Title: Trends, microbiology and outcomes of Infective Endocarditis in Children during 2000-2010 in the United States

Authors: Shipra Gupta MD[1], Ankit Sakhuja MD[2], Eric McGrath MD[1], Basim Asmar MD[1]

Affiliations:

[1]Division of Infectious Diseases, Department of Pediatrics, Children's Hospital of Michigan, Detroit MI

[2]Division of Nephrology, Department of Internal Medicine, University of Michigan, Ann Arbor MI

Corresponding Author:

Shipra Gupta MD

3901 Beaubien, Detroit, MI - 48201

Phone: 313 745 5862

Fax: 313 993 8846

Email: drshipragupta@yahoo.co.in

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ABSTRACT:

Keywords: Infective endocarditis, pediatrics, epidemiology, microbiology, outcomes

Background:

We studied the incidence, trend, underlying conditions, microbiology and outcomes of Infective endocarditis (IE) in children during 11 years using Nationwide Inpatient Sample (NIS) database. This is the largest all-payer inpatient care database in the United States containing data for more than 8 million hospital stays from over 1,000 hospitals.

Methods:

NIS data from 2000 to 2010 of primary discharge diagnosis of IE in children aged ≤19 years old were studied. Children with underlying congenital heart defects and acquired heart conditions were identified. Microbiological causative agents were recorded. Linear regression was used to assess trend of incidence over time.

Results:

An estimated 3,840 (95% CI: 3,395-4,285) children had a discharge diagnosis of IE. The overall incidence was 0.43 per 100,000 children. The incidence was stable over the study period (p=0.4 for trend). The majority of patients 56.2% were ≥11 years old and 15.4% were ≤ 1 year. Underlying cardiac conditions were present in 53.5% of patients. Overall 30.2% of cases were culture-negative. Among those with identified pathogens, Staphylococcus species were most common (43.1%) followed by Streptococcus species (39.5%). Viridans

Streptococcus group was most common in those with underlying heart disease (32.7%) and *S. aureus* was most common in those without heart disease (46.9%). Among culture-positive patients, there was a decline in proportion of Staphylococcal IE (p=0.03) and an increase in proportion of Streptococcal IE (p=0.04). Overall mortality was 2.8%. Patients with Staphylococcal IE had longer median length of stay (12 vs. 9 days; p<0.01) and the highest mortality (4.7%).

Conclusion:

The incidence of IE in children has remained unchanged in the US during the 11 year study period. Among culture-positive patients there was a significant decrease in Staphylococcal IE and a significant increase of Streptococcal IE. Staphylococcal IE was associated with increased LOS and highest mortality.

INTRODUCTION:

During the past decade there has been an increase in the risk factors for infective endocarditis (IE). The advancements in cardiovascular surgery have led to improved survival of children with congenital heart disease (CHD) beyond infancy and into adulthood (1). These children are at increased risk of developing post-operative infections including IE due to presence of prosthetic devices placed for correction or palliation of heart defects (2-5). There has also been an increase in the use of central venous catheters in children for medication infusion and blood drawing, thus increasing the risk of catheter-related infections, including IE (6). With the increase in these risk factors, there is an expected increase in incidence of endocarditis. Also, the advancements in microbiologic techniques has lead to improved recovery and better identification of organisms in blood and tissue cultures, thereby improving the etiologic diagnosis of previously culture-negative labeled IE cases.

The overall incidence of endocarditis has increased during the past several years. In a recent report by Bor et al, during the period 1998-2009 hospital admissions for IE in the US rose from 25,511 (9.3 per 100,000 population) to 38,976 (12.7 per 100,000 population). The endocarditis admission rate increased 2.4% annually after adjustment for population growth and aging. Pediatric cases (<18 years) accounted for 1.9% of total cases (7). In a more recent report by Pant et al, based on national data for the period 2000-2011 the incidence of IE increased from 11 per 100,000 in US population to 15 per 100,000 (8).

In children, hospitalization rates due to infective endocarditis (IE) are lower as compared to adults. One report from a single institution estimated that IE cases during 1972 to 1982 accounted for 1 in every 1280 (0.78 per 1000) pediatric admissions annually (9). More recent data from a multi-center study estimated that there were between 0.05 to 0.12 IE cases per 1000 hospital admissions during 2003 to 2010 (10, 11). IE incidence is higher in children with underlying congenital heart disease (CHD) and was estimated as a cumulative incidence of 6.1 per 1000 children (12). There is paucity of data regarding recent national trends of IE in children. We used a nationally representative sample of hospitalized children to assess the recent trends in incidence, microbiology and outcome of infective endocarditis during the period 2000-2010.

METHODS:

Study Design and Data Source

We performed a retrospective study using national data from the Healthcare Cost and Utilization Project - Nationwide Inpatient Sample (NIS). NIS is the largest all-payer inpatient care database publicly available in the US that contains data from a 20-percent stratified sample of U.S. community hospital (13). Each hospitalization is treated as an individual database entry and information regarding common demographic variables - age, race and sex along with primary insurance, hospital characteristics - teaching status, location (rural vs. urban), size of hospital and hospital region are available. Data from 2000-2010 period were used for this study. We used the provided principal diagnosis, secondary

diagnoses and procedural diagnoses associated with each hospitalization in the database for this study.

Study Population

We included hospitalizations of patients with age≤19years. In accordance with previous literature [7] we defined infective endocarditis as designated by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for acute and subacute endocarditis (421.X), gonococcal endocarditis (098.84), meningococcal endocarditis (036.42), candidal endocarditis (112.81) and histoplasma endocarditis (115.04, 115.14, 115.94). [7] We excluded those with non-infectious or chronic endocarditis.

Study Variables

We identified demographic characteristics (age, sex and race), hospital characteristics (teaching status, location, bed-size and region) and primary payer using appropriate variables from the NIS database. The causative organisms and predisposing cardiac conditions using ICD-9-CM codes are detailed in supplemental Table S1 and S2.

Outcomes

Our primary outcome of interest was all cause in-hospital mortality. We also looked at length of stay (LOS) for those hospitalized with IE. In addition, we looked at complications of IE during that hospitalization – acute kidney injury (AKI), stroke, mechanical ventilation use, acute myocardial infarction, central nervous system (CNS) abscess, meningitis, encephalopathy, convulsions and

extracorporeal membrane oxygenation (ECMO) use. We assessed the proportion of those undergoing cardiac valve replacement during that admission. The ICD-9-CM codes used to identify these complications are provided in Table S3.

Statistical Analysis

We performed all statistical analysis using STATA 13.1 (College Station, TX). Using the weights provided in NIS database, we generated national estimates for the number of overall IE hospitalizations. The incidence of IE hospitalizations per 100,000 population was calculated by utilizing annual population estimates from the United States Census Bureau. We used the chi square test to compare categorical variables and linear regression to assess the significance of trends over time. A p value of ≤0.05 was deemed significant.

RESULTS:

Incidence of IE:

An estimated 3,840 (95% CI: 3,395-4,285) children had a discharge diagnosis of IE representing an overall incidence of 0.43 per 100,000 children. The incidence of IE was stable over the study period (p=0.4 for trend). (Fig I)

Study population demographics and hospital status (Table 1):

The general characteristics of the study population and treating hospital are summarized in Table 1. The majority of patients,56.2%, were 11-19 yrs old and

15.4% were ≤ 1year old. Males comprised 54.0% of patients, 45.9% were white, 13.7% black and 13.7% Hispanic.

Underlying cardiac conditions were present in 53.5% of patients. These subjects were mostly ≤10 years old, male and white. They were also more often admitted to teaching hospitals (84.9%) when compared to patients without underlying cardiac conditions (78.5%) (p=0.06). Among those with cardiac conditions, 81.4% had congenital heart disease, 15.2% rheumatic heart disease, 7.5% prosthetic valve, 3.9% cardiac device and 3.6% had cardiomyopathy.

Microbiology :

A code for any organism was not included in 30.2% of IE discharges and thus were considered culture-negative. In those with culture-positive IE, Staphylococcus species were the most common (43.1% hospitalizations) pathogen followed by Streptococcus species (39.5%). When categorized further, *Staphylococcus aureus* accounted for 36.6% of hospitalizations and viridans Streptococcus Group (VSG) for 26% whereas 11.1% of hospitalizations were coded for more than one microorganism (Fig II). VSG was the most common pathogen in those with underlying heart condition (32.7%) and *Staphylococcus aureus* was most common in those without underlying heart condition (46.9%) (Table 2).

Among patients with positive cultures, the proportion of Staphylococcal IE decreased from 46.9% in 2000 to 33.1% in 2010 (p=0.03 for trend) whereas the

proportion of Strep spp. IE increased from 35.1% in 2000 to 45.0% in 2010 (p=0.04 for trend).

Outcomes:

The overall mortality of IE during the study period was 2.8%. Mortality was higher in those with staphylococcal IE in comparison to non-staphylococcal IE (4.7% vs. 1.9%; p=0.04) (Table 3). The median length of hospital stay was 10 days (IQR 5-19d). Median length of stay was longer by 3 days in patients with Staphylococcus species infection compared to those with other causative organisms (12d vs. 9d; p<0.001). Median hospital length of stay was not different between those with or without underlying cardiac conditions.

Overall 7.1% of IE patients had evidence of acute kidney injury (AKI). Proportion of AKI was higher in those with staphylococcal IE vs. non- staphylococcal IE (10.8% vs. 5.5%; p=0.006). AKI occurred less often in children with underlying cardiac condition than those without (5.0% vs. 9.5%; p=0.02). Mechanical ventilation was used in 7.8% of all patients. There was a trend for increased use of mechanical ventilation in those with staphylococcal IE compared to others (10.3% vs. 6.8%; p=0.07). Stroke was seen in 5.6% of patients. The proportion was similar between those with and without cardiac conditions as well as those with staphylococcal IE vs. others. Cardiac valve replacement surgery was performed in 9.2% of patients. Complications of acute myocardial infarction, CNS abscess, meningitis, encephalopathy, convulsions and ECMO use were too few for meaningful interpretation.

DISCUSSION:

Using nationally representative data our study showed that the mean incidence of infective endocarditis in children was 0.43 per 100,000 children with a stable annual incidence during the 11-year study period. Staphylococcus species were the most commonly recovered pathogens from patients with culture-positive IE. Staphylococcal IE was also associated with longer LOS and had the highest mortality rate. However, the proportion of Staphylococcal IE showed a decline during the study period.

Infective endocarditis incidence of 0.43 per 100,000 children noted in our study is similar to previously reported regional and national estimates that varied between 0.34 to 0.64 per 100,000 children (14, 15). The incidence of IE in the pediatric population is lower than that in adults, which was most recently reported to be 15 per 100,000 population (8).

During the study period there was a stable trend in the incidence of IE in children, which is similar to what Pasquali et al reported recently (10). This is, however, in contrast to the increasing trends of IE in the adult population recently reported by Pant et al (8). This increasing incidence has been attributed to an increase in the size of at risk population, such as older, diabetic and hemodialysis-dependent patients (16, 17).

Day et al had previously described a bi-modal age distribution of IE cases with peaks in infancy and later teens during the period 2000-2003 (18). In our study, however, the majority of IE cases were in children 11 years and older (56.2%). There was also a high proportion of IE cases in children without underlying

cardiac conditions (46%) which is similar to previously reported estimates from multicenter hospitalization data in which 58% of IE cases did not have underlying cardiac condition identified (18). This could possibly represent undiagnosed or missed cardiac conditions in children with IE during late childhood. In contrast, Rosenthal et al reported a decreasing proportion of IE in children with no underlying heart disease from 31% to 18 % during 1977 to 2004(19). However, their data were from a single children's hospital that served as a referral center for children with congenital heart disease leading to sampling bias.

In our study 30.2 % of the hospitalizations were not coded for an organism, which is within the range of previously reported incidence range of 2.5 to 31% of culture-negative IE (20). Most common causes for culture-negative IE are either antimicrobial therapy prior to obtaining blood cultures or IE caused by pathogens that are slow growing or difficult to recover by standard blood culture techniques. We saw a trend towards decline in the incidence of culture-negative IE cases from 35.5% in 2000 to 18.3% in 2010 (p=0.06 for trend). We speculate that this is likely due to improvement in molecular diagnostic techniques to identify 16s Ribosomal RNA or DNA from tissue or blood (21).

In a recent study by Day et al Staphylococci or Streptococci were the predominant IE pathogens identified in more than 90% of their culture-positive cases (18). The majority of our study culture-positive IE cases were caused by Staphylococcus species (43.1% hospitalizations) followed by Streptococcus species (39.5%). However, there was a decline in Staphylococcal IE over the

study period. This is in contrast to recent trend noted in adult IE cases as reported by Pant et al where they was relative increase in Staphylococcal IE of 18.9% during the period of 2000 to 2011 (8). We found an increasing trend for Streptococcal IE during the study period (p for trend=0.04). We wanted to assess the impact of the 2007 ACC/AHA IE antibiotic prophylaxis guidelines on rates of Streptococcal IE (22). However, we did not find any significant change in Streptococcal IE in children when comparing rates during 2000-2007 with rates 2008-2010. This result is concordant with previously reported studies where no change was noted during similar period (7, 10, 23, 24).

The overall mortality for IE cases in our present study was 2.8%, as compared to previously reported mortality rates of 1.1 to 18% (10, 25). Staphylococcal IE was associated with increased mortality that is anecdotally reported in multiple reports, especially with *S. aureus* (4, 18, 25, 26). Staphylococcal IE was also associated with significant morbidity with increased use of mechanical ventilation and acute kidney injury.

Although we have used a nationally representative database, our study has important limitations. First, we used ICD-9-CM codes for identification of patients with infective endocarditis. Although, this methodology has been used in both adult and pediatric studies, we cannot exclude variations in coding practices that may have led to over or under-estimation of IE incidence rates. Also we were unable to ascertain if these cases fulfilled Modified Duke criteria for diagnosis of IE as well further classification of IE. Limited microbiologic data was available with the ICD-9-CM coding and data describing which valves were affected could

not be ascertained. Possible coding errors as well as lack of information after discharge including total treatment duration pose considerable limitation to the study. Second, as NIS does not have unique patient identifiers, we were unable to identify readmissions or transfers between hospitals. Lastly, the outcome data could not be further subcategorized according to different IE pathogens because of very few numbers of such patients.

Conclusions:

Our study has several important findings. Firstly, the incidence of IE in children has remained stable during the study period. Secondly, *S. aureus* was the commonest causative organism in pediatric IE cases; however, there was a declining trend during the study period. Staphylococcal IE was associated with higher mortality, LOS, AKI and need for mechanical ventilation. Thirdly, the trend for Streptococcal IE related hospitalizations were increasing over the study period.

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None

Author contributions:

SG has made substantial contributions to conception and design of the study. All authors have made substantial contributions to analysis and interpretation of data. SG has drafted the initial manuscript. All authors have revised the manuscript for important intellectual content and have provided the final approval for the version to be published.

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Legends for illustrations:

Fig I: Incidence trends of infective endocarditis in US children during 2000-2010

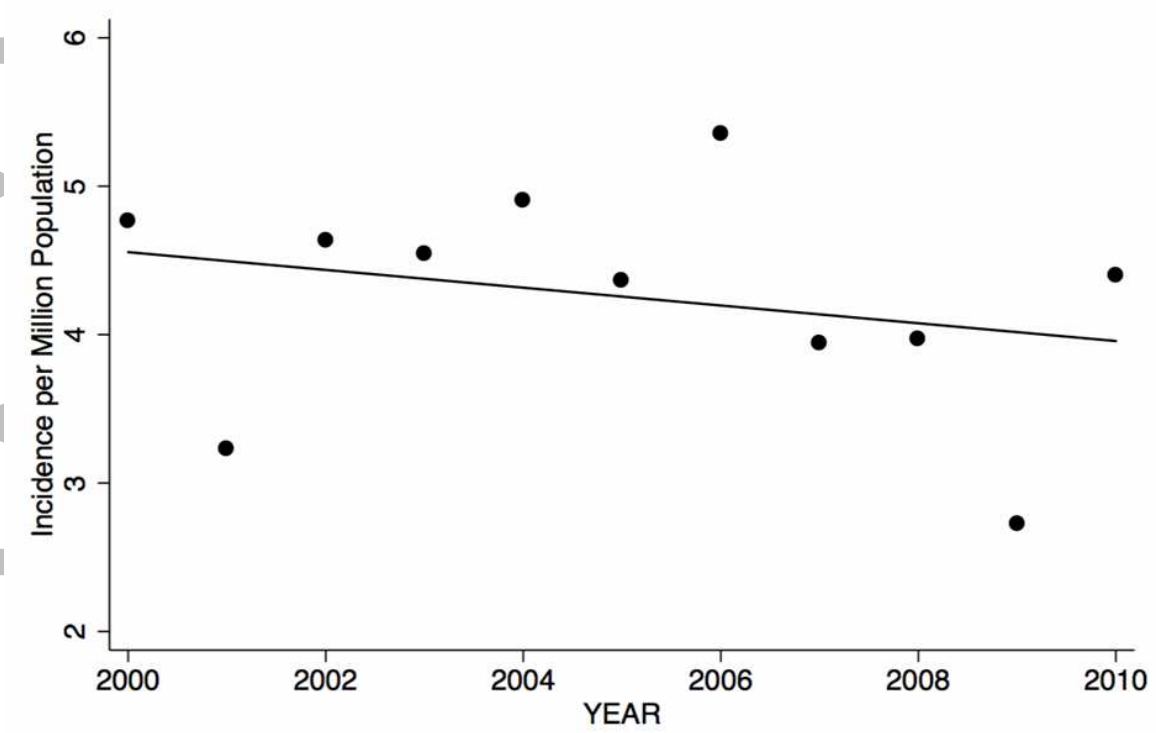

Fig II: Distribution (%) of microorganisms isolated in culture-positive infective endocarditis cases in US children during 2000-2010

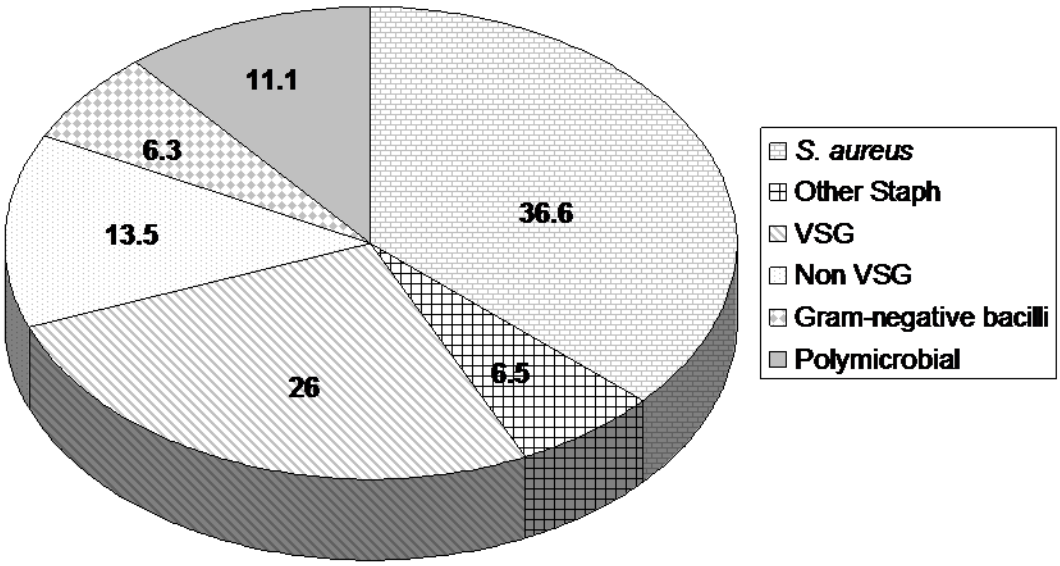

Table 1: Demographics of US children with infective endocarditis and treating hospital characteristics (2000-2010)

Characteristic	Percent
Age	
≤1 yr	15.4
2-5 yr	11.7
6-10 yr	16.6
11-19 yr	56.2
Male	54
Ethnicity *	
White	45.9
Black	13.7
Hispanic	13.7
Asian	2.6
Native-American	0.8
Others	4.2
Insurance	
Medicaid	37.6

Private	51.5
Medicare	0.7
Others	4.4
Self-pay	4.7
Teaching hospital	81.9
Region	
South	38.7
West	21.3
Midwest	20.1
Northeast	19.8

* 19.1% of cases did not have data on race/ethnicity.

Table 2: Causative organisms of infective endocarditis in US children with and without underlying cardiac condition (2000-2010)

Organism	Underlying cardiac conditions	No underlying cardiac conditions
S. aureus	**28.1%**	**46.9%**
Staph spp	6.6%	6.3%
Viridans Strep.	**32.7%**	**17.9%**
Other Strep	16.5%	9.9%
Gram-Negative Bacilli	5.3%	7.5%
Polymicrobial	10.9%	11.5%

Table 3: Difference in outcomes of US children with Staphylococcal vs. Non-Staphylococcal infective endocarditis* (2000-2010)

Outcomes	Staphylococcal IE	Non-Staphylococcal IE	p value
LOS	12 days	9 days	<0.001
Complications			
Acute Kidney Injury	10.8%	5.5%	0.006
Stroke	7.4%	4.8%	0.15
Mechanical ventilation	10.3%	6.8%	0.07
Mortality	4.7%	1.9%	0.04

* includes culture-negative IE cases

Table S1: ICD-9-CM codes used to identify causative organisms of infective endocarditis in US children (2000-2010)

Organism	ICD-9-CM
S. aureus	038.11, 038.12, 041.11, 041.12
Other staphylococci	038.1, 038.10, 038.19, 041.1, 041.10, 041.19
Viridans Streptococcus Group	041.00, 041.09
Non-viridans Strep	038.0, 038.2, 041.0, 041.01, 041.02, 041.03, 041.04, 041.05
Gram Negative Bacilli	038.4, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 041.85, 041.3, 041.4, 041.5, 041.6, 041.7
Anaerobic	038.3, 041.82, 041.83, 041.84
Other Bacterial Infections	038.8, 002.0, 036.42, 041.89, 041.81, 098.84, 083.0

Fungal Infections	112.81, 116.0, 115.04, 115.14, 115.94

Table S2: ICD-9-CM codes used to identify underlying cardiac conditions in US children with infective endocarditis (2000-2010)

Underlying cardiac condition	ICD-9-CM
Congenital Heart Disease	745, 745.0, 745.1, 745.10, 745.11, 745.12, 745.19, 745.2, 745.3, 745.4, 745.5, 745.6, 745.60, 745.61, 745.69, 745.7, 745.8, 745.9, 746, 746.0, 746.00, 746.01, 746.02, 746.09, 746.1, 746.2, 746.3, 746.4, 746.5, 746.6, 746.7, 746.8, 746.81, 746.82, 746.83, 746.84, 746.85, 746.86, 746.87, 746.89, 746.9, 747, 747.0, 747.1, 747.10, 747.11, 747.2, 747.20, 747.21, 747.22, 747.29, 747.3, 747.31, 747.32, 747.39, 747.4, 747.41, 747.42, 747.49, 747.5, 747.6, 747.60, 747.61, 747.62, 747.63, 747.64, 747.69, 747.8, 747.81, 747.82, 747.83, 747.89, 747.9
Rheumatic Heart Disease	393, 394, 394.0, 394.1, 394.2, 394.9, 395, 395.0, 395.1, 395.2, 395.9, 396, 396.1, 396.2, 396.3, 396.8, 396.9, 397, 397.0, 397.1, 397.9, 398, 398.0, 398.9, 398.90, 398.91, 398.99
History of Heart Transplant	V43.2, V43.21, V43.22

History of Artificial Valve	V42.2, V43.3
Cardiac Device in situ	V45.0, V45.00, V45.01, V45.02, V45.09
Cardiomyopathy	425, 425.0, 425.1, 425.2, 425.3, 425.4, 425.5, 425.7, 425.8, 425.9
Syphilitic Endocarditis	093.2, 093.20, 093.21, 093.22, 093.23, 093.24

Table S3: ICD-9-CM codes used to identify complications of infective endocarditis in US children (2000-2010)

Complications	ICD-9-CM codes
Acute Kidney Injury	584, 584.5, 584.6, 584.7, 584.8, 584.9
Acute Myocardial Infarction	410, 410.0, 410.00, 410.01, 410.02, 410.1, 410.10, 410.11, 410.12, 410.2, 410.20, 410.21, 410.22, 410.3, 410.30, 410.31, 410.32, 410.4, 410.40, 410.41, 410.42, 410.5, 410.50, 410.51, 410.52, 410.6, 410.60, 410.61, 410.62, 410.7, 410.70, 410.71, 410.72, 410.8, 410.80, 410.81, 410.82, 410.9, 410.90, 410.91, 410.92
Stroke	430, 431, 432.0, 432.9, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91
CNS abscess	320, 320.0, 320.1, 320.2, 320.3, 320.7, 320.8, 320.81, 320.82, 320.89, 320.9, 112.83, 114.2, 115.01, 115.11, 115.91, 324, 324.0, 324.1, 324.9
Encephalopathy	348.3, 348.30, 348.31, 348.39
Convulsions	780.3, 780.31, 780.32, 780.39
Mechanical Ventilation Use	96.70, 96.71, 96.72
ECMO use	39.65

Valve Replacement	35.2, 35.20, 35.21, 35.22, 35.23, 35.24, 35.25, 35.26, 35.27, 35.28