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The Changing “Face” of Endocarditis in Kentucky: A Rise in Tricuspid Cases

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Abstract

Background—Advancements in medical technology and increased life expectancy have been described as contributing to the evolution of endocarditis. We sought to determine whether there has been a change in the incidence, demographics, microbiology, complications, and outcomes of infective endocarditis over a ten-year time span.

Methods—We screened 28,420 transthoracic and transesophageal echocardiogram reports performed at our center for the following indications: fever, masses, emboli (including stroke), sepsis, bacteremia, and endocarditis in two time periods: 1999 through 2000 and 2009 through 2010. Data were collected from diagnosed endocarditis cases.

Results—Overall, 143 cases of infective endocarditis were analyzed (48 in 1999–2000 and 95 in 2009–2010). The endocarditis incidence per number of admissions remained nearly constant at 0.113% for 1999–2000 and 0.148% for 2009–2010 ($p = 0.153$). However, tricuspid valve involvement increased markedly from 6% to 36% ($p < 0.001$). Also, reported history of intravenous drug use increased from 15% to 40% ($p = 0.002$). Valvular complications doubled from 17% to 35% ($p = 0.031$). Septic pulmonary emboli increased from 10% to 25% ($p = 0.047$). Despite these noted differences, inpatient mortality remained unchanged at 25% and 28% ($p = 0.696$) for the two time periods, respectively.

Conclusions—The incidence of endocarditis at our center has not changed and mortality remains high, but the “face of endocarditis” in Kentucky has evolved with an increased incidence of tricuspid valve involvement, valvular complications, and embolic events.

Keywords

Tricuspid Valve Endocarditis; Echocardiography

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Introduction

Infective endocarditis is a microbial infection of the endocardial surface of the heart, most commonly affecting heart valves, but also other sites including septal defect, chordae tendineae and mural endocardium.¹ Described in detail by Sir William Osler in the late 19th century, endocarditis was universally fatal before the advent of antimicrobial agents. Despite tremendous advances in knowledge of the disease and development of antibiotics over the past several decades, infective endocarditis remains a difficult to treat and life threatening condition, with reported inpatient mortality rates up to 20% and 1 year mortality of 24-37%.²⁻⁶

With medical advances and increasing lifespan there is an increased exposure to invasive procedures which have been identified as new risk factors for endocarditis such as cardiac implantable electronic devices and long-term dialysis catheters.^{1-3,7,8} A history of valvular heart surgery^{1,2,9-11}, hemodialysis, and immunosuppression have also been associated with increased risk of infective endocarditis.^{2,3,6,12} Intravenous drug use remains an important risk factor for endocarditis given the recent increase in illegal drug use and narcotic prescription drug abuse in the United States and is associated with increased disease severity.^{13,14} However, an accurate assessment of regional variability of intravenous drug use is difficult to determine.

With clinical suspicion of infective endocarditis on the rise, we sought to determine whether there has been a change in the incidence, demographics, microbiology, complications and treatment outcomes of endocarditis over a ten-year period at our medical center.

Methods

The study received institutional review board approval. We retrospectively evaluated our experience with infective endocarditis by screening a total of 28,420 transthoracic and transesophageal echocardiogram reports performed at our medical center for the following indications: fever, masses, emboli (including stroke), sepsis, bacteremia and endocarditis during two 24-month periods separated by ten years: January 1, 1999 through December 31, 2000, and January 1, 2009 through December 31, 2010. Our echocardiogram data were contained in two archives: Softheart, Inc. version 3.11 software was reviewed for 1999-2000 echocardiogram reports, and Philips Xcelera version 3.1 software was employed for 2009-2010 echocardiogram reports. Admissions data were obtained from the Executive Vice President for Health Affairs office.

A review of International Classification of Diseases, Ninth Revision (ICD-9) codes from the 2009-2010 era uncovered only 1 new definite and 2 new possible cases compared to the echocardiogram based screening method. The ICD-9 codes for 1999-2000 were not available for comparison. Therefore, these cases were not included in the analysis, and the echocardiographic reports along with the medical records were used to identify cases.

Medical records were obtained and reviewed for cases in which the echocardiogram reports were read as “vegetation” or “probable vegetation.” The medical records were used to determine the diagnosis of infective endocarditis if they met the modified Duke criteria of

definite or possible endocarditis.¹⁵ The confirmed cases of endocarditis occurring from years 1999-2000 were compared to those from 2009-2010. One patient had two episodes of endocarditis during the study period; only the first episode of endocarditis was included in the analysis. Complicated endocarditis was defined as those with: valve abscess, perforation, flail or fistula.

Medical records were also reviewed for patient demographics, medical history, predisposing conditions (such as intravenous drug use, poor dentition, immunocompromised state: history of organ transplantation, oral steroid use on admission, human immunodeficiency virus, or neutropenia), laboratory results including blood cultures, histopathologic findings, echocardiographic findings, antibiotic regimen, and prior cardiac surgery. Hospital mortality, 30-day mortality, and surgical complications rates were also recorded. All-cause readmission rates to our center were assessed. A follow-up evaluation of mortality was obtained by access to public records documenting patient death.

Statistical Analysis

For descriptive purposes, quantitative variables were summarized by mean $\pm$ standard deviation (SD) or, in cases of marked non-normality, by median with interquartile range (IQR); qualitative variables were summarized by numbers and percentages. Fisher's exact test or the chi-square test with Yates correction was used to compare groups (1999-2000 vs. 2009-2010) on qualitative variables. Student T-test was used to compare groups on quantitative variables, or in cases of marked non-normality, the Mann-Whitney U-test was employed. Kaplan-Meier curves and the log-rank test were used to portray and compare the groups' mortality experiences. Statistical analyses were done using SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina) software.

Results

Patient Characteristics

There were a total of 143 cases of infective endocarditis identified: 48 during 1999-2000 and 95 during 2009-2010. There was no significant difference in patient demographics including age and gender (Table 1) for the two periods analyzed. Females represented the minority of patients, 46% for 1999-2000 and 35% for 2009-2010. As seen in Table 1, patients' past medical histories were notable for an increase in intravenous drug use from 15% to 40% ($p = 0.002$). There were decreased rates of diabetes from 38% to 18% ($p = 0.014$), immunocompromised status from 25% to 6% ($p = 0.003$), history of organ transplantation from 17% to 3% ($p = 0.007$), and steroid use on presentation from 21% to 6% ($p = 0.021$). Human immunodeficiency virus was uncommon, representing less than 6% for both groups. In patients diagnosed with endocarditis, the presence of indwelling catheters and cardiac implantable electronic devices as associated risk factors did not change significantly.

Definite infective endocarditis was identified in 83% of cases in 1999-2000 and 90% in 2009-2010 ($p = 0.30$). The percentages of cases meeting definite pathologic endocarditis, definite clinical endocarditis, and possible clinical endocarditis criteria did not differ

significantly between the two periods (Table 1). No patient reached the diagnosis of infective endocarditis without meeting echocardiographic criteria.

Our center has seen an increase in the number of inpatient admissions from 42,359 in 1999-2000 to 64,159 in 2009-2010, and the number of echocardiograms nearly doubled in that time span from 9,650 (transthoracic echocardiograms = 9,040) performed in 1999-2000 to 18,770 (transthoracic echocardiograms = 18,204) performed in 2009-2010. Thus, the echocardiograms increased substantially in relation to admissions ($p < 0.001$). However, the incidence of infective endocarditis per admission at our institution has not changed significantly over this ten-year time span (0.113% vs. 0.148%, $p = 0.15$), when normalized for the growth in admission volume.

Endocarditis Characteristics

No significant change in the causative microbial pathogens was seen comparing 1999-2000 and 2009-2010 (Table 2). Staphylococcal species accounted for the majority of causative agents at 63% and 61% ($p = 1.00$). There was a modest increase in methicillin-resistant *Staphylococcus aureus* (MRSA) from 13% to 24% ($p = 0.13$), while the rates of enterococcal and fungal species involvement remained stable.

There was a significant increase in the rate of tricuspid valve involvement, from 6% to 36% ($p < 0.001$) (Table 3). The rates of native aortic, mitral, pulmonic, prosthetic valve or multiple valve involvement did not change significantly. The rate of valve abscess, perforation, flail or fistula increased significantly from 17% to 35% ($p = 0.031$). Large vegetations (≥ 10 mm) were seen in 50% of cases in 1999-2000 and 41% in 2009-2010 ($p = 0.37$).

The incidence of patients with embolic complications during this time period increased from 29% to 49% ($p = 0.031$) and was mostly driven by the identification septic pulmonary emboli (10% vs 25%) (Table 4). In particular, there was an increase in septic pulmonary emboli, from 10% to 25% ($p = 0.047$). Intracranial, splenic and peripheral embolization did not change significantly.

Surgical Treatments, Medical Therapy and Outcomes

There were no significant differences in the rate of surgery or the indications for those undergoing surgery (Table 5). There was a significant decrease in surgical complications from 64% to 17% ($p = 0.016$). Type of valve replacement (prosthetic or mechanical), valve site, multiple valves or repeat surgery rates showed no significant differences between the two periods.

Medical Therapy

Ampicillin and ciprofloxacin showed significant decline in usage between the two time periods (Table 6). However, utilization of cefepime, daptomycin, levofloxacin, piperacillin/tazobactam and vancomycin all increased. There were no differences in other antibiotics.

Outcomes

Results for clinical outcomes are shown in Table 7. Inpatient mortality remained similar over the ten-year time span at 25% and 28% ($p = 0.70$). Thirty-day mortality, length of hospitalization, readmission rate and endocarditis recurrence remained largely unchanged. Overall, there was no significant mortality difference in patients with complicated endocarditis compared to those without, 34% vs. 28% ($p = 0.55$). The Kaplan-Meier curves show no significant difference over the ten-year time span in survival over three years of follow-up ($p = 0.65$) (Figure).

Discussion

Our study results show the spectrum of endocarditis has evolved from 1999-2000 to 2009-2010 at our institution. We found a marked increase in tricuspid valve endocarditis, intravenous drug use, total number of emboli, septic pulmonary emboli, and severe valvular complications in patients presenting with infective endocarditis.

However, since the number of echocardiograms nearly doubled during this time frame, the incidence of endocarditis per admission at our institution has not changed significantly over this ten-year time span 0.113% in 1999-2000 and 0.148% in 2009-2010. This finding is similar to those from population-based surveys showing a stable endocarditis incidence.^{4,16} A recent study of an older population with infective endocarditis showed no increase in adjusted rates of hospitalization or mortality which is in contrast to our younger population with increased tricuspid valve lesions, intravenous drug use and higher mortality.¹⁷

Right-sided endocarditis has been reported to account for 10-25% of all endocarditis cases.^{2-4,18} At our center, right-sided endocarditis accounted for 13% of cases during 1999-2000 and increased to 39% in 2009-2010. Historically, the major risk factor for right-sided endocarditis has been intravenous drug use.¹² The increase in right-sided infective endocarditis in our population is likely due to the increase in the incidence of intravenous drug use from 15% to 40%, which is higher than those previously reported with a range of 3% to 10%.^{2,3,5,6,16} However, according to Cooper et al., there has been a nationwide increase of almost 40% in infective endocarditis cases due to intravenous drug use from 2000-2001 to 2002-2003.¹⁹

Streptococcal species accounted for less than 20% of endocarditis cases in our study. This is roughly consistent with a reported prevalence of approximately 30%.² To our knowledge, there is only one study from 1970-2000 that reported Streptococci as the most common causative agent of infective endocarditis.¹⁶ In that study by Tleyjeh et al., intravenous drug use prevalence (3%) was markedly lower than in our study. Studies have shown intravenous drug use is associated with increased rates of *S aureus* endocarditis.^{3,14} The leading pathogen for endocarditis during both periods of our study was *S aureus*, which is more consistent with the results from several other studies.^{1-3,6} There was no significant increase in MRSA from 1999-2000 to 2009-2010. Medical therapy has evolved over time with the advent of new antibiotics during our study period. These authors cannot speculate on the potential impact of these differences in antibiotic therapy on the reported findings.

The temporal trend of increased complications from endocarditis in our investigation is evidenced by the increases in septic pulmonary emboli, the overall number of total embolic events, and valvular complications. Since there is a higher rate of tricuspid involvement with intravenous drug use, this corresponds to the increase in septic pulmonary emboli. This is also consistent with other studies that show intravenous drug use is associated with higher rates of embolism.^{3,14} Embolic and valvular complications are not uncommon findings. A French population-based survey reported increased valvular perforations from 7% to 21% and embolic events from 37% to 59% when comparing 1999 to 2008 data.⁴

Complicated endocarditis is typically associated with higher mortality. However, with our increasing burden of tricuspid valve cases and associated valvular complications there was not a significant increase in mortality compared to those cases without complicated endocarditis. A potential explanation is that tricuspid valve complications such as emboli and flail leaflets are better tolerated than those of the mitral and aortic valves.

Despite advances in medical and surgical care, our inpatient mortality has remained largely unchanged from 1999-2000 to 2009-2010 at 25% and 28%, respectively. Our inpatient mortality is higher compared to that in other studies. For example, Murdoch et al. reported an inpatient mortality rate of 17.7% during 2000-2005, while Duval et al. reported inpatient mortality of 15.4% in 1999 and 21.2% in 2008.^{2,4} Our long-term mortality showed no significant change between the two study periods. Mortality at one year has been reported to be approximately 37% during 1993-1999.⁶ Factors associated with increased mortality in patients with infective endocarditis include *S aureus* infection, embolic events, and vegetation size.^{5,6,8,20-23} Compared to other studies, we have detected a high *S aureus* infection rate, higher embolic event rate, and higher percentage of large vegetations, which are potential reasons why our inpatient mortality rates are higher.

Surgical complication rates were significantly reduced in 2009-2010 compared to 1999-2000. However, the rate of surgical treatment remained essentially unchanged 23% in 1999-2000 and 24% in 2009-2010 despite having significantly complex valvular disease in 2009-2010. Typically, conservative management is recommended in patients with right-sided endocarditis.²⁴ However, limited data exist for the surgical indications, timing and outcomes for right-sided endocarditis, in particular, those with a history of intravenous drug use.²⁵

Aggressive approaches to tricuspid valve endocarditis such as tricuspid valvectomy, though never included as primary treatment in guideline recommendations, generated some initial enthusiasm but has fallen out of favor as a long-term solution. Our case series included a small number of tricuspid valve operations which were undertaken for persistent bacteremia, large vegetations, recurrent septic pulmonary emboli or intracardiac abscess formation. Meaningful statistical analysis of mortality comparing those that underwent tricuspid valve surgery and those that did not cannot be performed due to the limited number of procedures.

The current endocarditis guidelines for surgical intervention do not specifically address right-sided lesions.²⁶ Thus, the approach to tricuspid valve endocarditis remains problematic

and is presently handled on case-by-case basis. The apparent trend in right-sided disease may warrant reexamination of criteria for valve surgery in these patients.

There are limitations in our study. Since this is a single-center retrospective evaluation of infective endocarditis, and because there may have been a change our referral base from 1999-2000 to 2009-2010, the underlying patient populations of which our samples are representative may differ in some ways that have the potential to bias comparisons across the two eras. However, as we have demonstrated, the incidence of endocarditis remains similar. With the screening methods used, endocarditis cases not meeting the major echocardiogram criterion may have been missed. According to other studies, approximately 3% of endocarditis cases were diagnosed by meeting all five minor criteria, and thus, did not meet a major echocardiographic criterion.^{2,27} Our medical center is a tertiary referral center, which is more likely to have higher acuity patients and may not reflect the same endocarditis characteristics found in community hospitals.

Conclusion

Infective endocarditis continues to be a serious disease that causes significant morbidity and mortality despite medical advances. The incidence of endocarditis at our center has not changed, but the “face of endocarditis” in Kentucky has evolved with an increased incidence of tricuspid valve involvement, valvular complications, and embolic events.

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Figure. Kaplan-Meier Curves of Overall Survival in Patients with Infective Endocarditis (IE)*
Kaplan-Meier curves showing estimated survival function since hospital discharge. There was no significant difference in survival experience between patients diagnosed with IE in 1999-2000 and 2009-2010 by log-rank test. *Four patients from each group were lost to follow up after hospital discharge.

Table 1
Patient Characteristics

Patient Characteristics	1999-2000 N = 48	2009-2010 N = 95	P-Value
Age (Years), (mean $\pm$ SD)	50.9 $\pm$ 16.0	46.9 $\pm$ 18.2	0.21
Female, N (%)	22 (46)	33 (35)	0.21
Systolic Blood Pressure (mmHg), (mean $\pm$ SD)	122.0 $\pm$ 26.4	118.8 $\pm$ 20.9	0.43
Heart Rate (BPM), (mean $\pm$ SD)	94.3 $\pm$ 17.0	96.7 $\pm$ 17.7	0.44
Fever, N (%)	32 (67)	49 (52)	0.11
History of Infective Endocarditis, N (%)	5 (10)	19 (20)	0.17
History of Intravenous Drug Use, N (%)	7 (15)	38 (40)	0.002
Predisposing Heart Disease, N (%)	13 (27)	21 (22)	0.54
Immunologic Phenomena, N (%)	3 (6)	5 (5)	1.00
Hypertension, N (%)	28 (58)	43 (45)	0.16
Coronary Artery Disease, N (%)	10 (21)	20 (21)	1.00
Congestive Heart Failure, N (%)	12 (25)	14 (15)	0.167
Diabetes, N (%)	18 (38)	17 (18)	0.014
End Stage Renal Disease, N (%)	13 (27)	14 (15)	0.11
History of Stroke, N (%)	9 (19)	11 (12)	0.31
History of Cardiac Surgery, N (%)	12 (25)	28 (29)	0.69
Indwelling Catheter, N (%)	10 (21)	26 (27)	0.42
Implanted Device, N (%)	3 (6)	10 (11)	0.54
History of Transplantation, N (%)	8 (17)	3 (3)	0.007
Immunosuppressed, N (%)	12 (25)	6 (6)	0.003
Steroid Use on Admission, N (%)	10 (21)	6 (6)	0.021
Human Immunodeficiency Virus, N (%)	3 (6)	1 (1)	0.11
Definite endocarditis by Pathology Criteria	5 (10)	10 (11)	1.00
Definite endocarditis by Clinical Criteria	35 (73)	75 (79)	0.53
Possible endocarditis	8 (17)	10 (10)	0.30
Major Echocardiogram Criterion met, N (%)	48 (100)	95 (100)	1.00
Major Microbiological Criterion met, N (%)	20 (42)	48 (51)	0.38
Minor Microbiological Criterion, N (%)	21 (44)	31 (33)	0.20

BPM = Beats Per Minute.

SD = Standard Deviation.

Table 2**Microbial Findings**

Organism	1999-2000 N = 48	2009-2010 N = 95	P-Value
Staphylococcus, N (%)	30 (63)	58 (61)	1.00
MRSA, N (%)	6 (13)	23 (24)	0.13
MSSA, N (%)	12 (25)	27 (28)	0.70
Streptococcus, N (%)	8 (17)	13 (14)	0.63
VRE, N (%)	1 (2)	3 (3)	1.00
Non-VRE, N (%)	7 (15)	10 (11)	0.59
Fungal, N (%)	2 (4)	7 (7)	0.72

MRSA = Methicillin-resistant *Staphylococcus aureus*.

MSSA = Methicillin-sensitive *Staphylococcus aureus*.

VRE = Vancomycin-resistant Enterococci.

Table 3
Echocardiographic Findings

Location	1999-2000 N = 48	2009-2010 N = 95	P-Value
Aortic Valve, N (%)	16 (33)	29 (31)	0.85
Mitral Valve, N (%)	23 (48)	35 (37)	0.21
Pulmonic Valve, N (%)	3 (6)	5 (5)	1.00
Tricuspid Valve, N (%)	3 (6)	34 (36)	< 0.001
Prosthetic Valve, N (%)	10 (21)	20 (21)	1.00
Multiple Valves, N (%)	5 (10)	12 (13)	1.00
Cases of Abscess, Perforation, Flail or Fistula, N (%)	8 (17)	33 (35)	0.031
Large Vegetations (≥ 10mm), N (%)	24 (50)	39 (41)	0.37

Table 4
Characteristics of Embolization

Location	1999-2000 N = 48	2009-2010 N = 95	P-Value
Patients with Embolic Events, N (%)	14 (29)	47 (49)	0.031
Intracranial, N (%)	6 (13)	19 (20)	0.35
Septic Pulmonary, N (%)	5 (10)	24 (25)	0.047
Splenic, N (%)	3 (6)	4 (4)	0.69
Peripheral, N (%)	2 (4)	5 (5)	1.00
Total Embolic Events, N (%)	16 (33)	52 (55)	0.021

Table 5
Surgical Treatments and Outcomes

	1999-2000* N = 11	2009-2010 N = 23	P-Value
Indications for Surgery: N (%)			
Severe Valve Dysfunction	10 (91)	21 (91)	1.00
Heart Failure	6 (55)	7 (30)	0.26
Complicated Endocarditis	8 (73)	19 (83)	0.66
Vegetation Size	8 (73)	16 (70)	1.00
Failed Medical Therapy	4 (36)	4 (17)	0.39
Surgical Complications, N (%)	7 (64)	4 (17)	0.016

* 1 patient had resection of mass, no valvular involvement.

Table 6**Antibiotic Therapy**

Antibiotic	1999-2000 N = 48	2009-2010 N = 95	P-Value
Ampicillin	10 (21)	6 (6)	0.021
Cefepime	0 (0)	14 (15)	0.003
Ciprofloxacin	8 (17)	0 (0)	<0.001
Daptomycin	0 (0)	16 (17)	0.001
Levofloxacin	5 (10)	28 (30)	0.012
Piperacillin/Tazobactam	6 (13)	40 (42)	<0.001
Vancomycin	32 (67)	82 (86)	0.008

Outcomes

Table 7

	1999-2000 N = 48	2009-2010 N = 95	P-Value
Inpatient Mortality, N (%)	12 (25)	27 (28)	0.70
30-day Mortality, N (%)	9 (19)	24 (25)	0.41
Surgical Treatment, N (%)	11 (23)	23 (24)	1.00
Days of hospitalization, (median [IQR])	13.0 [9.0, 24.5]	13.0 [8.0, 27.0]	0.81
Readmission, N (%)	20 (42)	31 (33)	0.36
Recurrence, N (%)	3 (6)	9 (9)	0.75

IQR = Interquartile Range.