revisions of the manuscript for important intellectual content: DeSimone, Sohail, Tleyjeh, Correa de Sa, Lahr, Steckelberg, Anavekar, Wilson, Baddour. Drafting of the manuscript: DeSimone, Sohail, Tleyjeh, Correa de Sa, Baddour. Statistical analysis: DeSimone, Lahr, Baddour. Obtained funding: DeSimone, Baddour. Administrative, technical, or material support: Wilson, Baddour. Study supervision: DeSimone, Steckelberg, Wilson, Baddour. Institutional review board: Mayo Clinic IRB approved; study ID: 10-007212

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Conflicts of Interest Disclosures: None

References:


Figure Legends:

**Figure 1.** Temporal trends in age- and sex-adjusted incidence rate of infective endocarditis (IE) caused by viridans group streptococci (VGS) from 1999 to 2010 in Olmsted County, Minnesota.

**Figure 2.** Total number of hospital discharges with ICD-9-CM discharge diagnosis of 421.0, 041.00, and 041.09 from 1999 to 2009 from the Nationwide Inpatient Sample.
<table>
<thead>
<tr>
<th>Time Era</th>
<th>VGS-IE cases</th>
<th>Incidence Rate (per 100,000 person-years)</th>
<th>95% Confidence Interval</th>
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<td>M</td>
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<tr>
<td>1999-2002</td>
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<tr>
<td>2007-2010</td>
<td>0 3 3</td>
<td>0.0</td>
<td>(0.0 – 0.0)</td>
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