Trends in Hospitalization for Infective Endocarditis as a Reason for Admission or a Secondary Diagnosis

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We postulate that the trends for infective endocarditis (IE) are different for patients admitted for this condition compared with those admitted for a different reason with IE as a secondary diagnosis. Using the Myocardial Infarction Data Acquisition System (MIDAS) database, we analyzed 21,443 records of patients hospitalized with diagnosis of IE from 1994 to 2015. There were 9,191 patients hospitalized with IE as the primary diagnosis, and 12,252 patients with IE as a secondary diagnosis. Piecewise linear models were used to detect changes in trends. A bootstrap method was used to assess the statistical significance of the slopes and break point of each model. Differences in co-morbidities and microbiological patterns were analyzed. Trend analysis showed a significant decrease in IE as the primary diagnosis starting in the year 2004 ($p < 0.01$). Hospitalizations with IE as a secondary diagnosis showed a linear increase in incidence ($p < 0.001$), without any change points. In primary diagnosis IE, the proportion of streptococci as a causative microorganism was higher compared with staphylococci ($p < 0.001$). On the contrary, in secondary diagnosis IE, the proportion of staphylococci was higher than streptococci ($p < 0.001$). The proportion of gram-negative and other organism IE was similar in both groups. In conclusion, this study showed 2 divergent temporal trends in hospitalizations for IE as a primary or secondary diagnosis starting in 2004. The profile of the microorganisms reveals a steady higher proportion of staphylococcal infection in secondary diagnosis IE compared with streptococcal infection. Different strategies are needed for the prevention of IE. **(Am J Cardiol 2019;124:430−434)**

The landscape of infective endocarditis (IE) started to change during the last decades of the 20th century with significant increase in the age of the patient. In the past, IE was closely associated with rheumatic heart disease and was most often caused by Viridans group streptococcus species, a class of organisms common to the oral flora.[1−4] New risk factors have emerged. Intravenous drug abuse, immunocompromised states, and device implants now contribute to a significant proportion of IE cases.[5] In recent years, several observational studies on IE trends have shown conflicting results. Although some report a steady rate of IE, despite the changes in the guidelines, others have reported an increasing incidence.[6−10] In this New Jersey population-based study, we analyzed the trends of IE, coded as primary diagnosis, compared with IE coded as secondary diagnosis IE. Different trends in IE as the reason for admission or secondary diagnosis may explain the conflicting reported results of the incidence of IE.

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Methods

We performed a retrospective, observational study using the Myocardial Infarction Data Acquisition System (MIDAS) database. This previously validated database includes discharge data for all patients with cardiovascular diseases admitted to every nonfederal hospital in New Jersey.[11] MIDAS provides information on patient demographics (age, gender, and race), co-morbidities, procedures, insurance type, length of stay, and discharge status.

We examined 21,443 records of patients admitted to New Jersey hospitals with a diagnosis of IE from 1994 to 2015 (ICD9 codes 421.0, 421.1, 421.9, and 424.9). There were 9,191 patients admitted with IE as primary diagnosis (Dx1) and 12,252 patients with IE as a secondary diagnosis (Dx2-9). Only first admissions for IE of individual patients were included in the analysis. Patients transferred from another hospital were considered a single episode of IE, and the diagnosis code position from the final institution was used. Four microbiology groups were included: staphylococcus, streptococcus, gram negative, or other (i.e., fungi). Microorganisms were identified by searching the diagnostic codes 0.41.x, 0.38.x, 112.x, 115.x, 117.x, and 003.x. The study was approved by the Robert Wood Johnson Medical School Institutional Review Board.

Categorical variables were analyzed (Tables 1 to 3) using chi-square tests for 2-way table. For the continuous variable age in Table 1, the means of the 2 groups were

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Table 1
Demographics and clinical characteristics

Variable	Total (n = 21,443)	IE primary diagnosis (Dx1) (n = 9,191)	IE secondary diagnosis (Dx2-9) (n = 12,252)	p Value
Mean age (±SD) (years)	63.5 ± 18.1	61.9 ± 18.7	64.6 ± 17.6	<0.0001
Male	12,415 (58%)	5,406 (59%)	7,009 (57%)	
Female	9,028 (42%)	3,785 (41%)	5,243 (43%)	0.0187
White	15,599 (73%)	6,945 (76%)	8,654 (71%)	<0.0001
Black	4,019 (19%)	1,469 (16%)	2,550 (21%)	<0.0001
Others	1,825 (9%)	777 (9%)	1,048 (9%)	0.8147
Congenital heart disease	282 (1%)	154 (2%)	128 (1%)	<0.0001
Rheumatic heart disease	4,029 (19%)	1,805 (20%)	2224 (19%)	0.0006
Hypertension	13,879 (65%)	5,341 (58%)	8,538 (70%)	<0.0001
Diabetes mellitus	7,127 (33%)	2,588 (28%)	4,539 (37%)	<0.0001
Renal disease	8,302 (39%)	2,709 (30%)	5,593 (46%)	<0.0001
Atrial fibrillation	6,272 (29%)	2,455 (27%)	3,817 (31%)	<0.0001
Chronic lung disease	8,662 (40%)	2,873 (31%)	5,789 (47%)	<0.0001
Cancer	2,926 (14%)	1,041 (11%)	1,885 (15%)	<0.0001
Human immunodeficiency virus	990 (5%)	212 (2%)	778 (6%)	<0.0001
Aortic valve surgery*	447 (2%)	215 (2%)	232 (2%)	0.0027
Mitral valve surgery*	733 (3%)	392 (4%)	341 (3%)	<0.0001

* During IE admission.

Table 2
Rate of procedures considered predisposing factors for infective endocarditis

Variable	Total n = 21,443	IE primary diagnosis (Dx1) n = 9,191	IE secondary diagnosis (Dx2-9) n = 12,252	p Value
CIED	2,761 (13%)	925 (10%)	1,836 (15%)	<0.0001
IABP/LVAD	454 (2%)	164 (2%)	290 (2%)	0.0004
Hemodialysis	3,463 (16%)	1,117 (12%)	2,346 (19%)	<0.0001
History of valve surgery	1,937 (9%)	675 (7%)	1,262 (10%)	<0.0001

CIED = cardiac implantable electronic device; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device.

compared using a 2-sample *t* test. We performed logistic regressions to study the trends in organism proportions. The predictors were year as a continuous variable, group Dx1 and Dx2-9 as categorical variables, and the interaction term between year and group. Change-point analysis was done to detect changes in the trend of overall incidence of IE. Change-point analysis consisted of fitting a trend up to a point where the slope changed direction to a new trend. A bootstrap method was used to assess the statistical significance of the slopes and change point of each model.

Results

From 1994 to 2015, a total of 21,443 patients were hospitalized in New Jersey with a diagnosis of IE. Table 1 depicts the demographics and clinical characteristics of patients with IE as Dx1 and Dx2-9. Although the proportion of males was similar in Dx1 compared with Dx2-9, the small difference was statistically significant. Likewise, this occurs for females, but with a higher proportion in Dx2-9. Controlling for multiple comparisons, the proportion of whites was higher in Dx1 compared with Dx2-9, whereas, the proportion of blacks was lower in Dx1 compared with Dx2-9. There were no statistically significant differences in other races. The proportion of patients with congenital heart disease and rheumatic heart disease were higher in Dx1, whereas all other co-morbidities were higher in patients with Dx2-9. As expected, valve surgery during the IE admission was more frequent in Dx1. The procedures that we considered predisposing factors for IE are shown in Table 2. Cardiac implantable electronic devices, intra-aortic balloon pumps, hemodialysis, and history of valve surgery were more frequent in those with IE as a secondary diagnosis.

Controlling for multiple comparisons (Bonferroni correction) only the difference in proportion of staphylococcus

Table 3
Type of organisms found in primary and secondary infective endocarditis diagnosis

Organism	Total n = 14,056	IE primary diagnosis (Dx1) n = 6,173	IE secondary diagnosis (Dx2-9) n = 7,883	p Value
Staphylococcus	7,636 (54%)	2,864 (46%)	4,772 (61%)	<0.0001
Streptococcus	5,669 (40%)	2,980 (48%)	2,689 (34%)	<0.0001
Gram Negative	559 (4%)	262 (4%)	297 (4%)	0.1640
Other	192 (1%)	67 (1%)	125 (2%)	0.0138

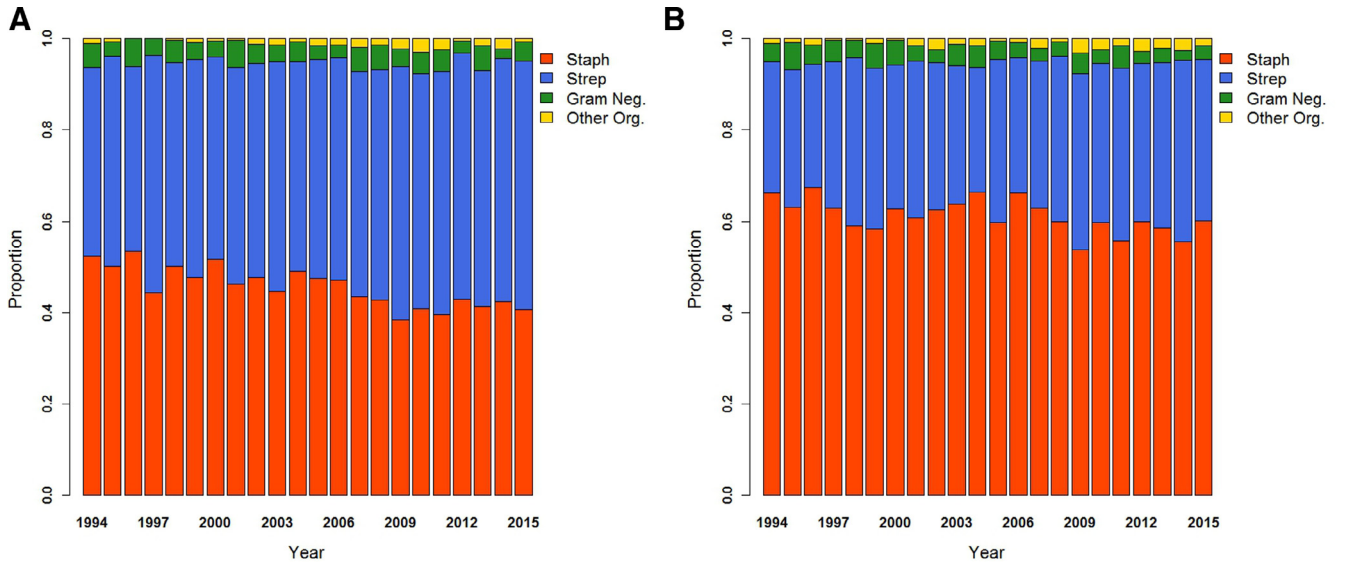

Figure 1. (A) Organism proportions by year for infective endocarditis as primary diagnosis (Dx1). (B) Organism proportions by year for infective endocarditis as secondary diagnosis (Dx2-9).

and streptococcus were different in Dx1 compared with Dx2-9. The proportion of streptococcus was higher in Dx1, and the proportion of staphylococcus was higher in Dx2-9 (Table 3). Figure 1 shows the yearly trends in organism proportions. In Dx1, the proportion of staphylococcus decreased from 54% in 1994 to 40% in 2015 ($p < 0.0001$). The proportion of streptococcus increased from 42% in 1994 to 56% in 2015 ($p < 0.0001$). In Dx2-9, the proportion of staphylococcus compared with streptococcus was higher throughout the years without significant changes from 1994 to 2015 (69% to 61%, $p = 0.97$). There was no significant increase in the proportion of streptococcus from 1994 to 2015 (29% to 35%, $p = 0.53$).

The incidence of IE in New Jersey increased from 1994 to 2015 with divergent trends between Dx1 and Dx2-9 starting around 2004 (Figure 2). Change-point analysis detected a significant shift in the rate of IE between 2004 and 2005 (Figure 2). The incidence in IE in Dx1 shows a significant

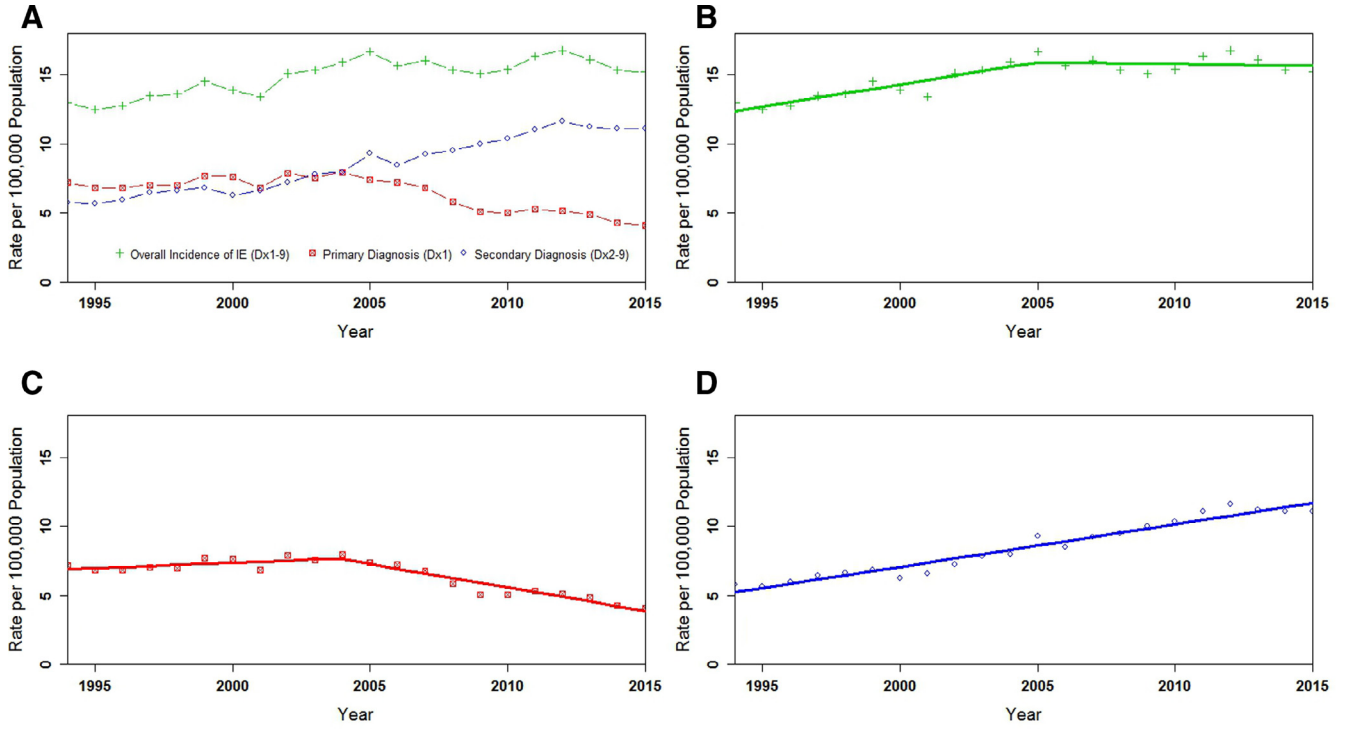

Figure 2. Incidence and change-point analysis of infective endocarditis (IE) in New Jersey between 1994 and 2015. (A) Overall incidence of IE (Dx1-9), and by primary diagnosis (Dx1) and secondary diagnosis (Dx2-9). (B) Change-point model of the overall incidence rate of IE (Dx1-9). (C) Change-point model of incidence rate of IE in primary diagnosis (Dx1). (D) Linear model of incidence rate of IE in secondary diagnosis (Dx2-9).

downward shift starting in 2004 (Figure 2) whereas IE in Dx2-9 showed a steady increase without any change point (Figure 2). Eleven percent of patients admitted with IE in Dx1 died during hospitalization and 17% of those admitted with IE in Dx2-9. Of those discharged alive 21% and 29% respectively died within a year.

Discussion

Since the last decades of the 20th century, epidemiologic studies have observed a shift in the source of IE.[1,2,4] Although early on, oral portal of entry of streptococcal infections were more common, currently an increasing number of IE cases with cutaneous portal of entry have been seen.[12–14] We, and other investigators, found an overall increase in the rate of admission for IE in the last 2 decades, possibly due to the aging population, associated co-morbidities, intravenous drug abuse, intracardiac devices, and the increasing number of patients on hemodialysis.[4,5,14] We analyzed our data in 2 different groups: (1) patients hospitalized with primary diagnosis of IE and (2) patients hospitalized for another reason with IE as a secondary diagnosis.

In the first group we observed a flat rate of IE between 1994 and 2004 with a steady decline thereafter. The reasons for the downward trend starting in 2004 are unclear, and probably not related to the 1997 and 2007 guideline changes.[10] One possibility is the rarity of rheumatic heart disease, together with more frequent and effective dental care by the general population. A similar declining trend starting in 2007 was reported by Bikdeli et al.[15] More recently, Thornhill et al in a paper correlating the number of antibiotic prescriptions for IE prophylaxis, showed a declining trend starting in 2004, and that is before the latest guideline changes.[10]

We observed a steady increase in the incidence of IE as a secondary diagnosis. These patients were hospitalized for reasons other than IE, and they developed IE during the hospitalization implicating health care as a possible source. The proportion of IE as a secondary diagnosis in this study was higher than the approximately 30% incidence reported for healthcare-associated IE.[16–18] This may be due to the following factors: (1) that is, originated in tertiary academic medical centers where both treatment and coding of IE may be different, (2) used the Duke criteria for the diagnosis of IE, (3) included only patients with native valve IE, and (4) frequently excluded patients with a history of drug abuse.

Several studies from Europe and a few from the United States have reported that despite the more restrictive guidelines for the prophylaxis of IE, the incidence has not changed during the last decade.[6–8,15] On the contrary, a number of recent studies have described a concerning rise in incidence as well as changes in the microbiology.[4,9,14,19,20] None of these studies have analyzed separately the source of IE acquisition, and most of them have focused on the temporal relation with changes in the guidelines.[7–10]

Staphylococcus and streptococcus are the most common microorganisms associated with IE. In our study, both staphylococcus and streptococcus have similar prevalence in IE as a primary diagnosis (46% and 48% of IE cases, respectively). In cases that carried IE as a secondary diagnosis, there was a statistically significant difference in incidence of staphylococcus IE (61%) than streptococcus IE (34%). The incidence of gram-negative organisms was similar in both primary and secondary diagnoses. We found a large proportion of IE cases associated with staphylococcus in both groups across all years studied. In patients with primary diagnosis of IE, the proportion of staphylococcus infections was nonpredominant and showed a declining trend. On the contrary, when IE was coded as a secondary diagnosis, staphylococcus was the predominant organism with a steady rate of approximately 60%. This microorganism profile fits well with a healthcare-associated pattern of IE in which traditional predisposing conditions are infrequent and IE guidelines prevention do not apply. The yearly rate of gram negative and other organism IE has remained constant.

This study possesses all the inherited limitations of retrospective, observational investigations. In addition, we have no information on blood cultures in 38% of patients with primary and 36% secondary diagnoses of IE. The frequency of blood culture negative IE has been estimated between 3% and 30%.[21] There may be several reasons for this such as: true negative blood cultures, use of antibiotics before admission, the information coded below the ninth diagnosis position, or simply not coded. The information was randomly missing, and would not change the results. Also, the diagnosis of IE is a clinical diagnosis, and validation studies for the accuracy of the ICD codes for IE are scant.[22] A valuable strength of the study are that we included all patients admitted with a diagnosis of IE avoiding selection bias of patients being referred to tertiary care hospitals. A unique feature is that the data were analyzed separately for primary and secondary diagnoses cases of IE which may help in tailoring different strategies for the prevention of this potentially catastrophic disease.

In conclusion, we show different trends of the incidence of IE between patients with primary diagnosis and patients with secondary diagnosis of IE. Patients admitted with IE as a secondary diagnosis had higher mortality both during hospitalization and within a year after discharge probably as a result of associated co-morbidities. Divergent trends began in 2004 preceding the latest IE prophylaxis guidelines, and may explain in part the controversial published results about the incidence trends of IE.

Disclosures

The authors have no conflict of interest to disclose.

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