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Clinical Research

Trends and Outcomes of Infective Endocarditis in Adults With Tetralogy of Fallot: A Review of the National Inpatient Sample Database

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See editorial by Opotowsky et al., pages 688–691 of this issue.

ABSTRACT

Background: Lesion complexity and prosthetic valves are known risk factors for infective endocarditis in patients with congenital heart disease. Tetralogy of Fallot (TOF) is the most common complex/cyanotic congenital heart disease and often requires prosthetic valve implantation. Population-based risk of endocarditis in TOF patients is unknown.

Methods: We reviewed the National Inpatient Sample (NIS) and identified admissions in TOF patients (>18 years), 2000 to 2014. The primary outcome was to describe incidence of endocarditis-related admissions. To assess trends, we divided the study period into tertiles: early (2000 to 2004), mid (2005 to 2009) and late (2010 to 2014) eras. The secondary outcome was to compare in-hospital mortality, complications, and health care resource utilization between admissions with and without endocarditis.

Results: There were 393 (2.1%) endocarditis-related admissions among 18,353 admissions, and the incidence of endocarditis-related

RÉSUMÉ

Introduction : La complexité des lésions et les prothèses valvulaires sont des facteurs de risque connus de l'endocardite infectieuse chez les patients atteints d'une cardiopathie congénitale. La tétralogie de Fallot (TF) est la cardiopathie congénitale cyanotique la plus complexe qui mène souvent à l'implantation d'une prothèse valvulaire. Le risque en population générale d'endocardite chez les patients atteints de la TF est inconnu.

Méthodes : Nous avons passé en revue la National Inpatient Sample (NIS) et relevé les admissions de patients atteints de TF (> 18 ans), de 2000 à 2014. Le critère d'évaluation principal permettait de décrire la fréquence des admissions liées à une endocardite. Pour évaluer les tendances, nous avons divisé la période d'étude en 3 périodes : la période initiale (de 2000 à 2004), la mi-période (de 2005 à 2009) et la dernière période (de 2010 à 2014). Le critère d'évaluation secondaire permettait de comparer la mortalité intrahospitalière, les complications et l'utilisation des ressources en soins de santé entre les admissions liées ou non à une endocardite.

The risk of infective endocarditis is higher in patients with congenital heart disease compared with the general population.[1-3] Among patients with congenital heart disease, the risk of infective endocarditis varies with complexity of congenital heart lesion, and patients with more complex lesions are at higher risk of infective endocarditis.[1] The risk of infective endocarditis is also higher in the patients with prosthetic valves.[2] Tetralogy of Fallot (TOF) is the most common complex/cyanotic congenital heart lesion in the adult congenital heart disease population, and patients with TOF often require prosthetic valve implantation.[4-6] There are no population-based studies evaluating the disease burden of endocarditis among patients with TOF. The purpose of this study was to describe the incidence, outcomes (in-hospital mortality and complications), and health care resource utilization in admissions of patients with TOF and infective endocarditis diagnoses (endocarditis-related admissions), using the National Inpatient Sample (NIS) database.

Methods

Patient selection and data collection

The NIS is the largest all-payer database of hospital inpatient stays in the United States. NIS contains discharge data from a 20% stratified sample of community hospitals and is a part of the Healthcare Cost and Utilization Project

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admissions increased over time: 1.9% (early era) vs 2.2% (mid-era) vs 2.4% (late era), $P < 0.001$. Overall in-hospital mortality was 6%. In addition to previously described risk factors for endocarditis, such as previous pacemaker/defibrillator or prosthetic valve implantation, we observed an association between endocarditis-related admissions and male gender, black race, and lower socioeconomic class. In comparison with admissions without endocarditis, the endocarditis-related admissions had higher in-hospital mortality, complications, and health care resource utilization measured by length of stay, inflation-adjusted hospitalization cost, and type of hospital discharge.

Conclusions: Incidence of endocarditis-related admissions increased over time and was associated with higher mortality, complications, and health care resource utilization. Further studies are required to investigate the observed temporal increase in incidence of endocarditis and explore new strategies to improve outcomes.

Résultats : Parmi les 18 353 admissions, 393 (2,1 %) admissions étaient liées à une endocardite; la fréquence de ces admissions augmentait au fil du temps (1,9 % pour la période initiale, 2,2 % pour la période intermédiaire, 2,4 % pour la dernière période, $P < 0{,}001$). La mortalité intrahospitalière globale était de 6 %. En plus des facteurs de risque d'endocardite précédemment énumérés, soit l'implantation antérieure d'un stimulateur cardiaque/d'un défibrillateur ou d'une prothèse valvulaire, nous avons observé une association entre les admissions liées à une endocardite et les personnes de sexe masculin, de race noire et de classe socioéconomique plus faible. En comparaison des admissions non liées à une endocardite, les admissions liées à une endocardite montraient une mortalité intrahospitalière plus élevée, de plus nombreuses complications et une plus grande utilisation des ressources en soins de santé mesurés par la durée du séjour, les frais d'hospitalisation ajustés en fonction de l'inflation et le type de sortie de l'hôpital.

Conclusions : La fréquence des admissions liées à une endocardite augmentait au fil de temps et était associée à une mortalité plus élevée, de plus nombreuses complications et à une plus grande utilisation des ressources en soins de santé. D'autres études sont nécessaires pour examiner l'augmentation temporelle observée du nombre de cas d'endocardites et pour explorer de nouvelles stratégies d'amélioration des résultats.

(HCUP) sponsored by the Agency for Healthcare Research and Quality.[7] Information regarding each discharge includes patient demographics, primary payer, hospital characteristics, principal diagnosis, up to 24 secondary diagnoses, and procedural diagnoses. The Mayo Clinic (Rochester, Minnesota) Institutional Review Board approved this study.

Using the HCUP-NIS data from 2000 to 2014, adult patients (>18 years of age) admitted with a primary or secondary diagnosis of TOF (International Classification of Diseases 9 Clinical Modification [ICD-9CM] code 745.2) were identified.[8,9] Using previously validated approaches,[10] infective endocarditis was identified using ICD-9CM 421, 421.0, 421.1, 421.9. Patient characteristics (age, sex, race, socioeconomic status, and primary payer) and hospital characteristics (teaching status and location, bed size, and region) associated with each discharge were identified from the HCUP-NIS database. The Deyo's modification of Charlson Comorbidity Index was used to identify the burden of comorbid diseases (Supplementary Table S1).[8,11,12]

Study design

The primary outcome was to describe the incidence and trends of endocarditis-related admissions. To assess trends in incidence of endocarditis-related admissions, we divided the study period into tertiles: early era (2000 to 2004), mid-era (2005 to 2009), and late era (2010 to 2014). The secondary outcome was to determine risk factors for endocarditis-related admissions and compare in-hospital mortality, complications, and health care resource utilization between admissions with and without endocarditis diagnosis. The complications assessed in this study were predefined based on previously published endocarditis-related complications,[1,2] and these include cardiac arrest, respiratory failure requiring endotracheal intubation, acute kidney injury requiring hemodialysis, and pacemaker implantation. Health care resource utilization was assessed using the following indices: hospital length of stay; inflation-adjusted hospitalization cost; and routine hospital discharge, defined as discharge to home.

Statistical analysis

As recommended by HCUP-NIS, survey procedures using discharge weights provided with the HCUP-NIS database were used to generate national estimates. Categorical data were expressed as count (%), and continuous data were expressed as mean ± standard deviation or median and interquartile range [IQR] for skewed data. X^2 and Students' *t*-tests were used to compare categorical and continuous variables, respectively. Poisson regression was used to analyze trends of endocarditis-related admissions over the duration of

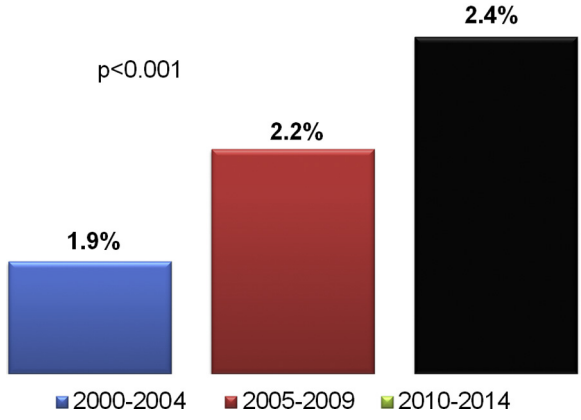

Figure 1. Bar graph showing temporal increase in the incidence of endocarditis-related admissions from early era (**blue**) through mid-era (**red**) to late era (**black**).

Table 1. Baseline characteristics of admissions with and without infective endocarditis

Characteristic	Infective endocarditis (N = 393)	No infective endocarditis (N = 17,955)	*P*
Age (years)	33.8 ± 11.2	38.4 ± 14.0	< 0.001
Female sex	143 (36.4)	9,672 (53.9)	< 0.001
Race			0.001
White	206 (51.5)	10,029 (55.9)	
Black	61 (15.3)	1,831 (10.2)	
Hispanic	38 (9.5)	1,620 (9)	
Asian	5 (1.3)	403 (2.2)	
Native American	—	67 (0.4)	
Others	20 (5)	490 (2.7)	
Missing	70 (17.5)	3,515 (19.6)	
Weekend admission	66 (16.6)	3,159 (17.6)	0.64
Primary payer			< 0.001
Medicare	86 (21.6)	5,056 (28.2)	
Medicaid	111 (27.9)	4,354 (24.3)	
Private	139 (34.9)	6,919 (38.6)	
Uninsured	42 (10.6)	963 (5.4)	
No charge	5 (1.3)	97 (0.5)	
Others	10 (2.5)	521 (2.9)	
Quartile of median household income for ZIP code			0.006
0-25th	99 (25.8)	4,131 (23.6)	
26th-50th	70 (18.2)	4,561 (26.1)	
51st-75th	117 (30.5)	4,588 (26.2)	
75th-100th	98 (25.5)	4,224 (24.1)	
Hospital teaching status and location			< 0.001
Rural	10 (2.5)	1,475 (8.2)	
Urban nonteaching	136 (34.2)	4,243 (23.6)	
Urban teaching	252 (63.3)	12,236 (68.2)	
Hospital bed size			< 0.001
Small	66 (16.5)	1,803 (10)	
Medium	100 (25.1)	3,618 (20.2)	
Large	233 (58.4)	12,534 (69.8)	
Hospital region			0.004
Northeast	113 (28.4)	3,801 (21.2)	
Midwest	71 (17.8)	3,794 (21.1)	
South	143 (35.9)	6,631 (36.9)	
West	71 (17.8)	3,729 (20.8)	
Charlson Comorbidity Index	0.7 ± 1.1	1.3 ± 1.7	< 0.001
Comorbidities			
Hypertension	57 (14.3)	3,226 (18)	0.07
Hyperlipidemia	10 (2.5)	1,258 (7)	< 0.001
Chronic kidney disease	32 (8)	974 (5.4)	0.03
Atrial fibrillation	37 (9.3)	2,802 (15.6)	0.001

Represented as percentage or mean ± standard deviation.

the study. Two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, New York).

Results

During the period between January 1, 2000, and December 31, 2014, there were an estimated 18,353 admissions in adults with TOF diagnoses, of which endocarditis was diagnosed in 393 (2.1%). Among the endocarditis-related admissions, the mean age was 33.8 ± 11.2 years, and 143 (36%) were female patients. There was a temporal increase in the incidence of endocarditis-related admissions: early era (1.9%) vs mid-era (2.2 %) vs late era (2.4%), $P < 0.001$ (Fig. 1). The endocarditis-related admissions were more likely to occur in large—bed-size hospitals (58%) compared with medium—bed-size hospitals (25%) and small—bed-size hospitals (17%), $P < 0.001$, and in urban teaching hospitals (63%) compared with urban nonteaching hospitals (34%) and rural hospitals (3%), $P < 0.001$. The mean length of hospital stay was 9.9 ± 10.5 days (10 [IQR 4 to 15] days), inflation-adjusted hospitalization cost was $66,342 ± 100,992 ($68,845 [IQR 34, 645 to 99, 754]), and in-hospital mortality 6.0%.

The baseline characteristics of the admissions with and without endocarditis are presented in Table 1. The risk factors associated with endocarditis-related admissions were male gender, black race, lowest income quartile, previous pacemaker/defibrillator implantation, and previous prosthetic valve implantations (Table 2). Compared with the admissions without endocarditis, endocarditis-related admissions had higher in-hospital mortality (6.0% vs 3.3%; $P = 0.004$) and high rates of complications such as cardiac arrest (2.5% vs 1.2%, $P = 0.04$), respiratory failure requiring endotracheal intubation (8.5% vs 5.2%; $P = 0.004$), acute kidney injury requiring hemodialysis (2% vs 0.5%; $P = 0.002$), and pacemaker implantation (3.5% vs 1.4%, $P = 0.002$) (Table 3). Similarly, endocarditis-related admissions were associated with

Table 2. Risk factors associated with admissions for infective endocarditis diagnosis

Total cohort (N = 18,353)	Odds ratio	95% confidence interval		*P* value
		Lower Limit	Upper Limit	
Age groups (years)				
19-49		Reference category		
50-59	0.69	0.45	1.06	0.09
60-69	0.29	0.11	0.77	0.01
Female sex	0.32	0.25	0.41	< 0.001
Race				
White		Reference category		
Black	1.54	1.10	2.16	0.01
Hispanic	0.94	0.64	1.38	0.76
Asian	0.53	0.20	1.39	0.20
Native American	0.00	0.00	—	0.99
Others	2.15	1.30	3.53	0.003
Primary payer				
Medicare		Reference category		
Medicaid	1.38	0.98	1.94	0.07
Private	1.39	1.01	1.92	0.04
Uninsured	1.64	1.00	2.69	0.05
No Charge	2.64	0.95	7.34	0.06
Quartile of median household income for zip code				
0-25th		Reference category		
26th-50th	0.53	0.36	0.76	0.001
51st-75th	0.92	0.66	1.27	0.59
75th-100th	0.72	0.50	1.03	0.07
Hospital teaching status and location				
Rural		Reference category		
Urban Non-Teaching	5.90	2.44	14.25	< 0.001
Urban Teaching	4.11	1.73	9.79	0.001
Hospital bed size				
Small		Reference category		
Medium	1.01	0.70	1.47	0.95
Large	0.56	0.40	0.79	0.001
Hospital region				
Northeast		Reference category		
Midwest	0.62	0.41	0.93	0.02
South	0.65	0.49	0.86	0.003
West	0.71	0.50	1.01	0.06
Charlson Comorbidity Index				
0-3		Reference category		
4-6	0.75	0.38	1.49	0.42
Prievious pacemaker	1.33	1.13	1.83	0.02
Previous defibrillator	1.57	1.29	1.11	0.10
Previous cardiac valve replacement	1.23	1.10	1.54	0.001

more health care resource utilization as measured by hospital length of stay (9.9 ± 10.5 vs 5.6 ± 11.0 days, $P < 0.001$) (10 [IQR 4 to 15] vs 6 [IQR 2 to 11] day, $P < 0.001$), inflation-adjusted hospitalization cost ($66,342 ± 100,992 vs $49,402 ± 95,946, $P = 0.001$), ($68,845 [IQR 34, 645 to 99, 754] vs $43,846 [IQR 29,642 to 81,896] day, $P < 0.001$), and discharge to home (47% vs 79%, $P < 0.001$).

Table 3. Clinical outcomes of infective endocarditis in tetralogy of Fallot

Characteristic	Total cohort		*P* value
	Infective endocarditis (N = 393)	No infective endocarditis (N = 17,955)	
In-hospital mortality	24 (6)	500 (3.3)	0.004
Length of stay (days)	9.9 ± 10.5	5.6 ± 11.0	< 0.001
Hospitalization costs (United States Dollars)	66,342 ± 100,992	49,402 ± 95,946	0.001
Discharge disposition			< 0.001
Home	176 (46.9)	13,730 (79.1)	
Transferred to other hospitals	77 (20.5)	809 (4.7)	
Skilled nursing facility	24 (6.4)	1,203 (6.9)	
Home with home health care	82 (21.9)	1,485 (8.6)	
Against medical advice	16 (4.3)	126 (0.7)	

Represented as number (percentage) or mean ± standard deviation.

Discussion

Based on this 15-year review of the HCUP-NIS database, we report an overall incidence of endocarditis-related admissions of 2.1% of all admissions in patients with TOF diagnoses, and this incidence increased over the study period. The overall in-hospital mortality for endocarditis-related admissions was 6%. Recent studies have reported increased risk of endocarditis in patients with congenital heart disease compared with the general population, with higher risk in the patients with complex congenital heart lesions and those with prosthetic valves.[1-3] In a single-centre study of 144 patients with congenital heart disease (mean age 32 years), with 164 episodes of endocarditis, Tutarel et al. reported an in-hospital rate of mortality of 6.9%.[1] In a multicentre study of more than 14,000 patients with congenital heart disease (mean age 38 years), Kuijper et al. reported endocarditis incidence of 0.1% per year, with higher incidence in complex congenital heart disease (including TOF) and patients with prosthetic valves.[2] Endocarditis was associated with 1-year mortality of 16% in that study.[2] The current study provides complementary data using population-based estimates, and the in-hospital mortality rate of 6% in the current study was comparable, with 6.9% reported by Tutarel et al.

The current study also showed a temporal increase in the incidence of endocarditis-related admissions from 1.9% in the early era to 2.4% in the late era. This finding is concerning because of the mortality and morbidity associated with endocarditis.[13-15] However, as the HCUP-NIS database captures individual hospitalizations and not specific patients, we can only speculate on the reasons for higher incidence of infective endocarditis.[7] We speculate that perhaps the observed increase in incidence of endocarditis may be associated with temporal increase in risk factors such as prosthetic valves, as demonstrated in longitudinal studies showing higher prevalence of prosthetic valves in the TOF population over time.[5,16] In addition to previously described risk factors for endocarditis such as earlier pacemaker/defibrillator or prosthetic valve implantation,[1-3,17,18] we observed an association between endocarditis-related admissions and male gender, black race, and lower socioeconomic class. These new findings require further investigations to determine if these risk factors are unique to the TOF population and may present new targets for intervention to decrease the health care disparities for this high-risk population.

In comparison with admissions of patients without endocarditis, a diagnosis of endocarditis was associated with higher in-hospital mortality, complications, hospitalization cost, and health care resource utilization, even after hospital discharge. These findings were not unexpected but nevertheless serve to highlight the importance of preventive strategies such as emphasis on good dental hygiene, appropriate use of endocarditis prophylaxis, and proactive screening and treatment of endocarditis to reduce in-hospital mortality.[17,18] Although the result of the current study does not directly link the rising trend of endocarditis incidence to prosthetic valve implantations, we think it is worthwhile to emphasize that the cumulative risk of prosthetic valve endocarditis should be taken into consideration and adequately discussed with the patient before deciding on the timing of valve replacement.

Limitations

The HCUP-NIS database contains data of individual hospital admissions rather than individual patients, and, as a result, we cannot control for "double counting" due to readmissions or inter-hospital transfers. The NIS data are exclusive, based on data from the United States; hence, it is unknown how our results will extrapolate to other cohorts from different geographic locations. The NIS database does not contain data about specific microbial diagnosis, medications (antibiotics), and type of surgical interventions (urgent vs emergent). Nevertheless, the results of the study provide a population-based overview of the risk (incidence and trend), outcomes (in-hospital mortality and complications), and health care resource utilization in patients with TOF admitted to hospitals with endocarditis.

Conclusions

The overall incidence of endocarditis-related admissions was 2.1% of all hospital admissions, and the incidence increased during the 15-year study period. In addition to the known risk factors for endocarditis, such as pacemaker/defibrillator and prosthetic valve implantation, we also identified gender, racial, and socioeconomic class differences in the incidence of endocarditis. Endocarditis-related admissions were associated with increased in-hospital mortality, complications, and health care resource utilization. The rising incidence of endocarditis-related admissions observed in this study is concerning, and the significance of the new risk factors (gender, race, socioeconomic class) remains unclear. Further studies are required to investigate the observed temporal increase in endocarditis incidence and explore new strategies to improve outcomes.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.02.006.