

## AHA SCIENTIFIC STATEMENT

# Prevention of Viridans Group Streptococcal Infective Endocarditis

## A Scientific Statement From the American Heart Association

**BACKGROUND:** In 2007, the American Heart Association published updated evidence-based guidelines on the recommended use of antibiotic prophylaxis to prevent viridans group streptococcal (VGS) infective endocarditis (IE) in cardiac patients undergoing invasive procedures. The 2007 guidelines significantly scaled back the underlying conditions for which antibiotic prophylaxis was recommended, leaving only 4 categories thought to confer the highest risk of adverse outcome. The purpose of this update is to examine interval evidence of the acceptance and impact of the 2007 recommendations on VGS IE and, if needed, to make revisions based on this evidence.

**METHODS AND RESULTS:** A writing group was formed consisting of experts in prevention and treatment of infective endocarditis including members of the American Dental Association, the Infectious Diseases Society of America, and the American Academy of Pediatrics, in addition to the American Heart Association. MEDLINE database searches were done for English language articles on compliance with the recommendations in the 2007 guidelines and the frequency of and morbidity or mortality from VGS IE after publication of the 2007 guidelines. Overall, there was good general awareness of the 2007 guidelines but variable compliance with recommendations. There was no convincing evidence that VGS IE frequency, morbidity, or mortality has increased since 2007.

**CONCLUSIONS:** On the basis of a review of the available evidence, there are no recommended changes to the 2007 VGS IE prevention guidelines. We continue to recommend VGS IE prophylaxis only for categories of patients at highest risk for adverse outcome while emphasizing the critical role of good oral health and regular access to dental care for all. Randomized controlled studies to determine whether antibiotic prophylaxis is effective against VGS IE are needed to further refine recommendations.

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**Key Words:** AHA Scientific Statements  
■ antibiotic prophylaxis ■ dental care  
■ endocarditis ■ oral health ■ viridans  
streptococci

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In 2007, the American Heart Association (AHA) published the first categorical revision to its guidelines on the prevention of infective endocarditis (IE) in >50 years since the AHA first published guidelines on this subject.<sup>1</sup> The 2007 guidelines challenged the historical, but theoretical, concept that antibiotic administration before a dental procedure is effective as primary prophylaxis for IE caused by viridans group streptococcal (VGS). In that effort, the 2007 writing group developed a classification system based on the greatest risk of adverse outcomes from VGS IE rather than the risk of acquisition of VGS IE. After an extensive literature review, the writing group of the 2007 guidelines made significant differences in conclusions and recommendations compared with previous AHA statements, as shown in Table 1.

According to the recommendations in the 2007 guidelines, compared with previous AHA guidelines, ≈90% fewer patients qualified for antibiotic prophylaxis (AP) for a dental procedure.<sup>2,3</sup> These major changes in recommendations in the 2007 guidelines have now been in practice for more than a decade and have been evaluated in a number of retrospective and observational studies.

The primary purposes of this updated AHA statement are to (1) review the studies published since the 2007 guidelines to assess the impact of the guidelines on practice; (2) determine whether there was an increased incidence of or mortality from VGS IE since 2007; (3) re-evaluate the rationale used to develop and promote the 2007 guidelines; (4) assess whether the changes recommended in 2007 guidelines remain valid; (5) review whether the 4 underlying cardiac conditions listed in the 2007 guidelines with the highest risk of poor outcome from VGS IE should be expanded, be reduced, or remain the same; and (6) if necessary, suggest revisions to the 2007 guidelines based on a comprehensive review of published studies.

## IMPACT OF 2007 GUIDELINE ON PRACTICE: ACCEPTANCE AND COMPLIANCE

**Question:** How well did clinicians implement the 2007 guidelines?

The writing group reviewed 2 general sources of data available to evaluate acceptance and compliance: surveys of clinicians in practice and results of studies that published compliance rates. Lockhart and colleagues<sup>2</sup> surveyed a random sample of 5500 dentists in the United States. Among the 878 respondents, >75% were satisfied or very satisfied with the 2007 guidelines. However, 70% of dentists reported that they had patients who continued to take AP although the guidelines no longer recommended it, most often for mitral

**Table 1. Major Changes in 2007 AHA Guidelines Compared With Previous 9 AHA Guidelines on Prevention of IE**

VGS IE is much more likely to be caused by transient VGS bacteremia from an oral source resulting from daily routine activities than from a dental procedure.
Therefore, only an exceedingly small number of cases of VGS IE could be prevented by AP for a dental procedure, even if such prophylaxis is 100% effective.
AP was no longer recommended as primary prophylaxis to prevent VGS IE in patients with underlying cardiac disease even if it poses an underlying lifetime risk for acquisition of VGS IE.
If AP is effective in preventing a very small number of cases of VGS IE, it should be recommended only for those patients with an underlying condition that poses the highest risk of an adverse outcome from VGS IE such as heart failure, aortic root abscess, need for cardiac valve replacement, need for complex surgical revisions in patients with congenital heart disease, recurrent VGS IE, or death.
Maintenance of good oral health and regular dental care are much more important to prevent VGS IE than AP for a dental procedure.

AHA indicates American Heart Association; AP, antibiotic prophylaxis; IE, infective endocarditis; and VGS, viridans group streptococcal.

valve prolapse but also for 5 other cardiac conditions, primarily because of physician recommendation (57%) or patient preference (33%).

A survey of 450 dentists in Alberta, Canada, focused on their interpretation of the 2007 guidelines and whether they would recommend AP for patients with high risk for IE.<sup>3</sup> Among the 194 respondents, there was in general lack of compliance with the 2007 recommendations. Prophylaxis was recommended for some of the AHA moderate-risk groups, and some dentists did not prescribe prophylaxis even for patients in the AHA high-risk group.

Another study published in 2017 evaluated compliance with the 2007 guidelines in dental practices in Olmsted County, MN. DeSimone and colleagues<sup>4</sup> reviewed dental records of patients with both moderate and high risk for IE before and after the 2007 guidelines publication to determine the use of AP by dentists. There was a significant ( $P<0.001$ ) decline from 64.6% before the guidelines to 8.6% after the guidelines in the use of AP for patients with moderate-risk cardiac conditions. Unexpectedly, in patients with high-risk cardiac conditions, there was a statistically significant ( $P<0.01$ ) decline in the use of AP after guidelines publication from 96.9% to 81.3%.

Thornhill and colleagues<sup>5</sup> reported an analysis of changes in antibiotic prescribing in large populations in the United States after the 2007 guidelines. They found that by August 2015 there was a 20% overall reduction in prescribing AP for the high-risk group, a decrease of 64% for the moderate-risk group, and a 52% reduction in the low- or unknown-risk group of patients.

In summary, on the basis of the results from surveys and clinical studies, there seemed to be good general awareness of the 2007 guidelines but variable compliance, which was demonstrated in both the US and UK

populations. These results underscore the importance of better communication of the AHA guidelines, the need for improved education for both patients and health care providers, and the value of shared decision making by patients and health care providers.

## VGS IE INCIDENCE AND MORTALITY SINCE 2007

**Questions:** Was there an increased incidence of VGS IE in patients with high risk of adverse outcome for whom AP was recommended or for patients with a low or moderate risk of adverse outcome from VGS IE for whom AP for a dental procedure was no longer recommended? How did VGS IE incidence and mortality change in the patients still receiving AP for a dental procedure and in the patients no longer receiving AP for a dental procedure after the publication of the new recommendations in 2007?

To assess these questions, the writing group undertook a critical review of published studies to determine whether there was an increased incidence of or mortality from VGS IE since the 2007 guidelines were published. The strengths, weaknesses, types of studies, and levels of evidence for each study reviewed are shown in Table 2. There are no published prospective, randomized trials of the efficacy of AP for a dental procedure. The studies reviewed are retrospective; are population or health system based; relied on claims data, registries, or epidemiological observations on the incidence of IE; and used various methods to identify cases of IE. All these studies have limitations. A major limitation has been the lack of specific *International Classification of Diseases* coding for VGS. In addition, the coding for the genus *Enterococcus* was included in the *Streptococcus* coding until the *International Classification of Diseases, 10th Revision* version became available. Other studies have statistical flaws (Table 2).

In summary, the writing group found no high-quality data that suggest that an increased frequency of or mortality from native valve VGS IE occurred in the United States or Canada after the 2007 guidelines. Some studies suggest that there is a trend toward an increase in the overall incidence of IE but not of VGS IE. On balance, the preponderance of published studies suggest that there is no convincing evidence of an increase in cases of VGS IE among patients with high, low, or moderate risk of acquisition of IE or adverse outcome from VGS IE since publication of the 2007 guidelines.

Data reported from the United Kingdom deserve additional comment. In 2008, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom recommended cessation of AP for dental procedures in all people at risk for IE.<sup>30</sup> Dayer et al<sup>8</sup> in 2018 analyzed the impact of the NICE guidelines before

and after publication. This study compared changes in prescribing AP for dental procedures and the incidence of IE after publication of the NICE guidelines. There was a 79% decrease ( $P<0.001$ ) in prescriptions, which confirmed high compliance with the NICE recommendations. This study used *International Classification of Diseases* codes to identify hospital admissions for IE from 2004 to March 2013, 5 years after publication of the NICE guidelines. Beginning in March 2008, the number of cases of IE increased significantly ( $P<0.001$ ) above the historical trend. By March 2013, 35 more cases per month were reported than would have been expected had the previous trend continued. The increase in the incidence of IE was significant both for individuals with low or moderate risk of IE and for those with high risk of IE. However, no data were available on the microbiological cause of IE in these patients.<sup>8</sup> Therefore, no valid conclusion may be drawn about the impact of the NICE guidelines on the incidence of VGS IE, the target of AP for a dental procedure. Nonetheless, NICE revised its advice and recommended against routine use of AP for dental procedures in high-risk patients. This change emphasized the importance of shared decision making between providers and high-risk patients in terms of whether to receive AP for a dental procedure.

A recent study by Quan and colleagues<sup>31</sup> used an electronic health records study and evaluated the impact of the NICE guidelines concerning AP during invasive dental procedures on the incidence of IE in England. This study confirmed the overall increase in IE from 1998 to 2017. The Quan et al study reported microorganism-specific IE. These authors did not detect an increase in the frequency of IE caused by oral streptococci related to the NICE guidelines publications.

## CURRENT EVIDENCE: AP FOR DENTAL PROCEDURES IN THE 4 GROUPS AT HIGH RISK OF ADVERSE OUTCOMES

**Question:** What is the current frequency of morbidity or mortality from VGS IE in the 4 high-risk groups defined in the 2007 guidelines?

The 2007 guidelines posited a new approach to define who, if anyone, would most likely benefit from AP for a dental procedure to prevent VGS IE whereby the risk of taking an antibiotic is less than the risk of not taking one. In that effort, the 2007 writing group developed a classification system based on greatest risk of adverse outcomes from VGS IE rather than the risk of acquisition of VGS IE. This fundamental difference between the 2007 AHA guidelines and the previous 9 AHA guidelines was among the most controversial changes made in the 2007 guidelines. This change in concept was not fully appreciated early after publication and is not appreciated by some to this day. In fact,

**Table 2. Published Articles on the Impact of Guidelines on IE (Chronological)**

Author, year of publication	Population, setting, (data source)	Study design, includes: (1) Control, (2) Duration of follow-up, (3) Ages	Reported: (1) Microbiology data? (2) AP prescribing data? (3) Change in IE incidence after 2007?	Key results	Comments and key citations
Rogers and Shiller, <sup>6</sup> 2008	Single academic medical center in the United States (University of California, San Francisco electronic health records)	Observational (pre/post, unadjusted) (1) Historical control, (2) 9 mo after guidelines (May 2001–January 2008), (3) Unclear	(1) No (2) No (3) No	No change in number of inpatient admissions for IE 9 mo after the 2007 change in guidelines compared with before 2007	Limited methods and results published as a research letter
Thornhill et al, <sup>8</sup> 2011	All National Health Services Centers in England, UK (England-wide monthly prescribing records and inpatient activity records)	Observational (pre/post) (1) Historical control, (2) 2 y after guidelines (January 2000–April 2010), (3) All ages	(1) Yes, <i>ICD-10</i> codes* (2) Yes (3) No	Despite a 78.6% reduction in AP prescription, no significant change in the general upward trend in IE cases or deaths over time. No change in cases attributable to oral streptococci	NICE guidelines are meaningfully different from the US guidelines. NICE guidelines do not recommend AP for the group at high risk for IE. This article is superseded by Thornhill et al <sup>8</sup> (same data set, longer follow-up).
DeSimone et al, <sup>9</sup> 2012	Olmsted County, MN (epidemiological data from the Rochester Epidemiology Project and national claims data from the National Inpatient Sample)	Observational (pre/post) based on Poisson regression (1) Historical control, (2) 3 y after guidelines (January 1999–December 2010), (3) Adults ≥18 y of age	(1) Laboratory data from medical record review (Olmsted County) and claims data (National Inpatient Sample) (2) No (3) No	No detectable increase in incidence rate of IE caused by VGS in Olmsted County, MN. No change in number of cases of IE caused by VGS in the National Inpatient Sample	Small number of IE cases (22 in 12 y). Substantial demographic, clinical, and health system-level differences between Olmsted County and the rest of the United States limit generalizing of their findings. Coding of microbiological data in the National Inpatient Sample ( <i>ICD-9</i> ) is suboptimal in both completeness and accuracy. Substantial overlap between the 3 DeSimone et al <sup>9-11</sup> articles.
Pasquali et al, <sup>12</sup> 2012	37 Children's hospitals, United States (Pediatric Health Information System Database)	Observational (pre/post) (1) Historical control, (2) 3 y after guidelines (2003–2010), (3) Children <18 y of age	(1) Selected <i>ICD-9</i> codes* (2) No (3) No	No evidence of an association between changes in guidelines and change in pediatric IE admissions. In secondary analyses, no change in IE hospitalizations among children 5–18 y of age or children with congenital heart disease and no detectable change in cases coded as streptococci	The study analyzed a large data set of 1157 pediatric IE cases.
Duval et al, <sup>13</sup> 2012	3 French regions covering 11 million inhabitants ≥20 y of age (population-based surveys)	Observational (pre/post) (1) Historical control, (2) 6 y after guidelines (survey years: 1991, 1999, 2008), (3) All ages	(1) Reported by microbiologist, strain confirmed with National Reference Centers (2) No (3) No	Scaling down AP indications was not associated with an increased incidence of oral streptococcal IE in the population or among patients with preexisting valve disease. There was an increase in staphylococcal IE in patients with previously known native valve disease.	French guidelines scaled back prophylaxis in 2002, similar to the 2007 AHA guidelines. This study also included data on dental procedures and use of AP before the episode of IE but no comparison group of patients who did not develop IE.
Bikdeli et al, <sup>14</sup> 2013	Medicare beneficiaries, United States (Medicare Inpatient Standard Analytic File)	Observational (pre/post) (1) Historical control, (2) 3 y after guidelines (1999–2010), (3) Adults ≥65 y of age	(1) No (2) No (3) No	No increase in adjusted rates of hospitalization or mortality associated with IE after 2007 AHA guidelines	Study noted a high burden of IE among older adults (70.6 per 100 000) but no trends attributable to guidelines change. Had limited data on exposures.
Dayer et al, <sup>8</sup> 2015	All National Health Services Centers in England, UK (England-wide monthly prescribing records and inpatient activity records—50 million population)	Observational (ecological; pre/post; interrupted time series with segmented regression) (1) Historical control, (2) 6 y after guidelines (January 2004–March 2013), (3) All ages	(1) No (2) Yes (3) Yes	AP prescriptions declined 79% after release of 2008 NICE guidelines and incidence of IE increased significantly (35 more cases per month above the historic trend). This increase was significant for both those at high risk and those at moderate/lower risk of IE.	This study provided longer follow-up on data presented in by Thornhill et al. <sup>7</sup> The observed percent increase in IE cases was much smaller than the percent decline in AP prescriptions.

(Continued)

Table 2. Continued

Author, year of publication	Population, setting, (data source)	Study design, includes: (1) Control, (2) Duration of follow-up, (3) Ages	Reported: (1) Microbiology data? (2) AP prescribing data? (3) Change in IE incidence after 2007?	Key results	Comments and key citations
DeSimone et al, <sup>10</sup> 2015	Olmstead County, MN (epidemiological data from the Rochester Epidemiology Project)	Observational (population-based pre/post analysis with multivariate Poisson model) (1) Historical, (2) 6 y of postguidelines follow-up (January 2007–December 2013), (3) Adults >18 y of age with IE (January 2007–December 2013)	(1) Yes—Laboratory data from medical record review (2) No (3) No	No significant change in overall incidence of IE; coagulase-negative staphylococcal IE trended downward over this period	The study included a small number of IE cases (51 in 2007–2013). Substantial demographic, clinical, and health system-level differences between Olmsted County and the rest of the United States limit generalizing of these findings. There is substantial overlap between the 3 DeSimone et al <sup>9–11</sup> articles.
DeSimone, et al, <sup>11</sup> 2015	Olmstead County, MN (epidemiological data from the Rochester Epidemiology Project)	Population-based survey for possible or definite cases of VGS-IE, compared with Nationwide Inpatient Sample discharge database for United States (multivariate Poisson model) (1) Historical, (2) 6 y after guidelines (January 1999–December 2013), (3) Adults >18 y of age	(1) Yes—Laboratory data from medical record review (2) No (3) No	Overall significant decline in incidence of IE; increased proportion of cases caused by <i>Staphylococcus aureus</i>	Small number of IE cases (51 in 2007–2013). Substantial demographic, clinical, and health system-level differences between Olmsted County and the rest of the United States limit generalizing of these findings. Substantial overlap between 3 DeSimone et al <sup>9–11</sup> articles. Superseded by the DeSimone et al <sup>15</sup> article (longer follow-up).
Pant et al, <sup>16</sup> 2015	US hospitals from participating states (National Inpatient Sample)	Observational (pre/post, segmented regression analysis) (1) Historical control, (2) 4 y of postguidelines follow-up (2000–2011), (3) All ages	(1) Yes—ICD-9 codes* (2) No (3) Yes	Significant rise in incidence of streptococcal IE but not staphylococcal IE after the 2007 guidelines. Authors noted no change in IE or valve surgery since 2007 guidelines. Data on VGS not provided.	Data on 457 052 IE cases in the United States from 2000–2011. Other investigators have raised methodological concerns about the statistical model used for this analysis. <sup>17,18</sup>
Mackie et al, <sup>19</sup> 2016	All Canadian hospitals except Quebec and Northern Territories (Canadian Institute for Health Information Discharge Abstract Database)	Observational (pre/post, piecewise linear regression model with a change-point analysis) (1) Historical control, (2) 5.5 y of postguidelines follow-up (April 2002–March 2013), (3) All ages	(1) ICD-9 or ICD-10 codes* (2) No (3) No	The number of cases of streptococcal IE decreased over time; this trend predated the 2007 AHA guidelines and continued unchanged after the guidelines were published.	The study included data on 9431 cases with some information about risk factors. <sup>20–22</sup> The presence of a cardiac rhythm device was found to be a risk factor for staphylococcal IE but not for streptococcal IE.
van den Brink et al, <sup>23</sup> 2017	All Dutch hospitals, the Netherlands (national health care insurance database extracted by the Dutch Healthcare Authority)	Observational (pre/post, interrupted time series) (1) Historical control, (2) 2 y of follow-up after 2009 ESC guidelines (2005–2011), (3) All ages	(1) ICD-9 or ICD-10 codes* (2) No (3) Yes	Steady increase in IE incidence between 2005 and 2011. After introduction of the 2009 ESC guidelines, IE incidence increased more than would be expected on the basis of historical trends. There was a significant increase in streptococcal IE cases.	The study included few cases of IE (216 between 2005 and 2011) and provided limited analytical details.
Keller et al, <sup>24</sup> 2017	All IE admissions to German hospitals (Nationwide Inpatient Statistic)	Observational (pre/post, linear regression) (1) Historical control, (2) 5 y after the revised ESC guidelines published (2005–2014), (3) All ages	(1) ICD-10 codes* (2) No (3) Yes	Increasing background rates of IE, with a 26% (unadjusted) increase after the 2009 ESC guidelines	The study included no individual-specific data on exposures.

(Continued)

Table 2. Continued

Author, year of publication	Population, setting, (data source)	Study design, includes: (1) Control, (2) Duration of follow-up, (3) Ages	Reported: (1) Microbiology data? (2) AP prescribing data? (3) Change in IE incidence after 2007?	Key results	Comments and key citations
Toyoda et al, <sup>25</sup> 2017	All hospitals participating in mandatory statewide databases in California and New York (California Office of Statewide Health Planning and Development and New York Planning and Research Cooperative System database)	Observational (multivariable Poisson regression adjusted for age, sex, and race; segmented regression analysis with variable time lags after guidelines change) (1) Historical control, (2) 6 y after AHA guidelines (1998–2013), (3) All ages	(1) ICD-9 codes* (2) No (3) No	Overall standardized incidence of IE was stable from 1998–2013; increase in standardized rate of staphylococcal IE but not streptococcal IE. No change in oral streptococcal IE after the 2007 AHA guidelines.	The study included limited individual-specific data on exposures and no information on dental procedures.
Sakai Bizmark et al, <sup>26</sup> 2017	US hospitals from participating states (Nationwide Inpatient Sample)	Observational (pre/post) (1) Historical control, (2) 5 y of postguidelines data (2001–2012), (3) Children <18 y of age	(1) ICD-9 codes* (2) No (3) No	Increasing background rates of IE hospitalizations in children; no change in IE before or after guidelines. However, a significant increase in incidence of IE caused by VGS was observed for children 10–17 y of age after AHA guidelines.	The study included many analyses (increasing the likelihood of a false-positive finding) and had limited individual-specific data on exposures.
Bates et al, <sup>27</sup> 2017	29 Children's hospitals, United States (Pediatric Health Information System Database)	Observational (pre/post, segmented regression analysis) (1) Historical control, (2) 7 y after guidelines (2003–2014), (3) Children <18 y of age	(1) No (2) No (3) No	Increasing background rates of IE; no change in IE after the 2007 AHA guidelines compared with before, including in children >5 y of age with CHD	
Thornhill et al, <sup>5</sup> 2018	Commercial health insurance, Medicaid, or Medicare supplemental insurance and linked prescription benefit data, United States (Truven Health MarketScan database)	Observational (pre/post, Poisson regression models) (1) Historical control, (2) 8 y after AHA guidelines (2003–2015), (3) Adults >18 y of age	(1) No (2) Yes (3) Yes	AP prescriptions declined 20% in high-risk, 64% in moderate-risk, and 52% in low- and unknown-risk groups. Compared with the baseline period, there was a slower decline in IE after the AHA guidelines. This was projected to result in 1.47 more cases of IE per month per 100 000 among moderate-risk patients and 19.53 more cases of IE per month per 100 000 among high-risk patients than what would have been expected if preguidelines trends had continued.	Variable AP practices among high-risk patients may imply that clinicians are having difficulty identifying patients for whom AP is currently recommended. A borderline significant increase in IE among moderate-risk patients despite a large decrease in AP prescriptions suggests that AP may not benefit the group as a whole. <sup>28</sup>
Garg et al, <sup>29</sup> 2019	All residents of Ontario, Canada (integrated province-wide claims data)	Observational (pre/post population-based, cross-sectional time series analysis) (1) Historical control, (2) 7 y after AHA guidelines (January 2002–December 2014), (3) Age ≥65 y (for AP prescriptions) and ≥18 y (for IE cases)	(1) Yes (2) Yes—for patients ≥65 y of age (3) Yes	Substantial reduction in AP prescriptions in the moderate-risk cohort after publication of the AHA 2007 guidelines. Minimal decrease followed by a slow increase in AP prescriptions in the high-risk group. Increasing rates of IE but a decrease in streptococcal IE over the study period. Change-point analyses suggested that the increase in IE in both high- and moderate-risk groups of patients ≥65 y of age occurred in the second half of 2010, 3 y after the AHA guidelines revision.	Because of the 3-y time lag between uptake of AHA guidelines (as noted by declining AP prescriptions), increase in IE in both high- and moderate-risk patients, and the observed decline in streptococcal IE over the study period, the authors concluded that the observed increase in IE is likely unrelated to the change in AP guidelines.

AHA indicates American Heart Association; AP, antibiotic prophylaxis; CHD, congenital heart disease; ESC, European Society for Cardiology; ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-10, *International Classification of Diseases, 10th Revision*; IE, infective endocarditis; NICE, National Institute for Health and Clinical Excellence; and VGS, viridans group streptococcal.

\*ICD-9 and ICD-10 coding of microbiological data is suboptimal in both completeness and accuracy. This is particularly important in IE because 2 of the most common pathogen groups (VGS and enterococcus) either lack specific codes (VGS) or had correct coding (enterococcus) only in the ICD-10 version; in the ICD-9 coding version, enterococcus was incorrectly designated as streptococcus.

the majority of the studies cited as being designed to test the impact and validity of the 2007 guidelines were actually designed to evaluate the impact of the recommendation on the risk of acquiring VGS IE, not on the risk of adverse outcome from VGS IE.

The writing group of the 2007 guidelines identified the 4 underlying cardiac conditions with the highest risk of adverse outcome from complications of VGS IE such as heart failure, need for cardiothoracic surgery, development of heart block requiring placement of a cardiac rhythm device, perivalvular extension and abscess, and other complications, including death. It is noteworthy that patients in 3 of the 4 groups at highest risk of adverse outcome from IE are also among the patients with the highest risk of acquisition of IE. In cardiac transplant recipients who develop valvulopathy, there are insufficient published data to accurately assess the risk of acquisition of IE. Among these 4 groups, a discussion of adverse outcome from VGS IE follows.

### **Group 1: Prosthetic Cardiac Valve or Prosthetic Material Used for Cardiac Valve Repair or Other Implantable Cardiac Devices Such as Transcatheter Aortic Valve Implantation**

Outcomes of patients with prosthetic valve endocarditis caused by VGS were evaluated and compared with outcomes of patients with native valve IE caused by VGS. The mortality rate of patients with VGS prosthetic valve endocarditis is  $\geq 20\%$ ,<sup>32–35</sup> in contrast to  $\leq 5\%$  in patients with native valve VGS IE.<sup>34,36,37</sup>

Moreover, patients with prosthetic valve endocarditis are more likely than those with native valve IE to develop heart failure or heart block or to require cardiac valve replacement surgery because of perivalvular extension, abscess, and other complications.

Advances in cardiac device development in this high-risk category of patients since publication of the 2007 guidelines are remarkable. They include a marked increase in the number of patients undergoing transcatheter implantation of prosthetic aortic valves or transcatheter placement of other cardiac valves. There are limited published data on IE complicating these procedures. Most infections in these patients are caused by staphylococci or enterococci and are associated with a high risk of morbidity and mortality.<sup>15,38–40</sup> Patient selection has influenced the risks because the initial use of transcatheter prosthetic valve placement was directed toward patients who were too ill or elderly to undergo open cardiovascular valve replacement surgery. Patients who undergo transcatheter prosthetic valve placement warrant AP for a dental procedure just like patients with surgically placed prosthetic valves.

Cardiac valve repair is another area of rapid growth, including the use of devices that include annuloplasty rings and clips. Although data on VGS IE outcomes related to the use of these repair devices are limited, patients who undergo transcatheter or open surgical valve repair with a prosthetic device warrant AP for a dental procedure because, should the prosthetic material become infected, many of them are too ill for open surgical valve placement.

VGS are an uncommon cause of infections complicating left ventricular assist devices or infection of an implantable heart. However, because the risk of morbidity and mortality is so high from an infection of these devices caused by any microorganism, AP for a dental procedure is suggested.

A variety of other prosthetic cardiovascular devices deserve comment. These include cardiovascular implantable electronic devices; septal defect closure devices (when there is complete defect closure); peripheral vascular grafts and patches, including those used for hemodialysis and coronary and other vascular stents; central nervous system ventriculoatrial shunts; vena caval filters; and pledgets. Infections of these devices are rare, and when they occur, most cases are caused by staphylococci. Therefore, AP for a dental procedure in these patients is not suggested.

### **Group 2: Previous, Relapse, or Recurrent IE**

Patients with a history of IE who develop relapse or recurrent IE are at greater risk of heart failure and increased need for cardiac valve replacement surgery and have a higher mortality than patients with a first episode of native valve IE.<sup>41–48</sup> Patients with multiple episodes of native or prosthetic valve IE are at greater risk of additional episodes of endocarditis, each of which is associated with the risk of more serious complications.<sup>49</sup> AP for a dental procedure is suggested for these patients.

### **Group 3: Congenital Heart Disease**

Congenital heart disease (CHD) is the most common underlying condition in children at risk for IE in middle- and high-income countries. Retrospective series and registry-based publications confirm that patients with complex cyanotic heart disease and those who have postoperative palliative shunts, conduits, or other prostheses are at highest risk of developing IE.<sup>50</sup> Since the 2007 guidelines, several publications have focused on IE in the growing global population of patients with adult CHD. Other studies evaluated the risk of IE in children and adults with CHD who undergo surgical or transcatheter pulmonary valve replacement. However, no definitive studies have evaluated the risk from IE among the various types of CHD. The data on the risk

of developing IE in those with CHD are consistent and have not shown an increase in VGS IE since the 2007 guidelines. CHD was found in 68% of patients admitted with IE between 2003 and 2010 according to the Pediatric Health Information System database.<sup>12</sup> There was no change in the frequency of IE in the period after the 2007 guidelines compared with the period before publication, and this lack of change was found again in a follow-up study tracking hospitalizations through 2014.<sup>27</sup> The discharge incidence of IE in children in the United States according to the Nationwide Inpatient Sample was 0.43 per 100 000 between 2000 and 2010 and was unchanged over the study period after the 2007 AHA guidelines. Underlying heart conditions were present in 53.5% of the total patients studied and 81.4% of those with CHD.<sup>51</sup> In a Taiwanese study, the incidence of IE was 1.11 per 1000 person-years in a database of 24 729 children with CHD and cardiac lesions, and the highest risks of IE were seen in those with cyanotic defects, endocardial cushion defects, left-sided lesions, and ventricular septal defects.<sup>52</sup> The risk of IE was increased in children who underwent the following procedures: central venous catheter insertion, cardiac catheterization, open heart surgery (higher with valve procedures), and shunt. In this study, dental procedures did not increase the risk of IE regardless of whether antibiotics were used before the procedures.<sup>52</sup>

Other recent studies of IE in adult CHD also reveal consistent findings. The Netherlands' CONCOR Registry (Congenital Cor Vitia) of >14 000 patients with adult CHD reported an overall incidence of IE of 1.33 cases per 1000 person-years, which was similar to that observed in other studies.<sup>53,54</sup> Use of prosthetic valve material was the only statistically significant procedural risk factor in the multivariate analysis (hazard ratio, 5.48 [95% CI, 3.58–8.38]). Pulmonary atresia/ventricular septal defect had the highest incidence (7.84 cases [95% CI, 3.77–14.13] per 1000 patient-years) and was the only statistically significant diagnostic risk factor (hazard ratio, 2.65 [95% CI, 1.12–6.24]) in multivariate analysis.

In addition to the clear evidence relating CHD subtypes to increased risk of IE and although there has been no definitive study defining the conditions at risk from VGS IE, there is recent information relating the risk from IE in the right ventricle to pulmonary artery conduits and surgical and catheter-based valve replacement. A systematic review of 50 studies found that the incidence of IE was higher for bovine jugular valve grafts compared with other right ventricle-to-pulmonary artery conduits (5.4% versus 1.2%;  $P < 0.0001$ ) during a median follow-up period of 24 and 36 months. This increased risk of IE may be related to the type of bovine-derived bioprosthetic material. With the use of this material, there was no difference

in IE development between surgical and catheter-based implantation, and in vitro studies suggested that the increased risk for IE may be related to the anatomic specifics of the bovine jugular vein systems used in many of the implanted devices.<sup>55</sup> To date, in every circumstance, when this material has been used, IE in implanted devices for CHD has required cardiac surgery to repair the infection-related consequences. Other studies have also shown the risk of IE to be consequential after Melody valve placement, as high as 3.2% to 25%; morbidity is high in all cases of IE in device implantations.<sup>56</sup> In accordance with the position of the writing group concerning these scenarios, AP for a dental procedure is suggested for these groups of patients in whom morbidity is high from IE, although there is no proven benefit.

#### Group 4: Cardiac Transplant Recipients

There are insufficient published data to accurately assess the risk of adverse outcome from IE in cardiac transplant recipients who develop valvulopathy. However, these patients are immunosuppressed, have multiple underlying comorbidities, and are at high risk of adverse outcome from any infection, including IE, and AP is suggested.

#### Summary

There is no convincing evidence from retrospective and observational studies that there was an increase in frequency of and morbidity or mortality from VGS IE since 2007 in the 4 high-risk groups defined in the 2007 guidelines. We cannot exclude the possibility that there may be an exceedingly small number of cases of VGS IE that could be prevented by AP for a dental procedure. However, if prophylaxis is effective, we believe that such therapy should be suggested only for those with the highest risk of adverse outcome from VGS IE, although we acknowledge that the effectiveness of such prophylaxis is unproven. The change in emphasis to suggest prophylaxis for only those patients with the highest risk of adverse outcome from VGS IE reduces uncertainties among patients and providers about who should receive prophylaxis for a dental procedure. Randomized controlled studies are necessary to resolve the issue of the efficacy of AP in preventing VGS IE. Until such studies are published, our extensive review suggests that after more than a decade since implementation, the 2007 guidelines adequately provide VGS IE AP for those patients with the highest risk of adverse outcome. We believe that there is no need to reconsider the novel concept of suggesting AP for individuals at high risk of adverse outcome from VGS IE outlined in the 2007 AHA guidelines (Table 3).



**Table 3. AP for a Dental Procedure: Underlying Conditions for Which AP Is Suggested**

Prosthetic cardiac valve or material
Presence of cardiac prosthetic valve
Transcatheter implantation of prosthetic valves
Cardiac valve repair with devices, including annuloplasty, rings, or clips
Left ventricular assist devices or implantable heart
Previous, relapse, or recurrent IE
CHD
Unrepaired cyanotic congenital CHD, including palliative shunts and conduits.
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by transcatheter during the first 6 mo after the procedure
Repaired CHD with residual defects at the site of or adjacent to the site of a prosthetic patch or prosthetic device
Surgical or transcatheter pulmonary artery valve or conduit placement such as Melody valve and Contegra conduit
Cardiac transplant recipients who develop cardiac valvulopathy
AP for a dental procedure not suggested
Implantable electronic devices such as a pacemaker or similar devices
Septal defect closure devices when complete closure is achieved
Peripheral vascular grafts and patches, including those used for hemodialysis
Coronary artery stents or other vascular stents
CNS ventriculoatrial shunts
Vena cava filters
Pledgets

AP indicates antibiotic prophylaxis; CHD, congenital heart disease; CNS, central nervous system; and IE, infective endocarditis.

## FEASIBILITY OF INCLUDING ADDITIONAL HIGH-RISK GROUPS

**Question:** Should the 4 categories of highest risk of adverse outcome be expanded to include patients with rheumatic heart disease, aortic stenosis, bicuspid aortic valve, mitral valve prolapse, or other valvar heart disease?

The 2007 guidelines no longer recommended AP for dental procedures for patients considered to be at moderate or low risk of adverse outcome from VGS IE. VGS IE or IE caused by another microorganism, regardless of the underlying cardiac condition, is a serious, life-threatening infection. Comorbid factors such as older age, obesity, diabetes, cardiopulmonary disease, vascular disease, hemodialysis, lack of access to a tertiary medical center, and immunosuppression and numerous other conditions affect morbidity and mortality in any patient with IE caused by VGS or by another microorganism.

A recent study by Thornhill et al<sup>20</sup> evaluated the risk of acquisition of IE and deaths resulting from IE among >50 million patients in the United Kingdom with

underlying cardiac risk factors. Their study confirmed the high risk of adverse outcomes in categories in the 2007 guidelines that included patients with previous IE, those with prosthetic valve replacement, and some patients with complex cyanotic CHD. However, patients in the moderate-risk group with rheumatic heart disease and congenital valve abnormalities had mortality rates similar to those in the high-risk group. These authors and others<sup>57</sup> questioned whether the AHA risk classification should be reconsidered. The study by Thornhill et al<sup>41</sup> did not report microorganism-specific data. Multiple studies, including those by these authors, reported an increase in the frequency of IE caused by *Staphylococcus aureus* and an unchanged or decreased frequency of IE caused by VGS.<sup>20</sup> Because the incidence of *S aureus* IE is increasing and the incidence of VGS IE is flat or decreasing, it is difficult to determine from the Thornhill et al study whether the high mortality in patients with rheumatic heart disease or congenital valvar disease was attributable to IE caused by microorganisms other than VGS, especially *S aureus*. IE caused by *S aureus*, enteric Gram-negative bacilli, or enterococci is associated with a higher morbidity and mortality with any underlying cardiac condition than IE caused by VGS, including in those with rheumatic heart disease and congenital valve disease. The administration of AP for a dental procedure, if effective, is intended only for the prevention of IE caused by VGS, not for prevention of IE caused by other microorganisms.

A recent multicenter study by Zegri-Reiriz et al<sup>58</sup> of 3208 patients reported that patients with bicuspid aortic valve or mitral valve prolapse had a high incidence of intracardiac complication and a need for surgery similar to that in the high-risk group of patients. The mortality of these patients was significantly lower than the mortality for high-risk patients. This finding possibly reflected lower patient age and fewer comorbidities but also that native valve replacement is associated with a lower risk of serious complications than surgery for infected prosthetic implanted material.

Reclassification of the risk categories to include patients previously classified as at low or moderate risk of adverse outcome would greatly expand the number of patients who qualify for AP for a dental procedure. The administration of prophylactic antibiotics is not risk free, even in those who receive only a single dose for prophylaxis. The emergence of multidrug-resistant microorganisms, including VGS, is a global threat. Antibiotic stewardship is now a major component of combating the development of resistance and cost control.

AP for a dental procedure targets a limited segment of bacterial endocarditis, specifically VGS IE in patients with the highest risk of adverse outcome. Outcomes of patients with IE caused by any microorganism, regardless of the underlying condition, are negatively affected by comorbidities or insufficient access to diagnostic, medical,

**Table 4. Dental Procedures and AP**

AP suggested
All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
AP not suggested
Anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of primary teeth, and bleeding from trauma to the lips or oral mucosa

The antibiotic regimens suggested for prophylaxis for a dental procedure in patients at a high risk of adverse outcome from viridans group streptococcal infective endocarditis are shown in Table 5.

AP indicates antibiotic prophylaxis.

and surgical care. This is reflected in the high mortality of IE, regardless of microbiological cause, in patients with rheumatic heart disease in high-prevalence settings.<sup>59</sup> Shared decision making remains an especially important approach in the populations most affected by limited access to the full spectrum of health care. These factors and those discussed previously do not warrant a change in the suggestion against AP for dental procedures in patients at low or moderate risk of adverse outcome from VGS IE as defined in the 2007 AHA guidelines.

In the 4 categories of patients with the highest risk of adverse outcome from VGS IE, the dental procedures for which AP is suggested or is not suggested are shown in Table 4.

## PROPHYLACTIC ANTIBIOTIC THERAPY FOR A DENTAL PROCEDURE: CONSIDERATIONS FOR PRACTITIONERS

### Adverse Drug Reactions

Fortunately, the overall risks of a serious adverse reaction such as hives, angioedema, and anaphylaxis are low for an antibiotic when used for prophylaxis for a dental procedure. A recent study in the United Kingdom suggested that a single dose of clindamycin may cause complications, including death, from *Clostridioides difficile* infection.<sup>59a</sup> Clindamycin may cause more frequent and severe reactions than other antibiotics used for AP, and its use is no longer suggested in this document. Up to 15% of community-acquired *C difficile* infection may be attributable to antibiotics prescribed for a dental procedure.<sup>60</sup> Fatal anaphylaxis from a single dose of a cephalosporin in patients with no history of a serious reaction is estimated to be <1 per 1 million doses.<sup>61,62</sup> Fatal reactions to a single dose of a macrolide are extremely rare.<sup>61,62</sup> Hancox and colleagues<sup>63</sup> reviewed the risk of a serious cardiovascular event, especially torsades des pointes with ventricular tachycardia, from azithromycin use in patients with a prolonged QTc interval of >450

milliseconds as detected by ECG. Therefore, these drugs should be used with caution in patients who are known to have a prolonged QTc interval. Doxycycline is an alternative in patients who are unable to tolerate a penicillin, cephalosporin, or macrolide. A serious reaction from a single dose of doxycycline is extremely rare.

Although patients may be labeled as allergic to penicillin or its derivatives, penicillin skin testing is negative in the vast majority ( $\approx 90\%$ ) of these patients, and these patients sustain no increase in adverse drug events compared with the general population when penicillin is administered.<sup>64,65</sup> A careful history should be obtained of the type and severity of allergic reaction to a penicillin. Although the expense or availability of expert allergy evaluation, which may include penicillin skin testing, may make it unavailable in some populations, we suggest that skin testing should be done if feasible.

### Development of Resistance

The inappropriate use of antibiotics is an issue of major worldwide concern, especially because it may result in the development of antibiotic resistance. The Centers for Disease Control and Prevention estimate that antibiotic-resistant infections cause 23 000 deaths, 2 million infections, and as much as \$20 billion in excess direct health care costs annually in the United States. Antibiotic stewardship is considered essential to maintain our ability to manage life-threatening infections by ensuring that antibiotics are used only in situations in which they are necessary and effective, that the most appropriate antibiotic choice is made, and that the dosage regimen used will be effective while avoiding the development of antibiotic resistance.

Concerning AP of IE in the dental setting, there are 2 areas of concern in antibiotic resistance among VGS. First, what is the level of resistance among VGS as part of the normal flora? VGS recovered from a variety of patient populations exhibited variable degrees of in vitro resistance to the oral antibiotics advocated for use as prophylaxis in the 2007 AHA guidelines. In particular, the rates of resistance to azithromycin and clarithromycin were higher than that for penicillin. Despite the recognition of in vitro resistance among some strains of VGS, the 2007 writing group made no changes in recommended antibiotics for dental prophylaxis. There is a difference between the use of an antibiotic to treat an established infection and the use of an antibiotic for prophylaxis. Treatment of an established infection requires the use of an antibiotic active in vitro against a specific pathogen. Prophylactic antibiotics are administered in a single dose for a low-magnitude, transient exposure to a microorganism. Studies done in animal models of experimental IE showed that prophylactic antibiotic therapy may be effective, even against VGS with variable susceptibility.<sup>66,67</sup>

**Table 5. Antibiotic Regimens for a Dental Procedure Regimen: Single Dose 30 to 60 Minutes Before Procedure**

Situation	Agent	Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin OR	2 g IM or IV	50 mg/kg IM or IV
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillin or ampicillin—oral	Cephalexin* OR	2 g	50 mg/kg
	Azithromycin or clarithromycin OR	500 mg	15 mg/kg
	Doxycycline	100 mg	<45 kg, 2.2 mg/kg >45 kg, 100 mg
Allergic to penicillin or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV

Clindamycin is no longer recommended for antibiotic prophylaxis for a dental procedure.

IM indicates intramuscular; and IV, intravenous.

\*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosing.

†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticarial with penicillin or ampicillin.

Second, for patients who require serial invasive dental procedures over a relatively short period (days or weeks) of time, what is the likelihood that AP will result in the selection of antibiotic resistance among colonizing strains of VGS? An investigation that included 29 young (mean age, 30 years) healthy volunteers reported that 21% were colonized with amoxicillin-resistant VGS before receiving a single-dose of 2 g amoxicillin.<sup>68</sup> The rate of resistance increased to 31% after amoxicillin dosing, and the proportion with reduced susceptibility to amoxicillin increased significantly on days 2 and 5 of treatment after dosing of amoxicillin and persisted for 24 days. An analysis of a 3-g sachet oral single dosing of amoxicillin in a study done in the United Kingdom demonstrated a nonsignificant increase in the number of resistant streptococci by day 3 that returned to baseline values by 21 days after amoxicillin dosing.<sup>69</sup> When this antibiotic was given at weekly intervals, the numbers of resistant VGS increased significantly after the second and third doses of amoxicillin and persisted for 4 to 7 weeks. These authors suggest that for at-risk patients requiring repeated dental procedures likely to result in bacteremia, either an alternative antibiotic regimen should be used each time, or there should be intervals of at least 4 weeks between treatment sessions.

## Other Considerations

It is not possible to make suggestions for AP that deal with every possible circumstance of every possible situation in every possible hypothetical situation. In most circumstances that fall outside the specific suggestions in Table 5, clinical judgment and shared decision

making with the patient are important. Some circumstances that occur frequently are discussed briefly here.

If AP is inadvertently not administered before a dental procedure, then it may be administered up to 2 hours after the procedure. In patients who are receiving a short course (7–10 days) of oral antibiotic therapy before a dental procedure, it is preferable to select a different class of antibiotic listed in Table 5. If possible, it is preferable to delay an elective dental procedure for at least 10 days after completion of a short course of antibiotic therapy. In patients undergoing multiple sequential dental appointments, if possible, it is preferable to delay the next procedure for 10 days after the last dose of antibiotic therapy. In patients who are receiving parenteral antimicrobial therapy for IE or other infections and require a dental procedure, the same parenteral antibiotic may be continued through the dental procedure.

## Cost-Effectiveness of AP

There are no high-quality cost-effectiveness analyses in the United States that examined the contemporary cost-effectiveness of AP from a US health system perspective. Franklin and colleagues<sup>70</sup> evaluated the cost-effectiveness of AP for IE in the British National Health Service, using a lifetime (50 years) analytical horizon and appropriate discounting for future costs and clinical outcomes. They concluded that AP in the United Kingdom was less costly and more effective than no AP for all patients at risk of IE, and they suggested that annual cost savings of £5.5 to £8.2 million and >2600 quality-adjusted life-years could be achieved. Given the methodological limitations of the analysis, it is likely that the risk of IE modeled in this analysis was a substantial overestimate, which would make AP appear to be more cost-effective than it truly is. Franklin and colleagues advocate for changing the NICE guidelines to restore AP for patients at high risk of adverse outcome from IE, thus making NICE recommendations concordant with the AHA and European Society of Cardiology guidelines. However, extrapolating from one health system to the other is particularly challenging because of large differences in costs and clinical outcomes among health systems.

## COMMUNICATION AND IMPLEMENTATION OF SUGGESTIONS IN THE 2021 AHA SCIENTIFIC STATEMENT

Clinical practice guidelines provide a compilation of quality-assessed evidence with critical evaluation by leading experts in the field with resultant recommendations that are highly desired by health care providers to guide complicated clinical decision making. Extensive communication of major updates and

recommendations to medical and dental health care providers is a major task of every update. Given the variability of patient populations and clinical practices, there may be patients and providers who may not adhere to every suggestion.

Variable compliance with IE prevention recommendations has been documented within and outside the United States. An appreciation of the patient groups for whom AP is recommended has been incompletely adopted by health care providers for decades; AP continues to be provided to some patients for whom it is no longer recommended and withheld from others for whom it is advised. Moreover, there are instances when providers disagree with recommendations or when patients request treatment that falls outside the guidelines.

The decision to use antibiotics before a dental procedure in hopes of avoiding VGS IE rests with both provider and patient. Shared clinical decision making improves outcomes, patient experience, and compliance. Informing patients of their choices and describing the potential risks and benefits of options in a way appropriate to the patient's health literacy help patients make informed decisions and develop an implementation plan.<sup>71,72</sup> It should be emphasized to the patient that there is no proven benefit from AP to prevent VGS IE from a dental procedure, and there are risks from administration of AP.

Communication of the shared decision among patients and care providers will improve the value of that conversation and, we hope, improve compliance with the AP suggestions. Ideally, the shared decision made for AP should be communicated to the dental health care provider directly or through patient materials. If this cannot be done through accessible medical records, then clear communication, with documentation, via the patient may be necessary to inform future interactions with the dental health care provider. The larger goal and greater opportunity of the critical conversation between the health care provider and the patient at risk of acquisition or adverse outcome from VGS IE go beyond making a decision about AP strategy. It is the time to optimize prevention of VGS IE by multiple approaches. This optimization includes a focus on dental health, risk stratification, avoidance of comorbidities and contributory risks, and vigilance for infection.

Current scientific data suggest that maintaining good oral health care in patients at risk of or from VGS IE has a major impact on preventing bacteremia with VGS from routine daily activities such as toothbrushing.<sup>73</sup> Because routine daily activities result in transient VGS bacteremia at a much higher frequency than a single dental procedure, optimizing oral health has a major impact on preventing VGS IE. Ideally, patients should receive biannual dental care. Often, because of lack of insurance or affordability, access to regular

**Table 6. Summary of Findings and Suggestions**

Key findings
VGS IE is much more likely to develop as a result of transient VGS bacteremia attributable to routine daily activities such as chewing food and toothbrushing than from a dental procedure.
An exceedingly small number of cases of VGS IE could be prevented by AP for a dental procedure, even if prophylaxis is 100% effective.
If AP for a dental procedure is effective in preventing a very small number of cases of VGS IE, it should be suggested only for those patients with the highest risk of adverse outcome from VGS IE.
There is no convincing evidence of an increased frequency of or morbidity or mortality from VGS IE in patients at low, moderate, or high risk of adverse outcome since publication of the 2007 document.
AP for a dental procedure is not suggested solely on the basis of an increased lifetime risk of acquisition of VGS IE
Suggestions
AP for a dental procedure that involves manipulation of gingival tissues, periapical region of teeth, or perforation of the oral mucosa is suggested only for patients with the highest risk of adverse outcome from VGS IE.
Maintenance of good oral health and regular access to dental care are considered more important to prevent VGS IE than AP for a dental procedure. We suggest that patients have biannual dental examinations when such care is available.
Shared decision making is important between patients and health care providers. There may be instances when a health care provider and a patient disagree with the suggestions in the 2021 scientific statement. In these cases, the health care provider should be familiar with and understand the 2021 suggestions to adequately inform patients of the risks and benefits of AP for a dental procedure so that an informed decision may be made.

AP indicates antibiotic prophylaxis; IE, infective endocarditis; and VGS, viridans group streptococcal.

dental care is limited for some patients. This is especially important in those patients at risk of the highest adverse outcome from VGS IE. The writing group recognizes the importance of connecting patients with a social worker or other services to facilitate access to dental care and assistance with insurance for dental coverage.

Circumstances relevant to inadequate patient access to care may strongly influence the risk of adverse outcome from VGS IE. For all patients with an increased risk of or from VGS IE, a plan for responding to IE symptoms should be reinforced at every health care contact. Patients should be aware of fever and other constitutional symptoms that raise concern about IE as the cause. These conditions should prompt contact with a health care provider for evaluation with blood cultures obtained before the initiation of antibiotics, regardless of the presumed cause of fever. The hope is that an early diagnosis of IE will result in improved patient outcomes. This is especially important for patients without ready access to health care. Empowering them with this information will encourage them and their families to seek and advocate for early care.

A summary of findings and suggestions is given in Table 6.

## ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on October 2, 2020, and the American Heart Association Executive Committee on October 27, 2020. A copy of the document is available at <https://professional.heart.org/statements> by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com.

The American Heart Association requests that this document be cited as follows: Wilson WR, Gewitz M, Lockhart PB, Bolger AF, DeSimone DC, Kazi DS, Couper DJ, Beaton A, Kilmartin C, Miro JM, Sable C, Jackson MA, Baddour LM; on behalf of the American Heart Association Young Hearts Rheumatic Fever, Endocarditis and Kawasaki Disease Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Cardiovascular and Stroke Nursing; and the Council on Quality of Care and Outcomes Research. Prevention of viridans group streptococcal infective

endocarditis: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e963–e978. doi: 10.1161/CIR.0000000000000969

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## Acknowledgments

The writing group acknowledges the lifetime contributions of David T. Durack, MD, PhD, in the field of endocarditis. Dr Durack was among the first to question the efficacy of AP for a dental procedure to prevent viridans group streptococcal endocarditis. His work was foundational to the categorical revisions published in the 2007 AHA document on prevention of endocarditis. The writing group thanks Lori Hinrichs for her superb assistance with the preparation of the manuscript.

## Disclosures

### Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
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Craig Sable	Children's National Medical Center	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

## Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
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Michael H. Picard	Massachusetts General Hospital	NHLBI (research support [collaborator])†; Actelion (support for core laboratory services [no direct compensation])†; Philips Healthcare (research support [no direct compensation])*	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

## REFERENCES

- Wilson W, Taubert KA, Gewirtz M, Lockhart PB, Baddour LM, Levison M, Bolger A, Cabell CH, Takahashi M, Baltimore RS, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116:1736–1754. doi: 10.1161/CIRCULATIONAHA.106.183095
- Lockhart PB, Hanson NB, Ristic H, Menezes AR, Baddour L. Acceptance among and impact on dental practitioners and patients of American Heart Association recommendations for antibiotic prophylaxis. *J Am Dent Assoc*. 2013;144:1030–1035. doi: 10.14219/jada.archive.2013.0230
- Jain P, Stevenson T, Sheppard A, Rankin K, Compton SM, Prushing W, Anderson R, Islam S, Mackie AS. Antibiotic prophylaxis for infective endocarditis: knowledge and implementation of American Heart Association guidelines among dentists and dental hygienists in Alberta, Canada. *J Am Dent Assoc*. 2015;146:743–750. doi: 10.1016/j.adaj.2015.03.021
- DeSimone DC, El Rafei A, Challener DW, Carr AB, Kelly JA, Rocca WA, St Sauver JL, Bock-Goodner CM, Lahr BD, Steckelberg JM, et al. Effect of the American Heart Association 2007 guidelines on the practice of dental prophylaxis for the prevention of infective endocarditis in Olmsted County, Minnesota. *Mayo Clin Proc*. 2017;92:881–889. doi: 10.1016/j.mayocp.2017.03.013
- Thornhill MH, Gibson TB, Cutler E, Dayer MJ, Chu VH, Lockhart PB, O'Gara PT, Baddour LM. Antibiotic prophylaxis and incidence of endocarditis before and after the 2007 AHA recommendations. *J Am Coll Cardiol*. 2018;72:2443–2454. doi: 10.1016/j.jacc.2018.08.2178
- Rogers AM, Schiller NB. Impact of the first nine months of revised infective endocarditis prophylaxis guidelines at a university hospital: so far so good. *J Am Soc Echocardiogr*. 2008;21:775. doi: 10.1016/j.echo.2008.04.001
- Thornhill MH, Dayer MJ, Forde JM, Corey GR, Chu VH, Couper DJ, Lockhart PB. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. *BMJ*. 2011;342:d2392. doi: 10.1136/bmj.d2392
- Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis. *Lancet*. 2015;385:1219–1228. doi: 10.1016/S0140-6736(14)62007-9
- DeSimone DC, Tleyjeh IM, Correa de Sa DD, Anavekar NS, Lahr BD, Sohail MR, Steckelberg JM, Wilson WR, Baddour LM; for the Mayo Cardiovascular Infections Study Group. Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines. *Circulation*. 2012;126:60–64. doi: 10.1161/CIRCULATIONAHA.112.095281
- DeSimone DC, Tleyjeh IM, Correa de Sa DD, Anavekar NS, Lahr BD, Sohail MR, Steckelberg JM, Wilson WR, Baddour LM. Temporal trends in infective endocarditis epidemiology from 2007 to 2013 in Olmsted County, MN. *Am Heart J*. 2015;170:830–836. doi: 10.1016/j.ahj.2015.07.007
- DeSimone DC, Tleyjeh IM, Correa de Sa DD, Anavekar NS, Lahr BD, Sohail MR, Steckelberg JM, Wilson WR, Baddour LM; Mayo Cardiovascular Infections Study Group. Incidence of infective endocarditis due to viridans group streptococci before and after the 2007 American Heart Association's prevention guidelines: an extended evaluation of the Olmsted County, Minnesota, Population and Nationwide Inpatient Sample. *Mayo Clin Proc*. 2015;90:874–881. doi: 10.1016/j.mayocp.2015.04.019
- Pasquali SK, He X, Mohamad Z, McCrindle BW, Newburger JW, Li JS, Shah SS. Trends in endocarditis hospitalizations at US children's hospitals: impact of the 2007 American Heart Association antibiotic prophylaxis guidelines. *Am Heart J*. 2012;163:894–899. doi: 10.1016/j.ahj.2012.03.002
- Duval X, Delahaye F, Alla F, Tattevin P, Obadia JF, Le Moing V, Doco-Lecompte T, Celard M, Poyart C, Strady C, et al; AEPEI Study Group. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: three successive population-based surveys. *J Am Coll Cardiol*. 2012;59:1968–1976. doi: 10.1016/j.jacc.2012.02.029
- Bikdeli B, Wang Y, Kim N, Desai MM, Quagliarello V, Krumholz HM. Trends in hospitalization rates and outcomes of endocarditis among Medicare beneficiaries. *J Am Coll Cardiol*. 2013;62:2217–2226. doi: 10.1016/j.jacc.2013.07.071
- Loverix L, Juvonen T, Biancarfi F. Prosthetic endocarditis after transcatheter aortic valve implantation: pooled individual patient outcome. *Int J Cardiol*. 2015;178:67–68. doi: 10.1016/j.ijcard.2014.10.136
- Pant S, Patel NJ, Deshmukh A, Golwala H, Patel N, Badheka A, Hirsch GA, Mehta JL. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol*. 2015;65:2070–2076. doi: 10.1016/j.jacc.2015.03.518

17. Kazi DS, Bolger AF. Caveat emptor: antibiotics, endocarditis, and statistical artifacts. *J Am Coll Cardiol*. 2016;67:2088–2090. doi: 10.1016/j.jacc.2015.09.116
18. Pant S, Patel S, Patel N, Deshmukh A, Mehta JL. Reply: caveat emptor: antibiotics, endocarditis, and statistical artifacts. *J Am Coll Cardiol*. 2016;67:2090–2091. doi: 10.1016/j.jacc.2016.01.075
19. Mackie AS, Liu W, Savu A, Marelli AJ, Kaul P. Infective endocarditis hospitalizations before and after the 2007 American Heart Association prophylaxis guidelines. *Can J Cardiol*. 2016;32:942–948. doi: 10.1016/j.cjca.2015.09.021
20. Thornhill MH, Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB. The effect of antibiotic prophylaxis guidelines on incidence of infective endocarditis. *Can J Cardiol*. 2016;32:1578.e9. doi: 10.1016/j.cjca.2016.02.074
21. Morris AM, Webb GD. What to think about antibiotic prophylaxis and infective endocarditis. *Can J Cardiol*. 2016;32:933–934. doi: 10.1016/j.cjca.2015.10.014
22. Mackie AS, Liu W, Savu A, Marelli AJ, Kaul P. Reply to letter from Thornhill et al: infective endocarditis hospitalizations before and after the 2007 American Heart Association prophylaxis guidelines. *Can J Cardiol*. 2016;32:1578.e11. doi: 10.1016/j.cjca.2016.04.002
23. van den Brink FS, Swaans MJ, Hoogendijk MG, Alipour A, Kelder JC, Jaarsma W, Eefting FD, Groenmeijer B, Kupper AJF, Ten Berg JM. Increased incidence of infective endocarditis after the 2009 European Society of Cardiology guideline update: a nationwide study in the Netherlands. *Eur Heart J Qual Care Clin Outcomes*. 2017;3:141–147. doi: 10.1093/ehjqcco/qcw039
24. Keller K, von Bardeleben RS, Ostad MA, Hobohm L, Munzel T, Konstantinides S, Lankeit M. Temporal trends in the prevalence of infective endocarditis in Germany between 2005 and 2014. *Am J Cardiol*. 2017;119:317–322. doi: 10.1016/j.amjcard.2016.09.035
25. Toyoda N, Chikwe J, Itagaki S, Gelijns AC, Adams DH, Egorova NN. Trends in infective endocarditis in California and New York State, 1998–2013. *JAMA*. 2017;317:1652–1660. doi: 10.1001/jama.2017.4287
26. Sakai Bizmark R, Chang RR, Tsugawa Y, Zangwill KM, Kawachi I. Impact of AHA's 2007 guideline change on incidence of infective endocarditis in infants and children. *Am Heart J*. 2017;189:110–119. doi: 10.1016/j.ahj.2017.04.006
27. Bates KE, Hall M, Shah SS, Hill KD, Pasquali SK. Trends in infective endocarditis hospitalizations at United States children's hospitals from 2003 to 2014: impact of the 2007 American Heart Association antibiotic prophylaxis guidelines. *Cardiol Young*. 2017;27:686–690. doi: 10.1017/S1047951116001086
28. Bolger AF. Preventing endocarditis: no rest for the worrier. *J Am Coll Cardiol*. 2018;72:2455–2456. doi: 10.1016/j.jacc.2018.09.025
29. Garg P, Ko DT, Bray Jenkyn KM, Li L, Shariff SZ. Infective endocarditis hospitalizations and antibiotic prophylaxis rates before and after the 2007 American Heart Association guideline revision. *Circulation*. 2019;140:170–180. doi: 10.1161/CIRCULATIONAHA.118.037657
30. National Institute for Health and Care Excellence. Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. 2008. Accessed March 17, 2008. <https://www.nice.org.uk/CG64>.
31. Quan TP, Muller-Pebody B, Fawcett N, Young BC, Minaji M, Sandoe J, Hopkins S, Crook D, Peto T, Johnson AP, et al. Investigation of the impact of the NICE guidelines regarding antibiotic prophylaxis during invasive dental procedures on the incidence of infective endocarditis in England: an electronic health records study. *BMC Med*. 2020;18:84. doi: 10.1186/s12916-020-01531-y
32. Baddour LM, Wilson WR. Infections of prosthetic valves and other cardiovascular devices. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Elsevier Churchill Livingstone; 2005:1022–1044.
33. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Bolger AF, Levison ME, Ferrieri P, Gerber MA, Tani LY, Gewitz MH, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association [published corrections appear in *Circulation*. 2005;112:2373; *Circulation*. 2007;115:e408; *Circulation*. 2007;116:e547; and *Circulation*. 2008;118:e497]. *Circulation*. 2005;111:e394–e434. doi: 10.1161/CIRCULATIONAHA.105.165564
34. Wilson WR, Danielson GK, Giuliani ER, Geraci JE. Prosthetic valve endocarditis. *Mayo Clin Proc*. 1982;57:155–161.
35. Wilson WR, Geraci JE, Wilkowske CJ, Washington JA 2nd. Short-term intramuscular therapy with procaine penicillin plus streptomycin for infective endocarditis due to viridans streptococci. *Circulation*. 1978;57:1158–1161. doi: 10.1161/01.cir.57.6.1158
36. Anderson DJ, Olaison L, McDonald JR, Miro JM, Hoen B, Selton-Suty C, Doco-Lecompte T, Abrutyn E, Habib G, Eykyn S, et al. Enterococcal prosthetic valve infective endocarditis: report of 45 episodes from the International Collaboration on Endocarditis-merged database. *Eur J Clin Microbiol Infect Dis*. 2005;24:665–670. doi: 10.1007/s10096-005-0007-9
37. Wilson WR, Wilkowske CJ, Wright AJ, Sande MA, Geraci JE. Treatment of streptomycin-susceptible and streptomycin-resistant enterococcal endocarditis. *Ann Intern Med*. 1984;100:816–823. doi: 10.7326/0003-4819-100-6-816
38. Amat-Santos IJ, Ribeiro HB, Urena M, Allende R, Houde C, Bédard E, Perron J, DeLarochelière R, Paradis JM, Dumont E, et al. Prosthetic valve endocarditis after transcatheter valve replacement: a systematic review. *JACC Cardiovasc Interv*. 2015;8:334–346. doi: 10.1016/j.jcin.2014.09.013
39. Gotzmann M, Czuderna A, Hehnen T, Aweimer A, Lind A, Kloppe A, Bösche L, Mügge A, Ewers A. Three-year outcomes after transcatheter aortic valve implantation with the CoreValve prosthesis. *Am J Cardiol*. 2014;114:606–611. doi: 10.1016/j.amjcard.2014.05.043
40. Latib A, Naim C, De Bonis M, Sinning JM, Maisano F, Barbanti M, Parolari A, Lorusso R, Testa L, Actis Dato GM, et al. TAVR-associated prosthetic valve infective endocarditis: results of a large, multicenter registry. *J Am Coll Cardiol*. 2014;64:2176–2178. doi: 10.1016/j.jacc.2014.09.021
41. Thornhill MH, Jones S, Prendergast B, Baddour LM, Chambers JB, Lockhart PB, Dayer MJ. Quantifying infective endocarditis risk in patients with predisposing cardiac conditions. *Eur Heart J*. 2018;39:586–595. doi: 10.1093/eurheartj/ehx655
42. Chu VH, Sexton DJ, Cabell CH, Reller LB, Pappas PA, Singh RK, Fowler VG Jr, Corey GR, Aksoy O, Woods CW. Repeat infective endocarditis: differentiating relapse from reinfection. *Clin Infect Dis*. 2005;41:406–409. doi: 10.1086/431590
43. Levison ME, Kaye D, Mandell GL, Hook EW. Characteristics of patients with multiple episodes of bacterial endocarditis. *JAMA*. 1970;211:1355–1357.
44. Erbel R, Liu F, Ge J, Rohmann S, Kupferwasser I. Identification of high-risk subgroups in infective endocarditis and the role of echocardiography. *Eur Heart J*. 1995;16:588–602. doi: 10.1093/oxfordjournals.eurheartj.a060961
45. Renzulli A, Carozza A, Romano G, De Feo M, Della Corte A, Gregorio R, Cotrufo M. Recurrent infective endocarditis: a multivariate analysis of 21 years of experience. *Ann Thorac Surg*. 2001;72:39–43. doi: 10.1016/s0003-4975(01)02703-5
46. Baddour LM. Twelve-year review of recurrent native-valve infective endocarditis: a disease of the modern antibiotic era. *Rev Infect Dis*. 1988;10:1163–1170. doi: 10.1093/clindis/10.6.1163
47. Welton DE, Young JB, Gentry WO, Raizner AE, Alexander JK, Chahine RA, Miller RR. Recurrent infective endocarditis: analysis of predisposing factors and clinical features. *Am J Med*. 1979;66:932–938. doi: 10.1016/0002-9343(79)90447-9
48. Kaplan EL, Rich H, Gersony W, Manning J. A collaborative study of infective endocarditis in the 1970s: emphasis on infections in patients who have undergone cardiovascular surgery. *Circulation*. 1979;59:327–335. doi: 10.1161/01.cir.59.2.327
49. Pallasch TJ, Wahl MJ. Focal infection: new age or ancient history? *Endodontic Top*. 2003;4:32–45.
50. Day MD, Gauvreau K, Shulman S, Newburger JW. Characteristics of children hospitalized with infective endocarditis. *Circulation*. 2009;119:865–870. doi: 10.1161/CIRCULATIONAHA.108.798751
51. Gupta S, Sakhuja A, McGrath E, Asmar B. Trends, microbiology, and outcomes of infective endocarditis in children during 2000–2010 in the United States. *Congenit Heart Dis*. 2017;12:196–201. doi: 10.1111/chd.12425
52. Sun LC, Lai CC, Wang CY, Wang YH, Wang JY, Hsu YL, Hu YL, Wu ET, Lin MT, Sy LB, et al. Risk factors for infective endocarditis in children with congenital heart diseases: a nationwide population-based case control study. *Int J Cardiol*. 2017;248:126–130. doi: 10.1016/j.ijcard.2017.08.009
53. Kuipers JM, Koolbergen DR, Groenink M, Peels KCH, Reichert CLA, Post MC, Bosker HA, Wajon EMCJ, Zwinderman AH, Mulder BJM, et al. Incidence, risk factors, and predictors of infective endocarditis in adult congenital heart disease: focus on the use of prosthetic material. *Eur Heart J*. 2017;38:2048–2056. doi: 10.1093/eurheartj/ehw591

54. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, Veen G, Stappers JL, Grobbee DE, Mulder BJ. Turning 18 with congenital heart disease: prediction of infective endocarditis based on a large population. *Eur Heart J*. 2011;32:1926–1934. doi: 10.1093/eurheartj/ehq485
55. Jalal Z, Galmiche L, Lebeaux D, Villemain O, Brugada G, Patel M, Ghigo JM, Beloin C, Boudjemline Y. Selective propensity of bovine jugular vein material to bacterial adhesions: an in-vitro study. *Int J Cardiol*. 2015;198:201–205. doi: 10.1016/j.ijcard.2015.07.004
56. Abdelghani M, Nassif M, Blom NA, Van Mourik MS, Straver B, Koolbergen DR, Kluin J, Tijssen JG, Mulder BJM, Bouma BJ, et al. Infective endocarditis after Melody valve implantation in the pulmonary position: a systematic review. *J Am Heart Assoc*. 2018;7:e008163. doi: 10.1161/JAHA.117.008163
57. Sun YP, O’Gara PT. Cardiovascular conditions predisposing to infective endocarditis: time to reconsider the current risk classification system? *Eur Heart J*. 2018;39:596–598. doi: 10.1093/eurheartj/ehx797
58. Zegri-Reiriz I, de Alarcón A, Muñoz P, Martínez Sellés M, González-Ramallo V, Miro JM, Falces C, Gonzalez Rico C, Kortajarena Urkola X, Lepe JA, et al; Spanish Collaboration on Endocarditis–Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España (GAMES). Infective endocarditis in patients with bicuspid aortic valve or mitral valve prolapse. *J Am Coll Cardiol*. 2018;71:2731–2740. doi: 10.1016/j.jacc.2018.03.534
59. Baskerville CA, Hanrahan BB, Burke AJ, Holwell AJ, Rémond MG, Maguire GP. Infective endocarditis and rheumatic heart disease in the north of Australia. *Heart Lung Circ*. 2012;21:36–41. doi: 10.1016/j.hlc.2011.08.010
- 59a. Thornhill MH, Dayer MJ, Prendergast B, Baddour LM, Jones S, Lockhart PB. Incidence and nature of adverse reactions to antibiotics used as endocarditis prophylaxis. *J Antimicrob Chemother*. 2015;70:2382–2388. doi: 10.1093/jac/dkv115
60. Thornhill MH, Dayer M, Lockhart PB, Prendergast B. Antibiotic prophylaxis of infective endocarditis. *Curr Infect Dis Rep*. 2017;19:9. doi: 10.1007/s11908-017-0564-y
61. Mazur N, Greenberger PA, Regalado J. Clindamycin hypersensitivity appears to be rare. *Ann Allergy Asthma Immunol*. 1999;82:443–445. doi: 10.1016/S1081-1206(10)62718-4
62. Bombassaro AM, Wetmore SJ, John MA. *Clostridium difficile* colitis following antibiotic prophylaxis for dental procedures. *J Can Dent Assoc*. 2001;67:20–22.
63. Hancox JC, Hasnain M, Vieweg WV, Crouse EL, Baranchuk A. Azithromycin, cardiovascular risks, QTc interval prolongation, torsade de pointes, and regulatory issues: a narrative review based on the study of case reports. *Ther Adv Infect Dis*. 2013;1:155–165. doi: 10.1177/2049936113501816
64. Durack DT. Drug therapy: prevention of infective endocarditis. *N Engl J Med*. 1995;332:38–44.
65. Durack DT. Antibiotics for prevention of endocarditis during dentistry: time to scale back? *Ann Intern Med*. 1998;129:829–831. doi: 10.7326/0003-4819-129-10-199811150-00015
66. Rouse MS, Steckelberg JM, Brandt CM, Patel R, Miro JM, Wilson WR. Efficacy of azithromycin or clarithromycin for prophylaxis of viridans group streptococcus experimental endocarditis. *Antimicrob Agents Chemother*. 1997;41:1673–1676. doi: 10.1128/AAC.41.8.1673
67. Glauser MP, Bernard JP, Moreillon P, Francioli P. Successful single-dose amoxicillin prophylaxis against experimental streptococcal endocarditis: evidence for two mechanisms of protection. *J Infect Dis*. 1983;147:568–575. doi: 10.1093/infdis/147.3.568
68. Khalil D, Hultin M, Rashid MU, Lund B. Oral microflora and selection of resistance after a single dose of amoxicillin. *Clin Microbiol Infect*. 2016;22:949.e1–949.e4. doi: 10.1016/j.cmi.2016.08.008
69. Woodman AJ, Vidic J, Newman HN, Marsh PD. Effect of repeated high dose prophylaxis with amoxicillin on the resident oral flora of adult volunteers. *J Med Microbiol*. 1985;19:15–23. doi: 10.1099/00222615-19-1-15
70. Franklin M, Wailoo A, Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. The cost-effectiveness of antibiotic prophylaxis for patients at risk of infective endocarditis. *Circulation*. 2016;134:1568–1578. doi: 10.1161/CIRCULATIONAHA.116.022047
71. Stacey D, Hill S, McCaffery K, Boland L, Lewis KB, Horvat L. Shared decision making interventions: theoretical and empirical evidence with implications for health literacy. *Stud Health Technol Inform*. 2017;240:263–283.
72. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, Cording E, Tomson D, Dodd C, Rollnick S, et al. Shared decision making: a model for clinical practice. *J Gen Intern Med*. 2012;27:1361–1367. doi: 10.1007/s11606-012-2077-6
73. Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Response to letter by Kaplan regarding “Bacteremia associated with toothbrushing and dental extraction.” *Circulation*. 2009;119:e14.