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Trends in Endocarditis Hospitalizations at US Childrens Hospitals: Impact of the 2007 American Heart Association Antibiotic Prophylaxis Guidelines

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Abstract

Background—In 2007, the American Heart Association recommended cessation of antibiotic prophylaxis for infective endocarditis (IE) prior to dental procedures for all but those at highest risk of adverse outcomes from IE. The impact of these guidelines is unclear. We evaluated IE hospitalizations at US children's hospitals during this time period.

Methods—Children <18yrs hospitalized from 2003–2010 with IE at 37 centers in the Pediatric Health Information Systems Database were included. Using Poisson regression, we evaluated the number IE hospitalizations over time (raw and indexed to total hospital admissions).

Results—A total of 1157 IE cases were identified; 68% had congenital heart disease (CHD). The raw number of IE cases did not change significantly over time (+1.6% difference post vs. pre guidelines, 95% CI –6.4 to +10.3%, p=0.7). When the number of IE cases was indexed per 1000 hospital admissions, there was a significant decline during the time prior to the guidelines (annual change = –5.9%, 95% CI –9.9 to –1.8, p=0.005), and a similar decline in the post-guidelines period, such that the difference between the two time periods was not significant (p=0.15). In subgroup analysis, no significant change over time in IE cases (raw or indexed) was found in the

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CHD subset, those 5–18yrs (subgroup most likely receiving dental care), or in cases coded as oral streptococci.

Conclusions—We found no evidence that release of new antibiotic prophylaxis guidelines was associated with a significant change in IE admissions across 37 US children’s hospitals.

Introduction

In 2007 the American Heart Association (AHA) published guidelines recommending cessation of antibiotic prophylaxis for infective endocarditis (IE) prior to dental procedures for all patients, with the exception of those with underlying cardiac conditions thought to be at highest risk of adverse outcome from IE (1). Prophylaxis prior to other procedures such as gastrointestinal and genitourinary procedures was no longer recommended (1). These replaced previous guidelines published in 1997, which recommended antibiotic prophylaxis for a broader range of patients undergoing a variety of procedures (2). The primary reasons cited for the revision in the guidelines included: “1) IE is much more likely to result from frequent exposure to random bacteremia associated with daily activities than from bacteremia caused by a dental, gastrointestinal tract, or genitourinary tract procedure, 2) Prophylaxis may prevent an exceedingly small number of cases of IE, if any, in individuals who undergo a dental, gastrointestinal tract, or genitourinary tract procedure, 3) The risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy, and 4) Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of IE (1).”

The impact of these new guidelines on clinical outcomes is unclear. A previous study focused on the adult population in the UK where *complete* cessation of antibiotic prophylaxis for IE was recommended, even in higher-risk patients (3). This study found no evidence of an upward trend in hospitalizations for IE in the UK after the change in guidelines (3). Children were not specifically evaluated in this previous study, and outcomes associated with the new guidelines in the pediatric population remain unclear. Analysis of the pediatric population is of particular interest, as this group encompasses patients with congenital heart defects who are thought to be at higher risk for the development of IE and IE-related adverse outcomes, and thus may be most likely to be impacted by the change in antibiotic prophylactic guidelines. The purpose of this study was to evaluate trends in hospitalization for IE over time, before and after the new antibiotic prophylaxis guidelines, across US children’s hospitals. We also evaluated the cohort of children with congenital heart disease (CHD), along with the subgroup of pediatric patients most likely receiving dental care (those 5–18 years of age).

Patients and Methods

Data Source

Data for this multi-center retrospective study were obtained from the Pediatric Health Information System (PHIS) Database, a large administrative database containing inpatient data from 41 children’s hospitals in the US affiliated with the Child Health Corporation of America (Shawnee Mission, KS). The database currently contains information from >5 million inpatient discharges, and has been used extensively in pediatric outcomes research (4–6). PHIS-participating hospitals provide discharge data including patient demographics, diagnoses, and procedures. Billing data are also available detailing medications, imaging studies, laboratory tests, and supplies charged to each patient. Data quality and reliability are assured through a joint effort between Child Health Corporation of America and participating hospitals. Systematic monitoring occurs to ensure data quality, including

bimonthly coding consensus meetings, coding consistency reviews, and quarterly data quality reports. This research, using a de-identified dataset, was not considered human subjects research in accordance with the Common Rule (45 CFR 46.102(f)) and the policies of The Children's Hospital of Philadelphia and Cincinnati Children's Hospital Medical Center Institutional Review Boards. This research was supported by the National Heart, Lung, and Blood Institute (1K08HL103631; SKP), the American Heart Association Clinical Research Program (SKP), the National Institute of Allergy and Infectious Disease (K01 AI73729; SSS), and Robert Wood Johnson Foundation Physician Faculty Scholar Program (SSS). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Study Population

PHIS-participating centers submitting complete data from 2003–2010 were included (n=37 centers). The study period was chosen in order to span the time period before and after the AHA antibiotic prophylaxis guidelines were published in 2007. From these centers, children <18 years of age hospitalized with IE were included. Only the first (index) hospitalization for IE was analyzed. For the purposes of this study, IE was defined as an International Classification of Disease, 9th revision (ICD-9) diagnosis code for “acute and subacute bacterial endocarditis” (421.0), and receipt of seven or more days of intravenous antibiotics during the hospitalization, beginning within seven days of hospital admission. This definition was chosen to minimize the possibility of including patients with a history of IE, but not active disease, and to minimize the inclusion of patients admitted for some other reason who acquired IE later during the course of a hospitalization, as we hypothesized these cases were less likely to be related to antibiotic prophylaxis prior to a dental procedure.

Data Collection

Data collection included patient demographic information and the presence of any ICD-9 diagnosis or procedure code related to CHD. Microbiology data were also collected, specifically data on organisms possibly representing oral streptococcal species (ICD-9 codes 038.0, 038.3, 041.00, 041.03, 041.05, 041.09), as these organisms are those which would most likely be impacted by the new guidelines.. Those with codes for Group A, B, or D streptococcus, pneumococcus, or staphylococcus species were excluded from this classification. Finally, in-hospital mortality data were collected.

Analysis

Study variables were described using standard summary statistics including frequency and percent for dichotomous variables and median and interquartile range for continuous variables. Poisson regression was used to estimate the rate of change in the annual number of IE hospitalizations over time (both raw and indexed to the total number of annual hospital admissions). Time was modeled in 6 month intervals as a linear trend allowing for change in slope at the time when the new AHA guidelines were published in 2007. Negative binomial models were also fitted and yielded similar results to Poisson regression; only data from Poisson models are shown. Several sensitivity analyses were performed. First, analyses were repeated while restricting the population to the CHD subset, a group at higher risk for endocarditis. In the CHD subgroup, the data were overdispersed for Poisson models and results from negative binomial models are presented. In the second sensitivity analysis, we restricted the population to only those aged 5–18 years, as this subgroup is the most likely to be receiving dental care and thus impacted by the change in guidelines. We also examined these two subgroups combined. Finally, we evaluated trends over time in the subset with a code for any oral streptococcal species. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC). A p-value <0.05 was considered statistically significant.

Results

Study population

A total of 1157 cases of hospitalization for IE during the study period were identified. Study population characteristics are displayed in Table 1. Median age was 2.9 years (interquartile range 2.5 months–12.4 years) and 68% of the cohort were coded as having CHD. In-hospital mortality for the overall cohort was 1.1%.

Hospitalization for IE over time

In analysis of the overall cohort, we did not detect a significant change in the raw number of IE cases over time, before and after the new guidelines were published in 2007: +1.6% difference post vs. pre guidelines (95% CI –6.4 to +10.3%, $p=0.7$; Table 2, Figure 1). When the number of IE cases was indexed per 1000 hospital admissions, there was a significant decline over time prior to the guidelines (annual change = –5.9%, 95% CI –9.9 to –1.8, $p=0.005$), and a similar decline in the post-guidelines period, such that the difference between the two time periods was not significant $p=0.15$; Table 2; Figure 2).

In sensitivity analysis, there were no significant differences detected in the number of cases of hospitalization for IE (raw or indexed to total hospitalizations) in the post vs. pre-guidelines period in either of the subgroups examined (those with CHD, and those 5–18 years of age; Table 2). Results were also similar when we examined data from these two groups combined. Finally, we examined the change in cases of IE over time associated with a code for oral streptococci. Overall, 52% of IE cases had a code for any streptococcal or staphylococcal organism. There was a trend toward a decrease over time in IE cases associated with a code for oral streptococci (Table 2).

Discussion

In this multicenter observational analysis, we did not detect a significant difference in hospitalizations for IE across 37 US Children's Hospitals before and after revision of the AHA antibiotic prophylaxis guidelines in 2007. IE, while uncommon, can be associated with significant morbidity and mortality including hospitalization for treatment of the infection, heart failure, embolization, stroke, cardiac valve replacement surgery, and death (1, 7). Mortality associated with IE varies depending on patient comorbidities and underlying cardiac condition. For example, patients with prosthetic cardiac valve IE have mortality rates as high as 20% in some series compared with much lower mortality rates associated with native valve IE. (1, 7–10). In a recent analysis of patients 0–21 years hospitalized with IE during 2000 and 2003, investigators reported an overall mortality rate of 5% (11). This differs from the mortality rate reported in our study of 1%. It is important to note that the case definition of IE in our study was specifically chosen to minimize the inclusion of patients admitted for some other reason who acquired IE later during the course of a hospitalization, as we hypothesized these cases were less likely to be related to antibiotic prophylaxis prior to a dental procedure. The previous study did not exclude these patients. It is likely that patients with hospital-acquired IE represent a high-risk subgroup with other comorbid medical conditions. In addition, the previous study included an older patient population (11). These and other differences may in part explain the differences in mortality rates.

For many years, antibiotic prophylaxis was the mainstay of preventive therapy for IE, with the aim of reducing bacteremia related to oral flora that may cause IE. Prophylaxis prior to dental procedures has been a primary focus, as oral streptococci have been implicated in up to 65% of IE cases (1, 12). However, there is limited evidence as to whether antibiotic prophylaxis prior to dental procedures prevents IE. As emphasized in the revised 2007 AHA

guidelines, there are some data to suggest that the cumulative risk over time of bacteremia is much greater from routine daily activities than that associated with a dental procedure (1, 13, 14). The estimated exposure to bacteremia over a 1 month period related to chewing food and routine dental hygiene such as brushing and flossing was estimated at 5370 minutes, vs. the estimated duration of up to 30 minutes of bacteremia associated with a tooth extraction (13). In addition, case-control studies have suggested that dental visits/treatment are not a risk factor for the development of IE (15). Thus, the new guidelines emphasize the maintenance of good oral hygiene in general, and recommend cessation of antibiotic prophylaxis prior to dental procedures for all but patients at highest risk of adverse outcome related to IE (1). The group recommended to receive antibiotic prophylaxis under the current guidelines includes those with: 1) Prosthetic cardiac valve or prosthetic material used for cardiac valve repair, 2) Previous IE, 3) Unrepaired cyanotic CHD including palliative shunts and conduits, 4) Completely repaired CHD with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure, 5) Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization), and 6) Cardiac transplantation recipients who develop cardiac valvulopathy (1). However, these recommendations remain controversial and some argue that the risks of IE in any patient outweigh the risk related to potential overtreatment with antibiotics (16, 17). There has never been a prospective randomized trial of antibiotic prophylaxis due to ethical issues, cost, and the large sample size required.

There are limited data regarding the clinical impact of the new antibiotic prophylaxis guidelines. The largest study to date was conducted in the UK where the National Institute for Health and Clinical Excellence recommended complete cessation of antibiotic prophylaxis (even in patients at higher risk for IE) in March 2008 (3, 18). Using National Health Service data, investigators evaluated prescribing practices and IE hospitalizations in England from January 2000 to April 2010 (3). They found a 78.6% reduction in prescription of antibiotic prophylaxis prior to dental procedures, and no significant difference in the rate of IE hospitalizations before vs. after the change in guidelines (3). This study did not specifically evaluate children or those with cardiac conditions (3).

To our knowledge, only one previous study in the US has reported on the impact of the 2007 AHA guidelines. Rogers et al. examined the unadjusted number of adults hospitalized for IE at their institution before and during the 9 months after the guidelines were published (19). They found that the number of hospitalizations during each 9-month time period ranged from 39–50, and did not find any evidence of a change in the number of hospitalizations over time in a preliminary descriptive report (19). Our study confirms these findings in a larger multicenter population examined over several years. In addition, we were also able to evaluate several important subgroups likely to be those most impacted by the change in guidelines. These included the subgroup of patients age 5–18 years most likely to be receiving dental care, and those coded as having CHD. In each of these subgroups, we found results that were similar to the results in the overall cohort. Interestingly, the overall cohort with IE in our study was also composed of a substantial number of patients less than 1 year of age, similar to data reported in other recent analyses (11). This suggests that efforts to reduce IE will require a better understanding of the etiology of IE and predisposing factors in this younger group of patients, as data to date are limited.

Finally, it is interesting to note that the number of cases of IE indexed to total hospital admissions in our study declined over time. The reasons for this are unclear. There have been recent national efforts aimed at reducing hospital infections including catheter-associated blood stream infections, but these would likely impact IE cases acquired in-hospital, rather than the cases included in the current analysis (20). The new AHA

guidelines emphasize the importance of maintaining good oral hygiene and routine dental care in the prevention of IE; further investigation is needed to evaluate trends in dental visits and dental care over time and whether this can be related to rates of IE (1).

Limitations

There are several limitations to this study. First, the PHIS Database does not contain outpatient prescribing data. Therefore we were unable to correlate the outcomes assessed in the present study with changes in prescribing practices. A previous survey of pediatric cardiologists in the US, Canada, Australia, and New Zealand suggested substantial reduction in the use of antibiotic prophylaxis following the 2007 AHA guidelines for a variety of congenital heart lesions (21). However these investigators also found wide variability among those surveyed, as well as a reduction in the use of prophylaxis for some conditions where prophylaxis is still recommended (21). Thus, further study of changes in prescribing practices is warranted. In addition, the PHIS Database does not capture information regarding outpatient dental visits so we were also unable to analyze these data. Second, while this multicenter study was able to capture a relatively large sample size, it does not capture all hospitalizations for IE in the US; and thus it is uncertain whether these results are generalizable to the overall population potentially impacted by the guideline change. We also restricted our case definition of IE to minimize the possibility of including patients with a history of IE, but not active disease, and to minimize the inclusion of patients admitted for some other reason who acquired IE later during the course of a hospitalization, as we hypothesized these cases were less likely to be related to antibiotic prophylaxis prior to a dental procedure. Thus, results of our analysis may differ compared with other studies that include all patients hospitalized with IE. Third, while we were able to evaluate patients with a diagnosis or procedure code related to CHD in subanalysis, the administrative nature of the database precluded a more detailed evaluation of specific diagnoses. Further investigation specifically of those patients with cardiac conditions who previously received antibiotics but now no longer do under the new guidelines may be warranted. In addition, although we evaluated available microbiological data coded in the database, not all patients had these data coded. Finally, while this study compiled data from 37 hospitals, given the rarity of IE it is possible that we were underpowered to detect small differences in the rate of IE over time. However, none of the point estimates in the overall cohort or subgroups evaluated suggest a trend towards an increase in IE cases, making this less likely.

Conclusions

In this multicenter analysis we did not find a significant change in the number of hospitalizations at US Children's Hospitals for IE before and after revision of the AHA antibiotic prophylaxis guidelines. Evaluation of prescribing patterns and more detailed assessment of high-risk patients is warranted to further characterize outcomes related to the new guidelines.

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Figure 1. Number of IE cases over time

The grey boxes represent the number of total patients hospitalized with IE during the time period specified. The solid lines represent 95% Poisson confidence intervals. The dotted line represents when the new AHA guidelines were published.

Figure 2. Number of IE cases over time indexed to total hospital admissions

The black squares represent the number of patients hospitalized with IE per 1000 total hospital admissions during the time period specified. The solid lines represent 95% Poisson confidence intervals. The dotted line represents when the new AHA guidelines were published.

Table 1

Study population characteristics

	(N=1157)
Age	2.9 yr (2.5 mo – 12.4 yr)
0 – 1 year	528 (46%)
1 year – 5 years	134 (12%)
5 years – 12 years	236 (20%)
12 years – 18 years	259 (23%)
Gender, male	674 (58%)
Race/Ethnicity	
Non-Hispanic White	476 (42%)
Non-Hispanic Black	244 (22%)
Hispanic	236 (21%)
Asian	45 (4%)
Other	121 (11%)
Congenital heart disease	782 (68%)
Payer	
Government	647 (56%)
Private	336 (29%)
Other	166 (15%)
Census Region	
South	504 (44%)
West	251 (22%)
North Central	252 (22%)
Northeast	150 (13%)

Data for continuous variables displayed as median (interquartile range); data for dichotomous variables displayed as number (percent)

Table 2

Estimated annual change in IE hospitalizations

	Before Guidelines	p-value [*]	After Guidelines	Difference	p-value ^{**}
Number of IE cases					
Overall	+1.4% (-2.9%, +5.8%)	0.54	+3.0% (-1.9%, +8.1%)	+1.6% (-6.4%, +10.3%)	0.70
CHD patients only	-5.3% (-17.4%, +8.5%)	0.43	-11.8% (-24.0%, +2.4%)	-6.8% (-27.7%, +20.1%)	0.58
Age 5-18 y only	+1.8% (-5.9%, +10.1%)	0.66	+1.4% (-7.3%, +10.8%)	-0.4% (-14.2%, +15.7%)	0.96
Oral streptococcal only	-2.5% (-14.2%, +10.9%)	0.70	-19.1% (-32.4%, -3.1%)	-17.1% (-36.9%, +9.0%)	0.18
Number of IE cases/ 1000 hospital admissions					
Overall	-5.9% (-9.9%, -1.8%)	0.005	-11.5% (-15.7%, -7.1%)	-5.9% (-13.3%, +2.2%)	0.15
CHD patients only	-12.3% (-24.9%, +2.5%)	0.10	-23.5% (-35.2%, -9.6%)	-12.8% (-34.5%, +16.2%)	0.35
Age 5-18y only	-5.5% (-12.6%, +2.2%)	0.15	-12.9% (-20.4%, -4.7%)	-7.8% (-20.7%, +7.2%)	0.29
Oral streptococcal only	-9.2% (-20.2%, +3.2%)	0.14	-30.9% (-42.3%, -17.1%)	-23.9% (-42.1%, +0.1%)	0.05

Data are presented as estimated annual change in cases of IE and 95% confidence intervals. The data in the "Difference" column show the difference in the post- vs. pre-guidelines period

* p-value for estimated annual change before guidelines.

** p-value for estimated difference in the post- vs. pre-guidelines period; represents whether the estimated annual change differs significantly between time periods.

CHD=congenital heart disease