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Lead-associated endocarditis: the important role of methicillin-resistant Staphylococcus aureus.

Arnold J. Greenspon
Thomas Jefferson University, arnold.greenspon@jefferson.edu

Eugene S. Rhim
Thomas Jefferson University

George Mark
Thomas Jefferson University

Joseph Desimone
Thomas Jefferson University

Reginald T. Ho
Thomas Jefferson University

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Arnold J. Greenspon MD, Eugene S. Rhim MD, George Mark MD, Joseph DeSimone MD, Reginald T. Ho MD

Divisions of Cardiology and Infectious Diseases, Department of Medicine

Thomas Jefferson University Hospital

Philadelphia, PA

Address for Correspondence:
Arnold J. Greenspon M.D.
Director, Cardiac Electrophysiology Laboratory
Thomas Jefferson University Hospital
Jefferson Heart Institute
925 Chestnut St, Mezzanine
Philadelphia, PA 19107
215-955-8659

Abstract

Background: Infection is a potentially life-threatening complication of cardiac device implantation. Lead-associated endocarditis may be the most serious complication since it is associated with a high mortality.

Methods: The medical records of patients referred to our institution for the treatment of lead associated endocarditis between 1999 and 2007 were reviewed.

Results: A total of 51 of 107 patients referred for device related infections met the criteria for lead-associated endocarditis. Of these, 19 occurred within 6 months of their most recent procedure (early), while the remaining 32 occurred more than 6 months later (mean= 31.9 months post procedure). Devices included pacemakers in 33 patients and ICDs in 18 patients. The most common organism responsible for infection was *Staphylococcus aureus* (53%) followed by coagulase-negative staphylocci (22%) and streptococci (12%). Methicillin-resistant *Staphylococcus aureus* (MRSA), accounted for 67% of the *s. aureus* infections. Coagulase-negative staphylococci were responsible for only 26% of early and 19% of late cases. A distant site of infection was common (26/51=51%), particularly in patients with MRSA LAE. The device and leads were removed percutaneously in all patients. Only 1 patient failed to respond to intravenous antibiotics.

Conclusions: Our data suggests that methicillin-resistant *Staphylococcus aureus* is an important pathogen in lead-associated endocarditis. Since many infections occur months after the last device procedure, hematogenous spread of organisms from a distant site may be an important contributing factor. These data suggest that strategies to prevent

hematogenous infection, particularly with *Staphylococcus aureus*, are critical in patients with implantable cardiac devices.

KEY WORDS: endocarditis, device infections, pacemaker, implantable cardioverter-defibrillator, *Staphylococcus aureus*, lead extraction

Introduction

Infection is a potentially life-threatening complication of cardiac device implantation. In previous reports, the rate of infection varies from 0.13-19.9%.[1,2,3,4] The severity of infection ranges from localized infection in the device pocket to systemic infection associated with bacteremia and endocarditis. Lead associated-endocarditis (LAE) is the most serious complication related to cardiac device implantation with mortality ranging from 10-21%.[2,5,6,7,8,9,10] Previous reports have emphasized skin flora as the likely source for LAE. Coagulase-negative staphylococci are reported as the most likely organisms followed by *Staphylococcus aureus*. These reports are from an earlier period, before the importance of antibiotic-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) was emphasized. We hypothesized that MRSA may account for a greater percentage of device-related infections than previously reported. Therefore, we retrospectively reviewed cases of LAE referred to our institution to evaluate the clinical presentation, microbiology, and course of these patients.

Methods

We performed a retrospective review of the medical records of patients with lead-associated endocarditis referred to Thomas Jefferson University Hospital between 1999 and 2007. The study proposal was approved by the Institutional Review Board.

Definitions

A diagnosis of infective endocarditis was based on the modified Duke criteria.[11] Specifically, lead-associated endocarditis was defined as persistent bacteremia in the presence of a vegetation documented by echocardiography, a vegetation without

bacteremia in a patient treated with antibiotics, or persistent unexplained bacteremia without any another identifiable source. In patients with fever and persistent unexplained bacteremia, a diagnosis of LAE was presumed since bacteremia and fever resolved promptly upon removal of the device and leads despite the absence of a vegetation on imaging. A vegetation was defined as an oscillating intracardiac mass on the electrode leads or cardiac leaflets which was present in more than one echocardiographic plane. For the purposes of this analysis, early LAE was defined as infection occurring within six months of implantation or device replacement. If infection occurred more than six months following surgery, it was defined as late LAE.

Diagnosis and Treatment

Multiple blood cultures were obtained in each patient. A transthoracic echocardiogram was initially performed in all patients. If a vegetation was not present by transthoracic echocardiogram, a trans-esophageal echocardiogram was performed.

All patients underwent removal and extraction of all hardware. Prior to extraction, all patients had a temporary transvenous pacemaker placed via a femoral vein. A bacterial culture was performed on the pulse generator site. Following the procedure, intravenous antibiotics, based on the results of culture and sensitivity, were administered for a total of six weeks. If bacterial cultures were unrevealing, empiric antimicrobials were prescribed intravenously for six weeks. A new device was implanted on the contralateral side (if clinically indicated), once the patient had received at least 14 days of appropriate intravenous antibiotics. Relapse was defined as a recurrence of infection with the same organism.

Results

Baseline Characteristics

A total of 107 patients with device-related infections were referred to our center during the study period. Of these, 51 cases met the criteria for LAE and are included in this report. (Table I)

The mean age of the patients was 68±11 years (range 42 to 83 years). Seventy-seven percent were male. Devices included permanent pacemakers in 33 (65%) and ICDs in 18 (35%). LAE occurred following the initial implantation in 33 (65%), after a revision or upgrade in 8 (15%), and following a pulse generator replacement in the remaining 10 (20%). Sixteen patients (31%) had diabetes mellitus, 7 (14%) had chronic renal insufficiency (defined as a serum creatinine greater than 3 mg/dl) with 6 of these patients requiring chronic hemodialysis, and 2 were on chronic oral steroids.

The most common presenting symptom was fever (51%). Eleven patients (22%) presented with symptoms resulting from infection at a remote site, while pain at the generator site was the predominant complaint in three patients (6%). The remaining eight patients presented with nonspecific complaints such as malaise. LAE was diagnosed by the finding of bacteremia and vegetation in 33, vegetation without bacteremia on antibiotics in 1, and persistent bacteremia without any identifiable source in 17.

The timing of the LAE was divided into two groups based on the timing of the most recent device procedure. (Figure 1) By definition, all early infections occurred within 6 months of the most recent procedure (N= 19, mean=3 months, range 1-6 months). Late infections occurred a mean of 32 months post procedure (N= 32, range 7-78 months).

LAE occurred following a system upgrade or device replacement in 8/19 (42%) early cases vs. 10/32 (31%) late cases.

Echocardiography

Vegetations were visible by echocardiography in 34 patients. All patients underwent transthoracic echocardiography. However, vegetations were visualized by transthoracic echocardiography in only 6 of the patients. In 28 patients, a vegetation was only demonstrated by transesophageal echocardiography. No vegetations were seen in 17 patients. Vegetations were measured up to 3.5 cm. Vegetations greater than 2 cm in diameter were seen in six patients.

Bacteriology

Blood cultures were positive in 47/51 patients upon presentation to our institution; 18/19 patients with early LAE and 29/32 patients with late LAE had positive blood cultures. All patients with negative blood cultures had been previously treated with intravenous antibiotics prior to hospital admission or transfer. Overall, 17/51 patients had positive pocket or wound cultures. Seven of 19 (37%) early LAE and 10/32 (31%) late LAE patients had positive pocket cultures. In all cases, the organism responsible for the positive pocket culture was identical to the one obtained from the blood culture.

In the total group of 51 patients, *Staphylococcus aureus* was the most common cause of LAE (53%), followed by coagulase-negative staphylococci (22%) and streptococci (12%). Methicillin resistance was present in 67% of the patients infected with

Staphylococcus aureus. There were differences in bacteriology between early and late cases of LAE. (Figure 2) Though *Staphylococcus aureus* was the predominant organism in both early and late cases, more early LAE cases had methicillin-resistant organisms (83% vs 50%). Coagulase-negative staphylococci were responsible for only 26% of early cases and 19% of late cases.

A distant site of infection was present in approximately one half of the patients (26/51). (Table II) These sites included infected intravenous catheter sites (23%), wound infection or abscess (19%), osteomyelitis (27%), joint infections (12%), and intravenous drug use (12%). Interestingly, 15/18 patients with MRSA (7 EARLY, 8 LATE) had a distant site of infection. In patients with early LAE and MRSA, these sites included wound infections in 2 (cervical operative site, sacral decubitus), lumbar abcess in 1, joint infection in 2, and history of recent IV drug use in 2. In patients with late LAE and MRSA, the sites included osteomyelitis in 3, infected intravenous catheter in 3, spinal abscess following epidural injection for pain in 1, and urosepsis with indwelling catheter in 1.

Outcome

The device and leads were removed at the time of initial clinical presentation. The entire device system was successfully removed in all patients. All patients underwent percutaneous lead extraction with use of a lead-locking stylet and/or traction (n=24) or a laser sheath (n=27). No patient required surgical extraction. At the completion of the extraction procedure 8 patients remained pacemaker dependent and therefore needed continuation of temporary pacing. Seven of the eight patients had a temporary pacing lead inserted via the internal jugular vein contralateral to the extraction site. The

remaining patient received temporary pacing via the lead placed in the femoral vein at the start of the procedure. Three patients received active fixation and four patients received passive fixation temporary leads. The temporary leads remained in place until the time of re-implantation.

The extraction procedure was complicated by cardiac tamponade requiring urgent pericardiocentesis in 1 patient and clinical pulmonary emboli in 2 patients. Two patients had pulmonary emboli prior to the extraction procedure despite a negative trans-esophageal echocardiogram. Neither of these patients had emboli documented post procedure. Clinical pulmonary emboli were not seen any of the patients with vegetations measuring greater than 2 cm. in diameter, including the patient with a 3.5 cm vegetation. This patient was a 90 year old woman with MRSA bacteremia and renal failure. It was felt that she was too frail and ill to undergo an open extraction procedure.

Pulmonary emboli were apparent in the 2 patients following the development of post operative pleuritic chest pain and transient oxygen desaturation. In both cases, the oxygen saturation promptly returned to baseline with no hemodynamic sequelae. Both patients had vegetations seen on their pacing leads by transesophageal echocardiography performed at an outside institution. The size of these vegetations was not quantified. Several days later, one of these patients died following the development of shock due to persistent MRSA bacteremia in the presence of a spinal abscess. It was felt that death was not directly related to the extraction procedure. Two additional patients died during the index hospitalization of overwhelming sepsis and not as a result of the extraction procedure. The remaining 48 patients were treated with six weeks of intravenous antibiotics. All patients were assessed for the ongoing need for an implantable cardiac

device. Seventeen patients had their devices re-implanted on the contra lateral side during the index hospitalization following at least 14 days of intravenous antibiotics. An additional 2 patients returned following 6 weeks of IV antibiotics for re-implantation on the contralateral side. None received epicardial leads. Only 1 patient had recurrent LAE. This patient had chronic osteomyelitis which may have been the remote source of both infections. The surviving patients were followed for at least six months post procedure and had no evidence of recurrent infection.

Discussion

The rate of implantation of cardiac rhythm management devices continues to grow. Between 1990 and 2002, approximately 2.25 million pacemakers and 415,780 implantable cardioverter-defibrillators (ICD's) were implanted.[12] During this period of time the annual number of pacemakers implanted increased three-fold while the number of ICDs implanted increased ten-fold. The estimated rate of infection associated with these devices ranges from 0.13-19%[1-3] but has increased by 124% during the past 15 years.[13] This may relate to the fact that device-related infection is higher for ICDs than pacemakers.[14]

Lead associated endocarditis is present in only 10% of device-related infections but is associated with high mortality, morbidity and economic cost.[3] Prompt recognition and management is imperative as 6% of our patients died during the index hospitalization despite uncomplicated extraction of their hardware and administration of appropriate intravenous antibiotics. Previous reports have highlighted the importance of skin flora, such as coagulase-negative staphylococci as pathogenic organisms in these device

infections. However, while LAE more commonly occurs early post implantation, it may occur at any time following implantation or replacement. The present report highlights the changing bacteriology of LAE and the potential importance of LAE stemming from distant sites of infection particularly with organisms such as MRSA.

Bacteriology

The most common pathogens associated with LAE are skin flora.[2,3,5,7,9] Previous reports suggest that coagulase-negative staphylococci are the predominant organisms in approximately 60% of infections with *Staphylococcus aureus* accounting for an additional 20% of cases. Less common organisms include enteric Gram negative bacilli and streptococci. Klug and co-workers reviewed the clinical presentation and management of 52 patients with lead associated endocarditis.[7] All patients had permanent transvenous pacemakers. None had ICDs. Fourteen patients were classified as an acute infection with infection occurring early post implantation (within 6 weeks) while the remaining 38 patients developed infection more than 6 weeks following implantation and were classified as chronic infection. In patients with acute infection, *Staphylococcus aureus* (36%) was the most common organism isolated followed by coagulase-negative staphylococci (21%). By contrast, late infections were most often caused by coagulase-negative staphylococci (71%) followed by *Staphylococcus aureus* (13%). The importance of skin flora was stressed along with the subcutaneous site of pacemaker lead insertion as the likely portal for infection.

By contrast, we found that *Staphylococcus aureus* was the most common pathogen responsible for both early and late infections. We chose to divide LAE infections into early and late based on a six month window following the most recent procedure, since infection by *Staphylococcus aureus* arising from contamination of the operative site would most likely occur within that time frame. However, we realize that this cut-off is somewhat arbitrary and does not exclude the possibility that LAE after 6 months could arise from the operative site. In our population, *Staphylococcus aureus* accounted for 58% of early and 50% of late LAE. Importantly, MRSA was responsible for 53% of all

early LAE and 25% of late LAE. This highlights the emerging role of this organism in LAE.

Relationship between *S.aureus* bacteremia and LAE

Most patients who presented with MRSA infection and LAE demonstrated an additional remote site of infection. It is unclear whether these distant sites of infection represent the source of LAE or instead represent secondary seeding as a result of the LAE. Our data do suggest, however, that hematogenous spread of organisms, rather than local invasion from an infected operative site, is the more likely mechanism for LAE. Previous investigators have emphasized the high risk of device infection in patients who develop *Staphylococcus aureus* bacteremia.[15] Chamis and co-workers found that cardiac device infection occurred in approximately 70% of patients with *Staphylococcus aureus* bacteremia and an implanted cardiac device. Hematogenous spread of the organism was responsible for the infection in 27.3% of cases. Likewise, Camus and colleagues reported that sustained *Staphylococcus aureus* or coagulase-negative staphylocooci bacteremia was associated with device infection in 67% of their patients.[16] We found that 67% of our patients had no detectable signs of pulse generator pocket infection. This is in agreement with previous reports[15,16] which suggest that hematogenous spread of *Staphylococcus aureus* is an important cause of LAE.

Emergence of antibiotic resistant organisms

Methicillin-resistant *staphylococcus aureus* has emerged as an important pathogen in both hospital acquired and community acquired infections.[17,18,19] These infections are associated with both a high mortality and morbidity despite improvements in recognition and antibiotic treatment. The rise in the incidence of *Staphylococcus aureus* infections parallels the increase in the use of intravascular devices and implantable devices.[17] Although many of our patients were hospitalized for the treatment of noncardiac issues and developed infected intravenous or dialysis catheters or wound infections, a number developed MRSA in non-hospital settings (e.g. following IV drug abuse, paraspinal abscess following epidural analgesia, and osteomyelitis).

The reason for the increase in *Staphylococcus aureus* infections in patients with cardiac devices is not clear. One factor may relate to the increase in ICDs as a percentage of cardiac device implants.[12] As compared to patients with permanent pacemakers, ICD patients generally have more co-morbidities such as heart failure and renal failure. Such comorbidities, make them more likely to be hospitalized or have invasive procedures which may expose them to organisms such as *staphylococcus aureus*.

Treatment and outcome

Prompt recognition of LAE, treatment with intravenous antibiotics, and removal of all device hardware is important to a successful outcome.[2,3,5,7,8,9,10] It has been suggested that intravenous vancomycin be administered initially until a specific pathogen has been identified since it is generally effective against MRSA.[20] The choice of antibiotics may then be changed to the most appropriate antibiotic once the final results of culture and sensitivity are obtained. Previous investigators have stressed that transvenous extraction may be performed safely. Re-implantation is possible following a course of intravenous antibiotics. However, the timing of re-implantation is open to question. Seventeen of our patients had re-implantation of their device during the index hospitalization, following a course of fourteen days of intravenous antibiotics. One patient with a history of osteomyelitis had recurrent LAE. This suggests that prolonged administration of intravenous antibiotics may be necessary in patients with alternate sites of infection, such as bone, which generally require a long course of antibiotics for successful treatment. In cases where the offending source is easily treated or removed, such as an intravenous catheter or port, re-implantation may be possible following a shorter course of antibiotics.

All of our patients underwent percutaneous lead extraction. Patients with large vegetations may be at particular risk for pulmonary emboli. In these patients, thoracotomy and removal under direct vision should be considered.[2,3] However, in patients who are critically ill and at high risk for thoracotomy and general anesthesia, percutaneous extraction remains an appropriate option. Of interest is the fact that 6 of our patients had vegetations measuring greater than 2 cm in diameter. All had their leads safely extracted without clinical pulmonary emboli, including the patient with a 3.5 cm vegetation.

Limitations

The results of this investigation may be influenced by referral bias since we are a tertiary care center for lead extraction. Our population was quite ill with many co-morbidities and had a high incidence of *Staphylococcus aureus* bacteremia and LAE. In addition, LAE represented approximately one-half of those patients referred for treatment of device related infections. It is likely that many more patients with localized infection were cared for at their local institution. Therefore, other centers may not have the same experience. Nonetheless, the marked increase in *staphylococcus aureus* as the cause for LAE along with the high incidence of MRSA suggests that the bacteriology of LAE may be changing.

The diagnosis of LAE may be difficult to establish, particularly in patients with persistent, unexplained bacteremia on antibiotics who have no vegetation detectable by echocardiography. We are confident that our 17 patients with persistent unexplained bacteremia had LAE since their fever and bacteremia promptly resolved upon removal of the implantable device and leads. The possibility that rapid clinical improvement had nothing to due with device and lead removal cannot be completely excluded.

Conclusions

Infection, particularly lead-associated endocarditis, is a serious, life-threatening complication of cardiac device implantation. Prompt recognition and management is essential for improving outcome. Our data suggests that methicillin-resistant *Staphyloccus aureus* has emerged as an important pathogen. Since LAE is common in patients who develop *Staphylococcus aureus* bacteremia, strategies to prevent intravenous infection and hematogenous spread of organisms is critical in patients with implantable cardiac devices.

Figure Legends:

Figure 1 Timing of Lead-Associated Endocarditis (LAE): The timing of LAE (in months) with respect to the most recent procedure is displayed on a logarithmic scale for both Early and Late endocarditis. Late LAE occurred a mean of 31.9 months following the most recent procedure.

Figure 2A: Bacteriology of Early LAE: Staphylococci species accounted for most early LAE. MRSA was the predominant organism. Abbreviations: MRSA= Methicillin-resistant *staphylococcus aureus*, MSSA=Methicillin-sensitive *staphylococcus aureus,* CoNS= coagulase-negative staphylococcus, Strep= streptococcus.

Figure 2 B: Bacteriology of Late LAE: Similar to early LAE, Staphylococci were the predominant organisms responsible for late LAE. Though MSSA was more common, MRSA was responsible for 50% of *staphylococcus aureus* infections. Abbreviations: same as Figure 2 A

TABLE I: Demographics

Age (years)	68+11	
% Male	77	
Cardiac device		
	Permanent Pacemaker	33 (65%)
	ICD	18 (35%)
Most recent procedure		
	Primary implant	33 (65%)
	Upgrade or revision	8 (15%)
	Replacement	10 (20%)

TABLE II: Sites of Remote Infection n= 26

Source	Total	Early LAE n=9	Late LAEn=17
Intravenous Catheter	6 (23%)	1	5
Wound infection/abscess	5 (19%)	3	2
Osteomyelitis	7 (27%)	-	7
IV drug use	3 (12%)	2	1
Joint infection	3 (12%)	2	1
Other	2 (7%)	1	1

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