

## Endocarditis Complicating Central Venous Catheter Bloodstream Infections: A Unique Form of Health Care Associated Endocarditis

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### ABSTRACT

**Background:** Endocarditis complicating central venous catheter blood stream infection (CVC-BSI) is a serious complication and is being seen with increasing frequency.

**Methods:** All patients discharged from our institution with International Classification of Disease (ICD-9) codes of endocarditis and CVC-BSI were identified. The medical records of those meeting our inclusion criteria were reviewed.

**Results:** From October 1, 1998 until December 31, 2006, 24 patients were identified with inpatient mortality of 20.8%. Nine cases were nosocomial and 15 were non-nosocomial. The most common comorbidities were diabetes mellitus (45.8%), chronic kidney disease (58.4%), prior valvular abnormalities (37.5%), and multiple prior hospitalizations (65.2%). There were 13 external lines, 9 tunneled lines, and 2 implantable ports. Responsible microorganisms included *Staphylococcus aureus* in 54.6%, *coagulase-negative staphylococci* in 37.5%, *Candida* species (spp.) in 16.6%, and *enterococci* in 12.5%. Five cases were polymicrobial. The line tip was within the right atrium (RA) in 37.5%, the superior vena cava (SVC)-RA junction in 20.8%, the SVC in 33.3%, and the pulmonary artery in 4.2% of patients. Sites of endocardial involvement were the aortic valve in 6 patients, mitral valve in 7 patients, tricuspid valve in 6 patients, right atrial wall in 11 patients, and pacemaker wire in 2 patients. Isolated right-sided involvement occurred in 50% of cases, isolated left-sided in 33.4%, and bilateral involvement in 16.6%. Transesophageal echocardiography (TEE) was necessary for diagnosis in 10 cases (41.6%).

**Conclusions:** Endocarditis complicating CVC-BSI more often involves right-sided structures, with catheter tips in or near the right atrium, frequently requires TEE for diagnosis, and has significant inpatient mortality.

Key words: Infective endocarditis, Valvular heart disease, echocardiography < Imaging

### Introduction

Endocarditis is the fourth leading life threatening infectious disease in the United States following urosepsis, pneumonia, and intra-abdominal sepsis with approximately 15,000 to 20,000 new cases annually.<sup>1</sup> Of particular concern is the increasing incidence of health care-associated endocarditis which accounts for 7%–29% of endocarditis cases seen at tertiary care hospitals.<sup>2</sup> This trend parallels the increasing use of central venous catheters that have become an essential component of modern medical care. Although several case reports can be found in the literature, there are few case series addressing the unique clinical, echocardiographic, and microbiologic characteristics of central line associated endocarditis.<sup>3,4,5</sup> We reviewed all cases of central line related endocarditis treated in our institution over an 8 y period.

### Methods

The Hospital of Saint Raphael is a tertiary care, community teaching hospital. All patients discharged with International Classification of Disease (ICD) codes for the diagnoses of central venous catheter infection and endocarditis were identified from October 1, 1998 until December 31, 2006. Inclusion criteria were:

- Documentation of central venous catheter blood stream infection as has been described previously.<sup>6</sup>
- The presence of central line and subsequent infection temporally preceding the development of endocarditis.
- Endocarditis defined by use of the modified Duke criteria.<sup>7</sup> Only definite cases were included.

Cases were defined<sup>8</sup> as:

- Health care—nosocomially acquired: positive blood cultures occurred >48 h after admission.

- Health care—not nosocomially acquired: positive blood cultures were found at time of admission or within the first 48 h in patients:
  - Undergoing intravenous therapy at home
  - On hemodialysis or receiving chemotherapy with chronic indwelling central venous lines
  - With acute care hospitalization of more than 2 d in the preceding 90 d with an indwelling central venous line.

Patients were excluded if they had cardiac surgery related early prosthetic valve endocarditis.

## Results

From October 1, 1998 to December 31, 2006, 24 patients met the inclusion criteria. The patient demographics, clinical characteristics, and features on presentation are listed in Tables 1 and 2.

**Line Characteristics (see Table 3):** The sources of bacteremia were external catheters in 13 patients (54%), tunneled catheters in 9 patients (37.5%), and implantable ports in 2 patients (8.5%). The total duration of the line prior to onset of infection ranged from 1–975 d with a median of 19 d. There was inflammation at the skin exit site or the tunnel of the infected lines in only 2 cases. The line tip location was in the pulmonary artery in 1 patient (4.3%), the right atrium (RA) in 9 patients (39.1%), the SVC-RA junction in 5 patients (21.7%), within the SVC in 8 patients (35%), and in an unknown location in 1 patient.

**Microbiology:** For nosocomial cases, blood cultures became positive 3–24 d post admission. For non-nosocomial cases, blood cultures became positive from 0–2 d prior to admission. *Staphylococcus aureus* was identified in 13 cases (54.1%), *coagulase-negative staphylococci* in 9 cases (37.5%), *Candida* spp. in 4 cases (16.6%), and *enterococci* in 3 cases (12.5%). Multiple pathogens were found in 5 patients.

**Echocardiographic Characteristics (see Table 4):** All patients received a transthoracic echocardiogram (TTE) at a median of 2 d from the first positive blood culture. Fourteen patients went on to have a transesophageal study (TEE), at a median of 4 d after the transthoracic study. The TEE was diagnostic of the presence of endocardial involvement in 10 patients, in whom the previously performed TTE was unrevealing. The location of endocardial involvement included isolated right-sided involvement in 12 patients (50%), isolated left-sided involvement in 8 patients (33.4%), and bilateral involvement in 4 patients (16.6%).

**Complications:** A variety of embolic and septic complications were observed. Four patients developed a stroke (including 1 with a ruptured mycotic aneurysm and subarachnoid bleed). Five patients developed other embolic phenomena (4 patients with right-sided endocarditis with septic pulmonary emboli and 1 patient with renal infarction). Seven

Table 1. Demographic and clinical characteristics

Clinical Characteristics	Number of Patients (%)
Age	59.8±12.6
Gender (Male–Female)	9 (37.5%)–15 (62.5%)
Race (White–African American–Hispanics)	12 (50%)–11 (45.8%)–1 (4.2%)
Smoking (Current–Prior–Never)	7 (31.8%)–6 (27.2%)–8 (36%)
Alcohol abuse	2 (8.2%)
Residence (Home–Extended Care Facility)	19 (79.2%)–5 (20.8%)
Diabetes Mellitus–On insulin	11 (45.8%)–10 (41.6%)
Hypertension	15 (65.2%)
Chronic Kidney Disease	14 (58.3%)
–On Hemodialysis	10 (41.6%)
Cerebrovascular Accident	3 (12.5%)
Coronary Artery Disease	11 (45.8%)
Congestive Heart Failure	10 (41.6%)
–Systolic Dysfunction (EF<50%)	6 (25%)
Valvular Heart Disease Aortic–Mitral–Tricuspid	6 (25%)–1 (4.2%)–1 (4.2%)
Atrial Fibrillation	4 (16.6%)
Pacemaker	5 (20.8%)
Rheumatic or congenital heart disease	0
Lung disease	11 (45.8%)
Rheumatologic disease	1 (4.2%)
Deep venous thrombosis	2 (8.3%)
Malignancy	6 (25%)
Cirrhosis	3 (12.5%)
Prior central line infection	4 (17.3%)
Total parenteral nutrition	3 (12.5%)
Multiple prior hospitalizations (≥2 in prior 6 mo)	15 (62.5%)

patients developed septic shock. Four patients had prolonged fevers, 1 had septic thrombophlebitis, 1 developed septic arthritis, 1 had a cardiac abscess, and 1 had lumbar discitis. Exacerbation of congestive heart failure occurred in 7 patients.

**Table 2. Clinical Presentation**

Healthcare Associated	24 (100%)
Nosocomial	9 (37.5%)
Non-nosocomial	15 (62.5%)
Onset (d before or after admission)	
Nosocomial	2 to 24 d
Non-Nosocomial	-7 to 0 d
Fever	20 (83%)
Chills	12 (50%)
Nausea, vomiting	9 (37.5%)
Dyspnea	7 (29.1%)
Systolic Blood Pressure (SBP) at diagnosis	112±30 mm Hg (70–190 mm Hg)
SBP<90 mm Hg	4 (16.6%)
Diastolic Blood Pressure at diagnosis	63±18 mm Hg (34–120 mm Hg)
Heart Rate at diagnosis	100±20/ min (52–131/ min)
Temperature at diagnosis	101.4±1.6 (97.4–104.5 °F)
Intubation during index admission	5 (20.8%)
Heart Failure Exacerbation	4 (16.7%)
New Valvular Regurgitant Murmur	1 (4.2%)
Vascular Evidence of Endocarditis	3 (12.5%)
Immunologic Evidence of Endocarditis	Not reported in any patient
Janeway Lesions, Osler Nodes, Roth Spots	Not reported in any patient
White blood Cell Count at Diagnosis—mean	13,020 (3,100–38,500)
Hematocrit—mean	34.4 (25.6–46.1)
Erythrocyte Sedimentation Rate mm/hr (range)	78±39 (15–130)
Albumin g/dl—mean	3.0 (2.0–4.4)
Acute Renal Failure (rise in creatinine >0.5 mg/dl)	7 (out of 14 non-hemodialysis patients)

All patients were placed on appropriate, culture guided, antibiotic therapy for extended periods of time that ranged from 4–12 wks after the infected line was removed. Surgery

**Table 3. Line Characteristics**

Line Characteristics	Number of Patients
Tunneled	9 (37.5%)
Vaxcell	7
Hickman	2
External	13 (54.1%)
Triple Lumen Catheters (TLC)	5
Peripherally Inserted Central Lines (PICC)	6
Swan Ganz Catheter	1
Quinton Hemodialysis Catheter	1
Implantable	2 (8.4%)
Indications	
Hemodialysis	9 (37.5%)
Intravenous Access	6 (25%)
Total Parenteral Nutrition	4 (16.5%)
Hemodynamic Monitoring	1 (4.2%)
Chemotherapy	2 (8.4%)
Other (plasmapheresis, medication infusion)	2 (8.4%)
Line Tip Location	
Superior Vena Cava (SVC)	8 (33.3%)
SVC-Right Atrial Junction (SVC-RA)	5 (20.8%)
Right Atrium (RA)	9 (37.5%)
Pulmonary Artery	1 (4.2%)
Unknown	1 (4.2%)
Time from Line Placement to Development of Infection	Median 19 d (Range 1–975)
Time from Infection Onset to Line Removal	Median 1 d (Range 0–28)

was required during the index admission in 3 patients. One patient required removal of a right atrial mass associated with fungemia and 2 patients required removal of a pacemaker system.

Two patients had a clinical relapse with 1 patient requiring mitral valve repair and the second patient required removal of a pacemaker system. Five patients (20.8%) died during

Table 4. Echocardiographic characteristics

Echocardiographic Characteristics	Findings
Time from 1st Positive Blood Culture to First Transthoracic Echocardiogram (TTE)	Median 2 d (Range –1–8 d)
Findings on TTE (n = 24)	
Aortic Valve Vegetation	3
Mitral Valve Vegetation	4
Tricuspid Valve Vegetation	4
Pulmonic Valve Vegetation	1
Mural RA Vegetation	4
Pacerwire Vegetation	0
Multiple Abnormalities	2
Time from 1st Positive Blood Culture to First Transesophageal Echocardiogram (TEE; n = 14)	Median 6 d (Range 3–13 d)
Time from TTE to TEE (n = 14)	Median 4 d (Range 1–8 d)
Additional Abnormalities Detected on TEE:	
Aortic Valve Vegetation	3
Mitral Valve Vegetation	3
Tricuspid Valve Vegetation	2
Mural RA Vegetation	7
Pacerwire Vegetation	2
Multiple Abnormalities	4
TEE Abnormal with Prior Negative TTE	10 cases
TEE Detecting More Abnormalities than Prior Abnormal TTE	1 case
TEE Not Performed or Not More Useful than Prior TTE	13 cases
Cumulative Abnormalities Detected with Echocardiography	
Aortic Valve Vegetation	6
Mitral Valve Vegetation	7
Tricuspid Valve Vegetation	6
Pulmonic Valve Vegetation	1
Mural RA Vegetation	11
Pacerwire Vegetation	2
Multiple Abnormalities	8
Isolated Right-sided Involvement	12 (50%)
Isolated Left-sided Involvement	8 (33.4%)
Bilateral Involvement	4 (16.6%)

the index admission. Cumulative mortality at 1 y was 41.6% (10 patients).

### Discussion

This study presents an 8 y, single center, retrospective review of health care associated infective endocarditis associated with central line infections. It includes patients that acquired the infection in the hospital while receiving treatment for another health problem (nosocomial), as well as patients that presented from the community who had been receiving treatment via chronic indwelling central lines (non-nosocomial).<sup>8,9</sup>

Other investigators have reported an increase in the incidence of health care associated endocarditis<sup>4,10,11</sup> and we found a similar trend at our institution with a doubling of cases between 1999–2002 and 2003–2006. Of all endocarditis cases in the studied time period, 7.5% were health care associated and related to indwelling catheters. Other institutions<sup>2</sup> have reported incidence rates of 7%–29% of nosocomial endocarditis. In addition to infected central lines, other described sources of nosocomial endocarditis have been wound infections and invasive genitourinary or gastrointestinal procedures.<sup>4,12</sup>

The patients in our study had a significant burden of comorbid conditions. The most common of these were insulin-dependent diabetes, chronic kidney disease on hemodialysis, multiple prior hospitalizations, coronary artery disease, and heart failure. Preexisting valvular heart disease was not invariably present. This last point is important to note, as line related endocarditis may occur in patients without preexisting valvular heart disease.<sup>13</sup> More importantly, it appears that endocarditis may result from presumed damage to the endocardial surface induced by the catheter itself, as described in experimental animal models of endocarditis.

The clinical presentation in the majority of patients was that of an acute endocarditis. Persistent fever, leukocytosis, and elevated erythrocyte sedimentation rate (ESR) commonly heralded the presence of an infectious complication of the indwelling central line. Severe sepsis with septic shock was seen in 7 patients. Most patients lacked physician documentation of a new regurgitant murmur, as has been noted in other studies.<sup>10</sup> There was a significant lack of traditional vascular and immunologic phenomena in the majority of patients who were later diagnosed with endocarditis. There are many potential explanations for this, including the significant number of right-sided endocarditis cases, the acute presentations, and the prompt use of empirical antibiotic therapy.

In the majority of cases, the lines involved were either external or tunneled. External lines such as triple lumen catheters (TLCs) and peripherally inserted catheter (PICC) lines were usually seen in nosocomial cases of endocarditis since these are frequently placed while the

patient is in-hospital. The median time from placement to the development of infection for the external catheters was 12 d. Tunneled catheters were more commonly involved in non-nosocomial acquired cases, as these are traditionally long-term indwelling lines for outpatient therapies with the median time from placement to infection of 177 d. Hemodialysis lines have been reported to have higher rates of systemic infection.<sup>3</sup> It is noteworthy that there were no signs of infection at the skin exit site or in the tunneled part of all but 2 of these lines. In the 1 case of a port infection there was evident inflammation at the pocket site. Thus the majority of central line infections in our series were caused by bacterial contamination via the hub of the line rather than via the catheter tract.

The line tip location was within the right atrium or at the SVC-RA junction in 14 patients (58%). There has been considerable debate in the literature regarding the appropriate position of central line tips.<sup>14,15,16</sup> The consensus has been that the SVC is the ideal location for the catheter tip. The only exceptions are hemodialysis catheters that require high flow rates. It has been suggested that these be positioned in the upper right atrium. Our study demonstrates an association between the development of right-sided endocarditis and the presence of a catheter tip in or near the right atrium. The majority of cases with right-sided lesions had catheters in proximity to the right atrium. Experimental models of endocarditis have shown that injury to the endocardial surface of the heart can promote vegetation formation. Meticulous attention to line position at the time of insertion may be an important step in preventing endocarditis in patients with central lines.

*Staphylococci* were the cause of central line infections and endocarditis in the majority of cases. *S. aureus* was implicated in 13 cases (54.1%) with 10 being methicillin resistant (MRSA), consistent with other studies<sup>6,9</sup> that show a high incidence of *S. aureus* bacteremia in patients with central line infections as well as in nosocomially acquired endocarditis. MRSA bacteremias may be more persistent and difficult to treat as vancomycin has delayed bactericidal activity when compared with beta-lactam antibiotics which may contribute to mortality.<sup>9</sup> Four of the 5 patients that died during the index admission had MRSA infections that were associated with persistent bacteremias. *Coagulase-negative staphylococci* were also major pathogens in this series as has been seen in other reported series of central line associated bacteremias. Fungemia was associated with total parenteral nutrition (TPN) in 2 out of 4 cases and resulted in right-sided mural vegetations requiring surgical excision in 1 case.<sup>17</sup>

Evidence of vegetations on echocardiography is one of the major Duke criteria for the diagnosis of endocarditis and all patients included in this study had a positive echocardiogram. The TTE was not diagnostic in 10 patients and a subsequent TEE was required to make the diagnosis. In many of these patients, right-sided lesions found on TEE had been missed on TTE. It is possible that because of

the fairly prompt performance of the TTE in the majority of cases, small right-sided lesions may have been missed with a resultant decrease in sensitivity. TEE was obtained an average of 4 d after the TTE and vegetations may have progressed in size during that time interval which may artificially inflate the sensitivity of TEE versus TTE. Despite acknowledging this possibility, the combination of persistently positive blood cultures and fevers in a patient with a central line should prompt the performance of a if the TEE is negative or nondiagnostic.<sup>1,18,19</sup> Although some studies<sup>19,20</sup> support the cost efficiency of TEE as a first step, especially in patients with *S. aureus* bacteremia and intermediate probability of endocarditis, we found TTE to be adequate in over half of our patients.

It is important to note that not all thrombi associated with a central line tip are infected.<sup>20,21</sup> There have been case series describing the presence of right atrial thrombus in patients with the tip of the hemodialysis catheter in the right atrium.<sup>22,23</sup> Trauma to the endocardial surface prompting thrombus formation was the proposed mechanism. Thus, it is important to consider clinical and microbiologic information prior to deciding between thrombus or vegetation (infected thrombus) in these cases. Thrombus associated with central lines however is a predisposing factor for the development of subsequent infection.<sup>24</sup> By 1 report<sup>25</sup>, 36% of catheterized veins were associated with venous wall thrombosis, and there was a strong relationship between mural thrombosis and the development of catheter sepsis.

Of the 24 patients in our series, only 3 patients underwent surgery during the index hospitalization. In spite of appropriate antibiotic therapy, 5 patients (20.8%) died during their index admission and MRSA was the offending pathogen in 4 of these cases. The high mortality rates are also a reflection of the significant burden of illness seen in these patients. These findings parallel those from other studies<sup>10,26,27,28,29</sup> that have shown increased morbidity and mortality with *S. aureus*, comorbidity, age, higher APACHE scores (acute physiologic and chronic health evaluation), and lower albumin levels.<sup>30,31</sup>

### Study Limitations

The study included only definite cases of endocarditis. Thus we have excluded cases that clinically were classified as possible by the Duke criteria. In doing so we opted for increased specificity of our results at the expense of underestimating the true incidence of line related endocarditis. This was also a retrospective study, and there was no control group of patients with central line infections, but without endocarditis to compare to.

### Conclusions

Endocarditis complicating central line infections is associated with significant morbidity and mortality and is

seen with increasing incidence. The presentation is generally of acute endocarditis, frequently caused by *S. aureus* or *coagulase-negative staphylococcal* species. Two-thirds of cases are right-sided, often associated with the presence of a line tip in the right atrium, and frequently necessitating transesophageal echocardiography for diagnosis. Prompt removal of central lines, extended antibiotic coverage, and surgery in select cases are essential in management. MRSA, persistent bacteremias, and significant comorbidities are predictors of increased mortality.

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