Article:
Lockhart, P., Chu, V., Thornhill, M. orcid.org/0000-0003-0681-4083 et al. (6 more authors) (2022) A high-sensitivity method for identifying a rare subpopulation of patients with infective endocarditis for a prospective case-control study. JADA Foundational Science, 1. 100002. ISSN 2772-414X

https://doi.org/10.1016/j.jfscie.2021.100002

Journal Reprint Line (2022) 1, 100002

JFS JADA Foundational Science
jadafs.ada.org

ADA®

RESEARCH ARTICLE

A high-sensitivity method for identifying a rare subpopulation of patients with infective endocarditis for a prospective case-control study

Peter B. Lockhart, DDS[a]; Vivian H. Chu, MD, MHS[b]; Martin H. Thornhill, PhD, MBBS, BDS[a,c]; Jing Zhao, MD, PhD[d]; Frank X. Gohs, MS[d]; D. Matthew Sullivan, MD[e]; Geoffrey Rose, MD[f]; Patrick O'Gara, MD[g]

[a]Department of Oral Medicine, Atrium Health Carolinas Medical Center, Charlotte, NC; [b]Division of Infectious Diseases, Department of Medicine, Duke University School of Medicine, Durham, NC; [c]Department of Oral and Maxillofacial Medicine, Surgery and Pathology, School of Clinical Dentistry, University of Sheffield, Sheffield, United Kingdom; [d]Center for Outcomes Research and Evaluation (Core), Atrium Health Carolinas Medical Center, Charlotte, NC; [e]Information and Analytic Services, Atrium Health, Charlotte, NC; [f]Sanger Heart & Vascular Institute, Atrium Health, Charlotte, NC; [g]Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Boston, MA.

Graphical abstract

Table 1 Primary study site hospital admissions and infective endocarditis discharges.

FACTORS USED TO DETERMINE PEHRST SENSITIVITY	VALUES
Total adult* hospital admissions over 24 mo, No.	74,345
Admissions meeting at least 2 of 4 PEHRST† screening criteria,‡ no. (%)	11,944 (16)
IE discharge diagnosis§ patients previously identified by PEHRST, no. (%)	198 (100)

* Age at admission >17 y. † PEHRST: Prospective Electronic Health Record Screening Tool. ‡ CRITERIA: blood culture order, echocardiography order, infectious diseases consult, and cardiovascular consult. § Considering infective endocarditis International Classification of Diseases, 10th Edition codes I33.0, I33.9, I38, or I39.

Why Is This Important?

The parent study was a prospective case-control study designed to acquire novel data to assess an association between oral hygiene and disease and infective endocarditis (IE). Study enrollment was difficult because of the low incidence of IE in the general population and the highly restrictive study inclusion criteria.

The authors report the development of a prospective electronic health record screening tool (PEHRST) and investigate its effectiveness in identifying patients with IE. PEHRST, using the IE screening criteria, identified 11,944 of 74,345 patients admitted to the hospital. There were 198 patients discharged during the study period with a confirmed diagnosis of IE, all of whom had also been identified by PEHRST, resulting in a search tool sensitivity of 100%.

To the authors' knowledge, this report is the first to study the ability of the electronic health record to identify clinical factors felt to be associated with the risk of IE. PEHRST provided an efficient, highly sensitive method that greatly reduced the effort required by the study team, and the number of months needed for enrollment, by eliminating from consideration most (84%) ineligible patients. The cost savings in reduced resources were substantial and critical to the successful outcome of the 5-year parent study.

https://doi.org/10.1016/j.jfscie.2021.100002

Abstract

Background. Infective endocarditis (IE) is an uncommon disease, but it is associated with high morbidity and mortality. The low incidence and varied clinical presentation make identification of these patients recently admitted to hospitals particularly challenging. The authors designed a prospective electronic health record screening tool (PEHRST) to identify inpatients with IE for a prospective case-control study designed to determine levels of association between oral hygiene and periodontal disease indexes and IE.

Methods. The authors used PEHRST to identify, soon after admission, patients hospitalized with IE based on the presence of any 2 of the 4 screening criteria: orders for blood culture or echocardiography and completed consultations from infectious diseases or cardiovascular medicine. They determined the utility of this tool by comparing the prospectively generated PEHRST list of potential inpatients with IE with a retrospective list of inpatients with IE discharged during the same 2-year period.

(Continued on next page)

Results. Of the 74,345 patients admitted during the study period, PEHRST identified 11,944 (16%) with at least 2 of the 4 screening criteria. Retrospective claims data showed that 198 patients were discharged during this time period with an IE diagnosis, all of whom had been identified by PEHRST (sensitivity = 100%; 95% CI, 98.2% to 100%; specificity = 84%; 95% CI, 83.9% to 84.4%). An analysis of the timing of the 4 screening criteria indicated that the median days were all within 24 hours of admission.

Conclusions. PEHRST made possible the identification of rare patients with IE soon after hospital admission with high sensitivity, allowing the parent study to achieve sufficient enrollment of cases for the primary outcome measure.

Key words. Heart valves; bacteremia; blood culture; cardiology; electronic health records; research methodology.

Infective endocarditis (IE) is a disease with low incidence in the general population, estimated to occur in 3 through 10 cases per 100,000 person years in the United States.[1-4] Historically, upward of 30% of IE cases have been attributable to bacterial species gaining entrance to the circulation through the gingival tissues of the mouth, typically streptococci from bacterial plaque around the teeth.[5-7] Attributing an anatomic origin for IE based on bacterial species is problematic, given the diversity of oral bacterial species and the potential for some of the common oral species to be found in sites far removed from the oral cavity. Although the number of IE cases associated with implanted medical devices and injection drug use has increased, the overall incidence of IE cases due to oral bacterial species may have remained stable.[8-11]

Numerous studies have examined the occurrence of bacteremia from invasive dental office procedures and following the routine activities of daily living (eg, toothbrushing).[12,13] Such activities may serve as surrogate measures for risk of IE. Prior studies suggest a strong association between specific indexes of oral hygiene (ie, dental plaque and calculus) and bacteremia from oral species known to cause IE.[7,13,14] Although it is likely that inflammation of the gingival mucosa and the resultant ulceration from plaque and calculus increase the likelihood and frequency of bacteremia,[14] there is no direct evidence of association with IE. We designed a case-control study of inpatients with IE and a control group of outpatients in the hospital echocardiography (EC) laboratories with cardiac risk factors for IE but without IE. Identical demographic, medical and dental histories, and clinical examination information was gathered from case and control patients such that we could determine the level of association between oral hygiene and periodontal diseases and risk of IE.

A critical aspect of enrollment in this clinical study was identifying case patients as early in their hospitalizations as possible to avoid exclusion from the study because of urgent surgical intervention (eg, cardiac valve replacement) or increased medical compromise and to minimize the impact of hospitalization and systemic antibiotics used for treatment of IE on the study outcome measures of oral hygiene and periodontal disease. Our original intention was to use the more traditional method of identifying cases in collaboration with multiple hospital services and laboratories involved in the care of these patients. It became clear at the outset that recruitment would be difficult owing to the low incidence of IE, the highly restrictive study inclusion and exclusion criteria, and the necessity of maintaining high study visibility with a large number of inpatient services. Given these complex enrollment issues, we needed a methodology to screen the electronic health record (EHR) initially for study patients. Despite many advances in EHR solutions, there is no out-of-the box approach for IE as there has been for some clinical diagnoses (eg, sepsis and heart failure). In addition, the historic pitfalls of using billing and administrative data as a relatively resource-light method of assessing issues that demand closer attention where possible or studying issues where other research methods are infeasible underscored our desire to focus the research efforts on prospective clinical data points and a more refined informatics approach.[15]

The purpose of this report was to describe the development of a prospective EHR screening tool (PEHRST) and to investigate its effectiveness in identifying patients with IE soon after admission for possible inclusion in a clinical study of oral health as a risk factor for developing IE. Secondary aims included a determination of the extent to which this tool ensured early identification of potential participants for enrollment and detection of IE cases for each of 4 IE screening criteria.

Methods

Study setting and patient populations

The parent investigation, for which PEHRST was developed, is a 5-year, multicenter, observational, case-control study. A prestudy power analysis determined the need for 112 IE case patients and 224 control patients to determine whether measures of poor oral hygiene and periodontal disease are associated with IE. Participants (>17 years) were recruited from the primary study site inpatient (case patients) and outpatient (control patients) facilities.

Screening tool for early identification of case participants

The Cerner EHR system is used throughout the primary study site hospitals and care facilities. Using a Cerner Command Language query in the Cerner Discern Explorer solution, an expert panel of study investigators, together

with the Information Service division, developed a customized PEHRST. A consensus among the study principal investigator, the infectious diseases (IDs) specialist, and cardiologists posited that patients with IE would likely have at least 2 of the following 4 procedures early in their hospitalization: blood culture (BC) testing orders, EC testing orders, ID consultations, and cardiovascular (CV) consultations. PEHRST was designed to identify individuals with any 2 of these 4 IE screening criteria, based on the presumption that it would be sensitive enough to identify all patients with IE and yet be specific enough to greatly reduce the effort required to review large numbers of patients without IE. The query returned a daily report with specific EHR patient information pertaining to eligibility (eg, age). This report was reviewed by the study site coordinator, and the medical records of patients suspected of having IE were further evaluated, and if they appeared to be eligible, the patient's medical team was contacted. Patients were enrolled if they met the modified Duke criteria for diagnosis of IE[16] and a specific list of study inclusion and exclusion criteria.

Standard IE diagnosis and statistical considerations

Using PEHRST data outputs for the 24-month parent study period from January 1, 2017, through December 31, 2018, we identified individuals who met at least 2 of these 4 IE screening criteria. These patients had undergone a preliminary screening for enrollment. To determine the sensitivity for PEHRST, we queried our enterprise data warehouse to identify patients with discharge International Classification of Diseases, 10th Edition (ICD-10) code for IE (ie, I33.0, I33.9, I38, or I39) during the same 24-month study period for comparison with our list of patients identified by PEHRST and confirmed to have IE. Sensitivity was calculated as the proportion of true patients with a positive screening test.[17] Specificity was determined as the proportion of nondiseased participants with a negative screening test.[17] The exact 95% CI of sensitivity and specificity were also calculated. In addition, we determined the sensitivity for each of these 4 screening criteria and the timing for each during hospitalization. The frequency and percentage of early detection of IE cases for each of the 4 criteria (BC, EC, ID, CV) alone or in various combinations were summarized. Finally, we analyzed these ICD-10 codes to determine the frequency with which each code was used and where they appeared in the list of discharge diagnoses. Other descriptive summary statistics such as frequencies, means, medians, and percentiles were determined, as appropriate. The analysis was performed using SAS Enterprise Guide 7.1 (Version 9.4; SAS Institute Inc).

Results

Enrollment for the parent study began in July 2016. During the 24-month study period investigated, there were 74,345 patients admitted to this enrollment site (Table 1). PEHRST identified 11,944 patients with at least 2 of the 4 screening criteria, eliminating 84% of the total number of admitted patients from further consideration. A retrospective search of our system billing data revealed that there were 198 patients discharged during the study period with an ICD-10 discharge diagnosis code for IE. All but 1 of the ICD-10 IE codes were either I33.0 (86.4%) or I38.0 (13.1%). These codes were recorded as among the top 3 discharge diagnosis codes for 61% of these patients with IE (Table 1). All 198 patients had also been identified by PEHRST, resulting in a search tool sensitivity of 100% (95% CI, 98.2% to 100%) (Table 2). Requiring the presence of 3 of the 4 screening criteria would have reduced the number of patients identified by the tool further, from nearly 12,000 to just under 3,000 (Table 3). However, 28 of the 198 patients with IE would have been missed, for a sensitivity of 86%. Requiring all 4 screening criteria to be present would have decreased the tool's sensitivity to 38%.

Further analysis of the PEHRST tool indicated that screening criteria combinations that included BC orders identified 188 of the 198 (sensitivity = 95%) patients with IE discharge diagnosis (Table 3). Combinations that included ID consultation identified 179 (sensitivity = 90%)

Table 1 Primary study site hospital admissions and infective endocarditis (IE) discharges.

STUDY SITE HOSPITAL ADMISSIONS AND DISCHARGE DIAGNOSES	VALUES
Total adult* hospital admissions over 24 mo (2017-2018), No.	**74,345**
Admissions meeting at least 2 of 4 PEHRST screening criteria†, No. (%)	**11,944 (16)**
IE discharge diagnosis patients previously identified by PEHRST, No. (%)	**198 (100)**
IE tertiary International Classification of Diseases 10th Edition (ICD-10) Discharge Diagnosis Patients, ‡Level of discharge diagnosis	
Primary ICD-10 discharge diagnosis, No. (%)	37 (19)
Secondary or tertiary ICD-10 discharge diagnosis, No. (%)	83 (42)
Subsequent level discharge diagnosis, No. (%)	78 (39)
Total	198

* Age at admission >17 y. † PEHRST (Prospective Electronic Health Record Screening Tool) criteria: blood culture order, echocardiography order, infectious diseases consultation, and cardiovascular consultation. ‡ Considering IE ICD-10 codes I33.0, I33.9, I38, or I39.

Table 2 Prospective Electronic Health Record Screening Tool sensitivity and specificity.

PEHRST tool criteria met	Infective endocarditis present	Infective endocarditis absent	Total
Meet at least 2 of 4 tool criteria*			
Positive	198 (true positive [TP])	11,746 (false positive [FP])	11,944
Negative	0 (false negative [FN])	62,401 (true negative [TN])	62,401
Total	198	74,147	74,345
Infectious diseases consultation plus any of 3 tool criteria†			
Positive	179 (TP)	3,767 (FP)	3,946
Negative	19 (FN)	70,380 (TN)	70,399
Total	198	74,147	74,345

* Meet at least 2 of 4 tool criteria. Sensitivity = TP/(TP + FN) = 100%, exact 95% CI, 98.2% through 100%. Specificity = TN/(FP + TN) = 84%, 95% CI, 83.9% through 84.4%. Positive predictive value (PPV) = TP/(TP + FP) = 0.017; 95% CI, 0.014 through 0.019. Negative predictive value (NPV) = TN/(TN + FN) = 1.000, 95% CI, 0.999 through 1.000. FP rate = FP/(FP + TN) = 0.158, 95% CI, 0.156 through 0.161. FN rate = FN/(FN + TP) = 0.000, 95% CI, 0.000 through 0.018. Accuracy (ACC) = (TP + TN)/(P + N) = 0.842, 95% CI, 0.839 through 0.845. Positive likelihood ratio = TP rate/FP rate = sensitivity/1 − specificity) = 6.312, 95% CI, 6.209 through 6.418. Negative likelihood ratio = FN rate/TN rate = (1 − sensitivity)/specificity = 0.000, 95% CI, 0.000 through NaN. † ID consult plus any of the 3 tool criteria. Sensitivity = TP/(TP + FN) = 90.4%, exact 95% CI, 85.4% through 94.1%. Specificity = TN/(FP + TN) = 94.9%, 95% CI, 94.7% through 95.1%. PPV = TP/(TP + FP) = 0.045, 95% CI, 0.039 through 0.052. NPV = TN/(TN + FN) = 1.000, 95% CI, 0.999 through 1.000. FP rate = FP/(FP + TN) = 0.051, 95% CI, 0.049 through 0.052. FN rate = FN/(FN + TP) = 0.096, 95% CI, 0.059 through 0.146. ACC = (TP + TN)/(P + N) = 0.949, 95% CI, 0.947 through 0.951. Positive likelihood ratio = TP rate/FP rate = sensitivity/(1 − specificity) = 17.795, 95% CI, 16.842 through 18.801. Negative likelihood ratio = FN rate/TN rate = (1 − sensitivity)/specificity = 0.10, 95% CI, 0.07 through 0.16.

Table 3 Prospective Electronic Health Record Screening Tool criteria (PEHRST).

Screening criteria combinations	PEHRST patients (n = 11,944), no. (%)	Infective endocarditis diagnosis patients (n = 198), no. (%)
BC*, EC†, ID‡, CV§	421 (3.5)	75 (37.9)
BC, EC, ID	1,369 (11.5)	75 (37.9)
BC, EC, CV	1,012 (8.5)	5 (2.5)
BC, ID, CV	54 (0.5)	4 (2.0)
EC, ID, CV	56 (0.5)	1 (0.5)
BC, EC	3,019 (25.3)	10 (5.1)
BC, ID	1,862 (15.6)	18 (9.1)
BC, CV	202 (1.7)	1 (0.5)
EC, ID	155 (1.3)	2 (1.0)
EC, CV	3,765 (31.5)	3 (1.5)
ID, CV	29 (0.2)	4 (2.0)
All BC combinations	7,939 (66.5)	188 (94.9)
All EC combinations	9,797 (82.0)	171 (86.4)
All ID combinations	3,946 (33.0)	179 (90.4)
All CV combinations	5,539 (46.4)	93 (47.0)

PEHRST screening tool criteria timing relative to admission in infective endocarditis diagnosis patients (d)

Criteria	Median	75th percentile	90th percentile
BC	0	0	1
EC	0	1	3
ID	1	2	4
CV	0	2	6

* BC, blood culture order. † EC, echocardiography order. ‡ ID, infectious diseases consultation. § CV, cardiovascular consultation.

of these patients, and those that included EC orders identified 171 (sensitivity = 86%). Combinations that included the CV consultation identified 93 (sensitivity = 47%) IE cases. Combinations that included ID consultation showed the greatest reduction of around 8,000 patients with false-positive (FP) results identified by PEHRST (sensitivity = 90%, specificity = 95%).

An analysis of the timing of the 4 screening criteria for patients with IE required a manual review of all 198 records to ensure accuracy of the diagnoses and to capture the earliest date of each criteria pertaining to the IE admission of interest. The median timing for all 4 criteria was within 1 day after admission. Most of the patients (90%) had a BC order within 1 day after admission, while 90% had an EC order within 3 days after admission, and an ID and a CV consultation within 4 or 6 days (respectively) after admission (Table 3). Since all 4 search criteria were not present for every patient, timing analysis was only performed on patients with dates for all 4 search criteria. The limiting of the timing analysis to this subpopulation had a negligible effect on the results noted above.

Discussion

This prospective case-control study was designed to acquire novel data to assess the long-standing opinion that poor oral hygiene and periodontal diseases are significant risk factors of IE. The priority for PEHRST was to ensure early identification of a population of potentially eligible, hospitalized patients with IE who were rare by virtue of both the uncommon nature of this highly morbid disease and the stringent inclusion and exclusion criteria for this study. Although EHR screening has been successful for many other diseases, the focus of the current body of literature has been primarily on identification of patients for epidemiology studies or clinical management, rather

than the early enrollment of patients into prospective clinical trials.[18,19] To our knowledge, this report is the first to study the ability of EHR to identify clinical factors felt to be associated with risk for endocarditis. PEHRST had 100% sensitivity for identifying all 198 potentially eligible study participants during the 2-year period investigated, many of whom likely would not have been identified at all or as early in their hospitalization. PEHRST also reduced the effort required by the study team by eliminating from consideration most (84%) ineligible patients, leaving a manageable number for the study team to screen each day. In addition, the PEHRST-generated daily report contained relevant information that further facilitated screening by allowing for quicker identification of ineligible patients.

Although we cannot determine an accurate financial impact of this tool on the cost of this parent study, it reduced the resources required to identify potential cases. With the PEHRST tool, the study coordinators only needed to screen 16% of the total number of admitted patients, reducing the time needed daily to review potential cases to an average of about 90 minutes. We estimate that successfully identifying a similar number of potential cases could not have been achieved in the same enrollment period, may have required far more study coordinator time, and an unacceptable number of years of enrollment. In addition, in the absence of the PEHRST, identifying cases would have required collaboration with the many hospital services involved with these patients and would have resulted in an unacceptable number of missed cases. For these reasons, the benefits of cost savings in terms of reduced resources and increased sensitivity in identification of potential cases were substantial.

Although we achieved 100% sensitivity, we did have a FP outcome in 11,746 patients who required further screening by study coordinators; most of these cases were quickly eliminated from further evaluation by having 1 or more readily identifiable exclusion criteria. There are many reasons why a patient would meet at least 2 of the 4 screening criteria but not have IE. For example, many patients admitted to a hospital with a fever (whatever the cause) will be scheduled for a BC and ID consultation (2 of 4 criteria). Similarly, many patients admitted with cardiac problems (whatever the cause) will be scheduled for EC and a CV consultation (2 of 4 criteria), but only a small fraction will ultimately receive a diagnosis of IE.

In an effort to determine if we could improve tool performance, we examined the impact of eliminating each of the criteria and changing the threshold from at least 2 of 4, to at least 3 or more, or all 4 criteria. The modification that would have most significantly reduced the FP was any combination that included ID, which would have increased specificity to 95% but would have reduced sensitivity to the unacceptable level of 90% and missed 19 IE cases.

There was a strong need to identify the cases early in their hospitalization to avoid the exclusion criteria and to minimize the impact of the aspects of hospitalization (eg, systemic antibiotics) on study outcome measures (eg, increased dental plaque and gingival inflammation). The determination of the days between admission and the initiation of the screening criteria necessitated using the first date for each of these 4 criteria, especially for BC tests which are often repeated to evaluate antibiotic efficacy, and for transesophageal EC that may follow a transthoracic EC to aid diagnosis of IE. This required a retrospective review of all 198 cases with an IE discharge diagnosis to ensure the accuracy of the diagnoses and determine the dates for each of the 4 criteria, and relevant admission dates for patients with multiple hospitalizations for IE. An analysis of these dates indicated that the median number of days from admission for BC and EC orders and CV and ID consultation reports were all within 1 day.

There were limitations to this study. Patients transferred from specific hospitals were difficult to identify because BC and EC results were not fully interoperable between the transferring hospital EHR and the study site EHR. However, the authors found that all transferred patients were identified by the PEHRST tool based on the CV and ID consultations done soon after admission to the study site hospital. Given the differences in the usual sequence with which tool criteria are ordered, patients transferred to the study site hospital were not used for the timing aspect of our analysis. In addition, CV and ID consultation notifications were generated from completed consultations and not from the consultations ordered. The PEHRST ability to identify them as orders would have likely shortened the time between admission and identifying these 2 criteria.

The involvement of an informatician was critical in the development of our computer-assisted screening tool and accomplishing our primary study objectives to prospectively explore associations among oral hygiene and periodontal diseases and IE. Because the use of EHR evolves over time, alternative methods of identifying IE study patients, such as by electronic searching for key elements in the EHR to identify patients with an infected heart valve on echocardiogram, should be explored. Our customized PEHRST provided an efficient and highly sensitive method to identify a small subpopulation of hospitalized patients with IE for this prospective study. The cost savings in terms of the time spent by study coordinators in particular and the greatly reduced number of months needed to enroll this rare patient population was critical to a successful outcome of the 5-year parent study.

Conclusions

The concept on which PEHRST was constructed should be considered whenever it is necessary to identify potentially eligible patients for a study where the desired population is rare relative to the size of the pool of patients from which study patients are to be selected.

Email Peter.lockhart@atriumhealth.org. Address correspondence to Dr Lockhart.

Disclaimer. The National Institute of Dental and Craniofacial Research had no involvement in this study.

Disclosure. None of the authors reported any disclosures.

Funding. This study was funded by grant R01 DE023375-01A1 from the National Institutes of Health, National Institute of Dental and Craniofacial Research.

IRB Approval. This study was reviewed and approved by the institutional review board at Atrium Health.

The authors wish to thank Cathleen Petersen, RDH; Joel Napeñas, DDS; Jenene Noll, RN; Leslie Long-Simpson, BS; and Casey Stephens, MS, for their dedication and contributions to this study, and, Kathleen Sullivan, MA, for her editorial expertise.

References

1. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet. 2016; 387(10021):882-893. https://doi.org/10.1016/S0140-6736(15)00067-7.
2. Hoen B, Duval X. Clinical practice. Infective endocarditis. N Engl J Med. 2013;368(15):1425-1433. Published correction appears in *N Engl J Med*. 2013;368(26):2536 https://doi.org/10.1056/NEJMcp1206782.
3. Murdoch DR, Corey GR, Hoen B, et al; International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med. 2009;169(5):463-473. https://doi.org/10.1001/archinternmed.2008.603.
4. Thornhill MH, Gibson TB, Cutler E, et al. Antibiotic prophylaxis and incidence of endocarditis before and after the 2007 AHA recommendations. J Am Coll Cardiol. 2018;72(20):2443-2454. https://doi.org/10.1016/j.jacc.2018.08.2178.
5. Tleyjeh IM, Steckelberg JM, Murad HS, et al. Temporal trends in infective endocarditis: a population-based study in Olmsted County, Minnesota. JAMA. 2005;293(24):3022-3028. https://doi.org/10.1001/jama.293.24.3022.
6. Delahaye F, M'Hammedi A, Guerpillon B, et al. Systematic search for present and potential portals of entry for infective endocarditis. J Am Coll Cardiol. 2016;67(2):151-158. https://doi.org/10.1016/j.jacc.2015.10.065.
7. Bahrani-Mougeot FK, Paster BJ, Coleman S, Ashar J, Barbuto S, Lockhart PB. Diverse and novel oral bacterial species in blood following dental procedures. J Clin Microbiol. 2008;46(6):2129-2132. https://doi.org/10.1128/JCM.02004-07.
8. Schranz AJ, Fleischauer A, Chu VH, Wu LT, Rosen DL. Trends in drug use-associated infective endocarditis and heart valve surgery, 2007-2017: a study of statewide discharge data. Ann Intern Med. 2019;170(1):31-40. https://doi.org/10.7326/M18-2124.
9. Pant S, Patel NJ, Deshmukh A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. J Am Coll Cardiol. 2015;65(19):2070-2076. https://doi.org/10.1016/j.jacc.2015.03.518.
10. Mostaghim AS, Lo HYA, Khardori N. A retrospective epidemiologic study to define risk factors, microbiology, and clinical outcomes of infective endocarditis in a large tertiary-care teaching hospital. SAGE Open Med. 2017;5. https://doi.org/10.1177/2050312117741772, 2050312117741772.
11. Holland DJ, Simos PA, Yoon J, Sivabalan P, Ramnarain J, Runnegar NJ. Infective endocarditis: a contemporary study of microbiology, echocardiography and associated clinical outcomes at a major tertiary referral centre. Heart Lung Circ. 2020;29(6):840-850. https://doi.org/10.1016/j.hlc.2019.07.006.
12. Lafaurie GI, Noriega LA, Torres CC, et al. Impact of antibiotic prophylaxis on the incidence, nature, magnitude, and duration of bacteremia associated with dental procedures: a systematic review. J Am Dent Assoc. 2019;150(11):948-959.e4. https://doi.org/10.1016/j.adaj.2019.06.017.
13. Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. Circulation. 2008;117(24):3118-3125. https://doi.org/10.1161/CIRCULATIONAHA.107.758524.
14. Lockhart PB, Brennan MT, Thornhill M, et al. Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. J Am Dent Assoc. 2009;140(10):1238-1244. https://doi.org/10.14219/jada.archive.2009.0046.
15. Fawcett N, Young B, Peto L, et al. 'Caveat emptor': the cautionary tale of endocarditis and the potential pitfalls of clinical coding data-an electronic health records study. BMC Med. 2019;17(1):169. https://doi.org/10.1186/s12916-019-1390-x.
16. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30(4):633-638. https://doi.org/10.1086/313753.
17. Attia J. Moving beyond sensitivity and specificity: using likelihood ratios to help interpret diagnostic tests. Aust Prescr. 2003;26(5):111-113. https://doi.org/10.18773/austprescr.2003.082.
18. van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in the Netherlands, I: Patient characteristics. Arch Intern Med. 1992;152(9):1863-1868. https://doi.org/10.1001/archinte.152.9.1863.
19. Quan TP, Muller-Pebody B, Fawcett N, 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(1):84. https://doi.org/10.1186/s12916-020-01531-y.