

Right-Sided Infective Endocarditis and Pulmonary Infiltrates

An Update

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Abstract: Sixty years after its initial description, right-sided infective endocarditis (RSIE) still poses a challenge to all medical practitioners. Epidemiological data reveal a rising incidence attributable to the global surge in the number of intravenous drug users and the increased use of central vascular catheters and implantable cardiac devices. RSIE differs from left-sided infective endocarditis in more than just the location of the involved cardiac valve. They have different clinical presentations, diagnostic findings, and prognoses; hence, they require different management strategies. Cardiac murmurs and systemic emboli are usually absent in RSIE, whereas pulmonary embolism and its related complications dominate the clinical picture. Diagnostic delay of RSIE is secondary to the similarity in its initial presentation to other entities. Complications may ensue as a result of this delay. Diagnosis can be initially confirmed by using transthoracic echocardiography, except in patients with implanted cardioverter defibrillator, where a transesophageal echocardiogram is necessary. Various factors may increase mortality and morbidity in RSIE such as tricuspid valve vegetation size, fungal etiology, and low CD4 cell count in HIV patients. Oxacillin and vancomycin had been the traditionally used agents for the treatment of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*, respectively. More recently, daptomycin has shown promising results, which has led to its Food and Drug Administration (FDA) approval for the treatment of *S. aureus* bacteremia and associated RSIE. The aim of this article is to provide a comprehensive update on RSIE including epidemiology, pathogenesis, microbiology, diagnosis, management, and prognosis.

Key Words: right-sided infective endocarditis, tricuspid valve endocarditis, risk factors, diagnosis, pulmonary infiltrates

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In 1885, Osler¹ provided the first comprehensive description of infective endocarditis (IE); however, it was not until 1950 that Hussey and Katz² described a series of 8 intravenous drug users (IDUs) with right-sided infective endocarditis (RSIE). RSIE accounts for approximately 10% of the total IE cases.³ Based on predisposing risk factors, 4 main patient populations can be distinguished: IDUs, patients with implanted cardioverter defibrillators (ICDs), patients with central venous catheters (CVCs), and lastly patients with underlying right-sided cardiac anomalies. In contrast to left-sided infective

endocarditis (LSIE) where only about 20% are IDUs, IDUs constitute the main patient population in RSIE, with the tricuspid valve being almost always involved.⁴ In addition, the increased use of ICDs in the management of patients with cardiac arrhythmias and heart failure has led to an increase in the incidence of RSIE in this patient population as well.⁵ In a patient with an ICD, the development of RSIE usually signals a severe infection that has spread beyond the pocket, extending up to the insertion leads.⁶ In addition, RSIE in patients with ICD is problematic because it is characterized by frequent negative blood cultures, highly variable clinical presentation, and a frequent delay in diagnosis, all leading to increased mortality rates.⁷ RSIE is also seen in patients with various intravascular devices other than ICDs, for example, central lines, intra-aortic balloon pumps, and ventricular assist devices.⁸ Prevention and early recognition are key to avoiding additional disease burden in these patients. Moreover, the “3 nos” group is a recently defined group that encompasses the no IDUs, no ICDs, and no LSIE group of patients.⁹ This specific population of patients comes with a higher morbidity and mortality risk because it is composed mainly of middle-aged men with multiple comorbidities and health-care related infections. Some of these patients have intravascular catheters as the main source of bacteremia, particularly with staphylococci, with high rates of methicillin-resistant *Staphylococcus aureus* (MRSA, 33%), which suggests the nosocomial nature of their infection.⁹ Lastly, RSIE can also develop in patients with congenital heart diseases or in patients with surgically corrected congenital cardiac anomalies.^{10–12} This patient group will not be covered in this review.

The aim of this article is to provide an updated review of RSIE infection, its epidemiology, pathogenesis, microbiology, diagnosis, management, and prognosis.

EPIDEMIOLOGY

A global increase in the incidence of RSIE has been reported, primarily attributable to a global rise in the number of IDUs, along with the increased use of ICD/CVC in modern patient care.^{11,13–15} The lack of accurate data on the prevalence of illicit IDU hampered the proper estimation of RSIE incidence, but an incidence of 2–4 cases per 1000 years of IDU has been generally accepted.^{13,16,17} RSIE in IDUs is more common in males (ratio 3:1).¹⁶ A typical patient is a young male in his early 30s, an age that is significantly younger than all other age groups affected by IE.¹⁶ Female IDUs tend to have frequent involvement of the mitral valve, possibly due to the higher prevalence of subclinical mitral valve prolapse.^{18,19} Recurrence of RSIE is common in IDUs, with drug addicts having shorter time intervals between recurrent episodes.²⁰ Although IDU constitutes the highest risk factor for the development of RSIE, patients with an ICD and CVC account for approximately 9% of the total population affected by RSIE.^{21,22} A retrospective analysis of RSIE in non-IDUs showed that patients tended to be younger and had higher incidence of congenital heart disease and CVC use and a higher vegetation size when compared with those with LSIE.²³ The distribution of the valves involved in RSIE is estimated to be as follows: tricuspid valve (90%), pulmonary valve (5%),²⁴ and Eustachian

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valve (3%).²⁵ Concomitant LSIE and RSIE are not uncommon and account for approximately 13% of total IE cases.^{20,26,27} Moreover, involvement of the interventricular septum and right ventricular free wall has also been reported.²⁸ Finally, despite the decline of RSIE incidence in HIV-infected patients due to the advent of antiretroviral therapy, HIV-seropositive patients with CD4 cell counts less than 200 cells/mm³ remain at a greater risk for developing RSIE.²⁶ A recent report suggested a change in the epidemiology of RSIE in the past 5 years.¹¹ Patients were observed to present in their 40s instead of early 30s, with more IDUs having larger vegetations and more *S. aureus* infections. Also, more valve insufficiency and embolic events were reported with significantly reduced rates of abscess formation and valve perforation.¹¹

PATHOGENESIS

RSIE shows a strong predilection for the tricuspid valve, but the exact pathophysiology underlying this observation is still not very well understood. Intravenous (IV) drug injection bombards the tricuspid valve the most, and repeated injections have been associated with inoculation of small bacterial loads that may lead to cumulative subclinical endothelial damage, ultimately culminating in infection.^{13,29} Moreover, specific substances that may be injected with IV drugs, such as talc, generate direct endothelial damage and, therefore, predispose to infection.^{16,30} Also, particulate matter up to 10mm in size may cross the pulmonary circulation and damage the mitral or aortic valve.²⁰ Cannon and Cobbs³¹ were the first to show a link between talc-induced subendothelial granulations in the tricuspid valve and an increased risk for subsequent bacterial infection. It is unknown, however, whether this damage confers an increased risk of IE after IDU discontinuation. Another proposed mechanism involves antibody-inducing antigenic substances present in injected drugs that lead to immune complex formation and deposition mainly on the tricuspid valve, thus creating a nidus for bacterial adhesion.³² Moreover, IDUs have higher rates of nasal and cutaneous *S. aureus* colonization, further predisposing them to RSIE.³³ A summary of all proposed theories is highlighted in Table 1. However, a clear understanding of the pathophysiology of RSIE in patients with ICD/CVC is relatively more established, with the process starting by bacterial contamination at the period of implantation or through subsequent handling.³⁴

MICROBIOLOGY

S. aureus is the most common organism responsible for RSIE in both IDU and non-IDU, with MRSA being especially worrisome.^{35–40} MRSA was reported to produce highly aggressive RSIE with multiple pulmonary abscesses and subsequent development of

septic shock.^{41,42} Over the past 2 decades, the emergence of vancomycin-resistant *S. aureus*⁴³ and vancomycin-intermediate *S. aureus* (VISA) strains has become evident.⁴⁴ Infections with these strains are associated with high rates of treatment failures. This prompted a call for the development of new classes of antimicrobials with the ability to effectively target vancomycin-resistant *S. aureus* and VISA, such as the lipopeptides. Daptomycin was the first lipopeptide antibiotic indicated for the treatment of MRSA and VISA RSIE.^{45,46}

Less common pathogens causing RSIE include coagulase-negative staphylococci and *Streptococcus sp.* An association has been described between *Streptococcus pneumoniae* RSIE and chronic alcoholism.⁴⁷ Another association was reported between pentazocine IV drug abuse and Gram-negative bacilli RSIE.⁴⁸ Fungal RSIE such as infection with *Candida albicans* is more frequently reported in heroin abusers.^{49,50} Negative blood culture RSIE, more frequent in patients with ICD, has been reported where *Aspergillus sp.* was grown from the pacemaker.^{51,52} *Propionibacterium acnes* has also been described in blood culture–negative RSIE, and it usually presents with a long history of complaints and minor clinical signs of disease.^{53–56}

DIAGNOSIS

Clinical Presentation and History

The diagnosis of RSIE is often challenging, resulting in a delay of the timely initiation of appropriate antimicrobial therapy, therefore, adversely affecting mortality, morbidity, and treatment-related costs.^{57,58} Many signs that are typically associated with LSIE are usually absent in RSIE, for example, absence of typical pathological cardiac murmurs on auscultation at the time of admission or their development at a relatively late stage,^{59,60} lack of peripheral embolization, including splinter, and conjunctival hemorrhages, whereas septic pulmonary embolism complicates 75% of tricuspid valve endocarditis and presents with pleuritic chest pain, hemoptysis, and dyspnea.²² RSIE should be highly considered when encountering a patient with relevant risk factors and presenting with unrelenting spiking fever, bacteremia, and respiratory symptoms such as cough, chest pain, hemoptysis, and multiple pulmonary infiltrates on chest imaging.⁵⁸ Frequently, a delay in diagnosis leads to further complications, such as pulmonary infarcts, pulmonary abscesses, lung emphysema, and rarely pneumothorax.⁶¹ *S. aureus* RSIE can present with extracardiac infections involving the brain, spleen, and kidneys.³⁰ RSIE of the tricuspid valve specifically presents with the “tricuspid syndrome,” which is the constellation of persistent fever, pulmonary symptoms, anemia, and microscopic hematuria.¹¹ This was seen in 28% of the “3 nos” group in a descriptive study in a tertiary care center. This study suggests that in patients with persistent fever and respiratory signs and symptoms, RSIE should be considered in the differential diagnosis, even if classical predisposing factors (cardiac devices and IDU) were not present.⁹ Blood cultures are of paramount importance in the diagnosis, management, and prognosis of RSIE. Current guidelines recommend obtaining 3 sets of blood cultures, from different venipuncture sites, 1 hour apart, cultured in both aerobic and anaerobic media before antibiotic administration.^{62–64} It is imperative to consider blood culture–negative RSIE, especially when patients have a history of IDU or ICD associated with persistent fever and negative cultures after 7 days of incubation and subculturing of at least 3 blood samples in a standardized blood culture system.⁶⁵ The presence of implantable pacemakers or any cardiac devices is in fact considered a risk factor for culture-negative RSIE.⁶⁵ Around 7% of overall ICD-related IE are associated with negative blood cultures.⁶⁶ Clinicians have to keep in mind that there are many medical

TABLE 1. Pathophysiology of RSIE

- (a) Repetitive drug injections and inoculating quantities of bacterial load may generate cumulative subclinical endothelial damage to the tricuspid valve and ultimately infection
- (b) Injection of specific substance such as talc along with illicit drugs may generate transient or permanent endothelial damage to the tricuspid valve
- (c) Injection of external antigens precipitating immune complex valvular deposition creating a nidus for bacterial adhesion
- (d) Cocaine-induced vasospasm and thrombus formation detrimental selectively on the tricuspid valve
- (e) Higher nasal and cutaneous colonization rates with *Staphylococcus aureus* in intravascular drug user
- (f) The amplified matrix molecules’ expression on the right side increases the capacity of binding microorganisms

RSIE indicates right-sided infective endocarditis.

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TABLE 2. Diseases With Clinical Presentations Similar to RSIE

Atrial myxomas
Adult Still's disease
Antiphospholipid syndrome
Loeffler's endocarditis
<i>Pneumocystis jiroveci</i> pneumonia in HIV-infected patients
Pulmonary tuberculosis
Meningococemia

RSIE indicates right-sided infective endocarditis.

conditions that can present with a similar clinical picture to RSIE; those conditions are summarized in Table 2.

Imaging and Echocardiography

Chest radiographs often reveal important diagnostic clues in patients with RSIE. At presentation, more than 50% of chest radiographs show single or multiple pulmonary infiltrates with central cavitation compatible with septic pulmonary emboli.⁶⁷ Computed tomography scans, however, are superior to chest radiography in delineating the extent of septic pulmonary emboli.⁶⁷ Additional findings include thickening and enhancement of the visceral and parietal pleurae with extra pleural fat inflammation that are features of emphysema, a complication of untreated RSIE.⁶⁷ Nodules typically measure between 5 and 35 mm and favor basilar and peripheral lung locations, and they may increase in number on a daily basis.⁶⁷ Transthoracic echocardiography (TTE) is the diagnostic modality of choice in the initial workup of RSIE. TTE's high sensitivity in detecting RSIE may be comparable with transesophageal echocardiography (TEE).^{68–75} Hence, TEE remains nonmandatory in RSIE except in selected clinical situations for specific indications, which are highlighted in Table 3, for example, in patients with ICD when there is a clinical suspicion of RSIE.^{76–78} However, these findings were refuted in a recent study showing that TTE may be unsuitable for RSIE patients with no history of IDU or ICD because multifocal and atypically distributed vegetations may influence detection accuracy.⁷⁹ The low-pressure pulmonary circulation may allow further growth of right-sided vegetations, and as a result, large tricuspid valve vegetations of greater than 2 cm are frequent and can be confused with intracardiac tumors.⁷⁰ Other common problems that may complicate the echocardiographic diagnosis of RSIE include normal anatomical right heart variations, such as the presence of a prominent Chiari complex or a large Eustachian valve. Also, right atrial venous catheters or thrombi may be misdiagnosed as right-sided vegetations.^{73,75} Furthermore, it remains difficult to differentiate old from new vegetations based on echocardiography although old vegetations tend to be more hyperechogenic and calcified.⁸⁰ The use of 3-dimensional echocardiography is advised in patients with RSIE who have a

prosthetic tricuspid valve or a tricuspid annuloplasty ring; 3-dimensional TEE can locate challenging right-sided vegetations especially in the setting of artifacts on TTE or traditional TEE.⁸¹ Recently, 18F-fluorodeoxyglucose positron emission tomography/computer tomography (18-FDG PET CT), which has classically been used in the diagnosis of malignancies, has been increasingly reported to be of use in diagnosing deep-seated infections, including IE, especially in diagnosing extracardiac complications.⁸⁰ A study by Kestler et al,⁸² where 47 patients were matched to 94 controls, reported a sensitivity of 100% and a specificity of 80% when using 18F-FDG PET for the diagnosis of septic lesions. Nevertheless, these data should be interpreted with caution as another study by Kouijzer et al⁸³ examined 72 patients with Gram-positive bacteremia and reported a sensitivity and specificity of 39% and 93%, respectively.

PROGNOSIS

Compared with LSIE, RSIE is usually associated with a favorable prognosis and low mortality rates.³⁰ Conservative medical management is successful in most patients. Factors that were traditionally associated with poor prognosis included vegetation size (where a vegetation size >2 cm was associated with mortality rates similar to those seen in LSIE^{84,85}), fungal etiology, presence of acute respiratory distress syndrome,⁸⁶ and lastly, a CD4 count less than 200 cells/mm³ in HIV-infected patients.⁸⁷ Moreover, in patients with ICD, RSIE is associated with higher mortality rates and a worse clinical outcome. Victor et al⁷⁸ studied 210 patients with ICD and IE and reported an overall mortality rate of 18%. Four factors were found to be associated with increased mortality rates: systemic embolization, moderate-to-severe tricuspid regurgitation, abnormal right ventricular function, and abnormal renal function. Lead vegetation size and mobility were not found to be significantly associated with increased mortality. Unfortunately, most studies addressing RSIE in patients with ICD have limitations, such as variability in the population characteristics and diagnostic modalities.

MEDICAL MANAGEMENT

Early diagnosis, administration of empiric, and later targeted antibiotic therapy, combined with close follow-up, are vital for improving outcomes and reducing hospital stay in patients affected by RSIE. Even though empiric antibiotic therapy can be initiated immediately after collecting 3 sets of blood cultures, this may not always be necessary. In fact, for mild cases, a delay until drug susceptibility results are obtained is considered appropriate,⁸⁸ which allows for a definitive diagnosis with simultaneous reduction in unwarranted antibiotic use and, therefore, prevention of emergence of resistance. In institutions with a low MRSA prevalence, the most commonly used empiric regimen for RSIE is a combination of an antistaphylococcal β -lactam with an aminoglycoside.⁸⁶ As for institutions with a high prevalence of MRSA, a combination of vancomycin plus gentamicin would be indicated.⁸⁹ Daptomycin is Food and Drug Administration approved for the treatment of *S. aureus* bacteremia and RSIE.⁹⁰ The management of other less common bacterial pathogens consists of the same antibiotic regimen used for LSIE and treatment is to be tailored according to the susceptibility profile. Because *S. aureus* is the most common causative organism in RSIE, we will only discuss the treatment of methicillin-susceptible *S. aureus* and MRSA RSIE in this review.

Patients with RSIE caused by methicillin-susceptible *S. aureus* can benefit from a 2-week combination of gentamicin and flucloxacillin.⁹¹ The in vitro synergetic effect of an aminoglycoside accelerates resolution of fever and bacteremia,⁹² but it has not been shown to have a beneficial effect on mortality.^{93–95} Considering its potential nephrotoxicity and ototoxicity, it is important to closely monitor the patients during gentamicin use^{96,97} and limiting its use in some cases to the first 5 days

TABLE 3. Evaluating RSIE: When Is TEE Indicated?

(a) Implantable cardiac devices
(b) Central vascular catheters
(c) Poor acoustic transthoracic window (elderly or obese)
(d) Suspicion of left-sided infective endocarditis
(e) Suspicion of Eustachian valve involvement
(f) Suspicion of pulmonary valve involvement
(g) Negative or nonconclusive TTE and moderate or high clinical suspicion
(h) Negative or nonconclusive TTE and poor clinical course with no diagnostic alternative

RSIE indicates right-sided infective endocarditis; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

of therapy may be judicial.⁹⁸ In a randomized, controlled trial, patients with native valve endocarditis either received antistaphylococcal penicillin or vancomycin plus initial low-dose gentamicin or received daptomycin monotherapy. Initial low-dose gentamicin, as part of therapy for *S. aureus* bacteremia and native valve infective endocarditis, was shown to be nephrotoxic and was not advised to be used routinely.⁹⁶

Vancomycin for 4 weeks was considered in the past the drug of choice for MRSA RSIE.^{99,100} Nonetheless, due to its limited bactericidal activity and poor penetration into vegetation tissue,^{101,102} it can result in relatively high failure rates.⁹⁸ An additional serious concern is the emergence of *S. aureus* strains with heterogeneous resistance to vancomycin, which are associated with both very high treatment failure rates and increased mortality.¹⁰³ Despite its inactivation by the lung surfactant, daptomycin has been found to be effective in the treatment of septic pulmonary infarcts associated with RSIE. Compared with vancomycin, daptomycin offers the advantage of rapid bactericidal activity and a potent activity against *S. aureus* strains with heterogeneous resistance to vancomycin. Despite the reservations about using daptomycin in pneumonia, it has been found to be effective in the setting of septic pulmonary emboli in RSIE.^{104–107} A study by Levine and Lamp¹⁰⁸ reported a beneficial outcome in 86% of daptomycin-treated RSIE cases, and Dohmen et al¹⁰⁹ reported a treatment success rate of 91% when daptomycin was used after treatment failure with glycopeptides for RSIE. Daptomycin was recently approved by Food and Drug Administration for the treatment of RSIE and associated bacteremia at a dose of 6 mg/kg/day. In addition, due to its concentration-dependent killing, high-dose daptomycin (8–12 mg/kg/day) was suggested for the treatment of complicated staphylococcal infections, including RSIE, in previously failed therapy with vancomycin, or in patients who possess an *S. aureus* isolate with an elevated vancomycin minimum inhibitory concentration (MIC).¹¹⁰ New glycopeptides, including dalbavancin and telavancin, and the new cephalosporins ceftobiprole and ceftaroline, have not yet been studied for the treatment of endocarditis but appear active against MRSA, heteroresistant strains, and potentially VISA.¹¹¹ Linezolid, originally approved for skin and soft-tissue infections and pneumonia, was also used off-label for the treatment of IE in a case report of a prosthetic valve RSIE with MRSA and teicoplanin-heteroresistant *S. aureus*. The patient was treated successfully with IV linezolid and rifampin.¹¹²

Short-Course Therapy and Oral Regimens

Historically, the duration of treatment for RSIE was between 4 and 6 weeks. However, IDUs tend to be noncompliant and reluctant to remain in the hospital for long periods for the fear of drug withdrawal symptoms. In addition, it might be risky and unsafe to discharge these patients with a peripheral catheter for IV home therapy. This prompted the investigation for a shorter antibiotic course in this patient population and the search for an oral regimen. Studies have shown that RSIE can be treated with a 2-week course of antibiotics^{91,113,114}; a combination of an aminoglycoside with a β -lactamase-resistant penicillin for 2 weeks reported a 92% cure rate in *S. aureus* RSIE.¹¹⁵ A nonrandomized clinical trial comparing short- vs long-course therapy with cloxacillin or vancomycin combined with gentamicin for 2 weeks and cloxacillin or vancomycin for 4 weeks demonstrated a cure rate of 100% in the 2 treatment groups.¹¹⁶ Another interventional study from Spain compared the efficacy of cloxacillin alone versus cloxacillin and gentamicin for 2-week duration in 90 IDUs with isolated tricuspid valve endocarditis.¹¹⁷ Results showed that cloxacillin for 2 weeks alone can be sufficient for the treatment of this population, and combining gentamicin did not add any benefit. However, adding gentamicin might be warranted in planned longer therapy, *Streptococcus viridans* or MRSA infection, or concomitant involvement of the left side.

Overall, it is crucial for the patient to be closely monitored in a hospital setting when deciding on a 2-week antibiotic course. In

TABLE 4. When Is a 2-Week Course of Antibiotics Contraindicated in RSIE?

- Suspicion or confirmed left-side infective endocarditis^{113,118–121}
- Suspicion or confirmed MRSA or any other resistant pathogens¹¹⁹
- Patient with underlying cardiac complications¹¹³
- Distant metastatic site of infection
- HIV infection with CD4 counts <200 cells/mm³
- Large vegetation: >1.8 cm or >1 cm not decreasing in size after a 2-week course of antibiotics^{120,121}

MRSA indicates methicillin-resistant *Staphylococcus aureus*; RSIE, right-sided infective endocarditis.

addition, decision for therapy discontinuation should be taken by an infectious diseases specialist on the last day of the 2-week period. Contraindications for a 2-week course are summarized in Table 4.^{113,118–121}

Oral therapy for RSIE was studied in a clinical trial by Heldman¹²² who compared oral ciprofloxacin and rifampin for 4 weeks versus IV oxacillin or IV vancomycin (plus IV gentamicin for the first 5 days) for 4 weeks. Oral therapy showed a 90% cure rate and an improved toxicity profile. Dworkin et al¹²³ previously used an oral regimen on a population of 13 IDUs composed of IV ciprofloxacin and oral rifampin for 1 week followed by oral ciprofloxacin and oral rifampin for 3 weeks with a 77% cure rate. A single case of successful use of oral linezolid therapy for 4-week duration has been reported in a 28-year-old patient with MRSA RSIE.¹²⁴

Management of RSIE in Patients With an Implanted Cardioverter Defibrillator

Most patients with ICD suffering from RSIE will develop uncontrolled sepsis and serious complications. Therefore, the recommended treatment approach consists of complete hardware removal, mostly with percutaneous lead extraction, combined with aggressive directed antimicrobial therapy guided by susceptibility results for 4–6 weeks.¹²⁵ A retrospective analysis of 52 consecutive patients with ICD suffering from IE concluded that percutaneous lead extraction performed early, up to 3 days after admission, was associated with improved survival and shorter hospital stay.¹²⁶ These findings highlight the importance of a high index of suspicion in this category of patients even in the absence of classical clinical signs. Two recently published case reports showed positive outcome with a combination of medical and surgical interventions. One reported a patient with ICD-related IE complicated by osteomyelitis treated with a combination of high-dose daptomycin and fosfomycin in conjunction with ICD removal.¹²⁷ The other case is of a pacemaker lead RSIE caused by a daptomycin-nonsusceptible strain of VISA.¹²⁸ After 8 weeks of parenteral telavancin therapy, the patient achieved a microbiological and clinical cure.

Assessment of the need for new device implantation should be done, as patients may not require new device placement due to many factors, for example, reversal of the pathological processes or of the indications that were present at presentation. Removal of the device should be preceded by a careful reimplantation strategy, particularly in patients with pacemakers for third-degree atrioventricular block and resynchronization therapy devices. If needed, new device implantation should be performed on the contralateral side if possible. Otherwise, a transvenous lead can be tunneled to a device placed subcutaneously in the abdomen. If possible, reimplantation is delayed to allow for the resolution of infection.⁶⁶

Active fixation leads attached to pacing generators or defibrillators are now being used as a “bridge” until pacemaker implantation is deemed appropriate. The optimal time of a new device reimplantation is controversial, and differences in timing of reimplantation may vary depending on (1) blood culture (median time of 13 days for bacteremic patients versus 7 days for nonbacteremic patients) and (2) pathogen

identified (median 7 days for coagulase-negative staphylococci versus 12 days for *S. aureus*). It is important to note that there have been no clinical trials examining the optimal timing of new device implantation; however, several experts recommend waiting for the resolution of bacteremia documented by a negative blood culture.⁶⁶

PRINCIPLES OF SURGICAL MANAGEMENT OF RSIE

Valve surgery is rarely indicated for patients with RSIE as most cases resolve with adequate medical therapy. A valvectomy, however, is most commonly indicated for those suffering from either persistent bacteremia or severe right heart failure. Patients with large vegetation size (diameter >10mm) and persistent fever might also benefit from surgery although some authors feel that medical treatment is enough. Nevertheless, in the case of very large vegetations (>20 mm), poor outcome is expected with medical management alone.¹¹³ Other less common indications for surgery include complicated fungal RSIE with perivalvular abscess formation.⁸⁴ Surgery in HIV-positive patients is not contraindicated; however, a low CD4 counts (<200 cells/mm³) has been associated with low success rates when valvectomy is performed.⁸⁷ Finally, it is important to note that pulmonary emboli are not an indication for surgery because high response rate is observed with medical management, especially with daptomycin.

The 3 principles of surgery in RSIE are (1) radical debridement of vegetations and any infected tissue,¹²⁰ (2) vegetectomy and valve repair in IDUs whenever possible, avoiding artificial material, but if not technically feasible, then tricuspid valve replacement is performed,¹²⁹ and (3) elimination of valve regurgitation.¹³⁰ Surgeries can be divided into those that use prosthetic material and those that use native or autologous tissue (nonprosthetic techniques).¹²⁰

A. Surgical techniques using no prosthetic materials include 2 procedures:

- Vegetectomy: complete removal of vegetations. If significant valve regurgitation remains after vegetectomy, it should be complemented with valve repair.
- Valvectomy: removal of valve leaflets with chordae tendinae. Relapse rates are higher after vegetectomy.¹²⁰ In case, damage extends to be more than 1 leaflet and repair is not possible, valvectomy is recommended. In a series of 53 IDUs, Arbulu et al^{129,130} reported a survival rate of 64% at 22 years after valvectomy, subsequent severe tricuspid regurgitation was well tolerated, especially if pulmonary artery pressure was not elevated. Up to 33% of patients, however, may require subsequent valve implantation, and some may suffer severe right ventricular dysfunction as a complication. Valvectomy is contraindicated in patients with concomitant LSIE and elevated left atrial pressure.¹²⁰

B. Surgical techniques using prosthetic material:

Tricuspid valve replacement is rarely used, mainly due to good results of repair techniques. Valve replacement requires absence of drug abuse during and after surgery. Replacement using a homograft tissue valve is an option after valvectomy. Moreover, tricuspid valve replacement by a cryopreserved mitral homograft is a newly described method providing atrioventricular competence. Finally, implantation of a stentless aortic porcine valve—in an upside-down orientation—in the tricuspid position has been recently reported to be an effective surgical alternative.¹²⁰

CONCLUSION

RSIE remains most common among IDUs. In addition, patients with ICD and central catheters represent a rapidly growing subgroup at increased risk. A number of hypotheses have been

proposed to explain the pathogenesis of RSIE, most important of which are unusual immunological phenomena, direct inoculation, and endothelial damage by the injected drugs. *S. aureus* is the most common pathogen in RSIE. The diagnosis of RSIE requires a high index of suspicion because early diagnosis improves mortality rates and health-related costs, especially in patients with ICDs. RSIE needs to be suspected in every patient presenting with pulmonary manifestations, unremitting fever, and IE risk factors. RSIE has a relatively benign prognosis when compared with LSIE. Vegetation size greater than 2 cm and fungal etiology are the principal factors associated with poor prognosis. Uncomplicated RSIE can be conservatively managed with a short antibiotic course of 2 weeks. Daptomycin has proved to be effective in the management of MRSA RSIE complicated by pulmonary emboli. Whereas most RSIE cases resolve with appropriate antimicrobial treatment with no need for surgical intervention, patients with ICD require prompt percutaneous lead extraction in combination with medical management.

REFERENCES

- Osler W. The Gulstonian Lectures, on malignant endocarditis. *Br Med J*. 1885;1:467–470.
- Hussey HH, Katz S. Infections resulting from narcotic addiction; report of 102 cases. *Am J Med*. 1950;9:186–193.
- Frontera JA, Gradon JD. Right-side endocarditis in injection drug users: review of proposed mechanisms of pathogenesis. *Clin Infect Dis*. 2000;30:374–379.
- Moreillon P, Que YA. Infective endocarditis. *Lancet*. 2004;363:139–149.
- Voigt A, Shalaby A, Saba S. Rising rates of cardiac rhythm management device infections in the United States: 1996 through 2003. *J Am Coll Cardiol*. 2006;48:590–591.
- Uslan DZ, Sohail MR, St Sauver JL, et al. Permanent pacemaker and implantable cardioverter defibrillator infection: a population-based study. *Arch Intern Med*. 2007;167:669–675.
- Cacoub P, Leprince P, Nataf P, et al. Pacemaker infective endocarditis. *Am J Cardiol*. 1998;82:480–484.
- Tsao MM, Katz D. Central venous catheter-induced endocarditis: human correlate of the animal experimental model of endocarditis. *Rev Infect Dis*. 1984;6:783–790.
- Ortiz C, López J, García H, et al. Clinical classification and prognosis of isolated right-sided infective endocarditis. *Medicine (Baltimore)*. 2014;93:e137.
- Knirsch W, Nadal D. Infective endocarditis in congenital heart disease. *Eur J Pediatr*. 2011;170:1111–1127.
- Yuan SM. Right-sided infective endocarditis: recent epidemiologic changes. *Int J Clin Exp Med*. 2014;7:199–218.
- Yameogo NV, Sondo KA, Yameogo AA, et al. Epidemiological and clinical features, ultrasound findings and prognosis of right-sided infective endocarditis in a teaching hospital in Ouagadougou. *Cardiovasc J Afr*. 2013;24:171–173.
- Sande M, Lee B, Mills J, et al. Endocarditis in intravenous drug users. In: Kaye D, ed. *Infective Endocarditis*. 2nd ed. New York: Raven Press; 1992:345–359.
- Cabell CH, Jollis JG, Peterson GE, et al. Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med*. 2002;162:90–94.
- Akinosoglou K, Apostolakis E, Marangos M, et al. Native valve right sided infective endocarditis. *Eur J Intern Med*. 2013;24:510–9.
- Weinstein WL, Bruschi JL. *Infective Endocarditis*. 1st ed. New York, NY: Oxford University Press; 1996.
- Berlin JA, Abrutyn E, Strom BL, et al. Incidence of infective endocarditis in the Delaware Valley, 1988–1990. *Am J Cardiol*. 1995;76:933–936.
- Freed LA, Levy D, Levine RA, et al. Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med*. 1999;341:1–7.
- Michel PL, Acar J. Native cardiac disease predisposing to infective endocarditis. *Eur Heart J*. 1995;16(suppl B):2–6.
- Mathew J, Addai T, Anand A, et al. Clinical features, site of involvement, bacteriologic findings, and outcome of infective endocarditis in intravenous drug users. *Arch Intern Med*. 1995;155:1641–1648.
- Naidoo DP. Right-sided endocarditis in the non-drug addict. *Postgrad Med J*. 1993;69:615–620.
- Revilla A, López J, Villacorta E, et al. Isolated right-sided valvular endocarditis in non-intravenous drug users. *Rev Esp Cardiol*. 2008;61:1253–1259.

23. Lee MR, Chang SA, Choi SH, et al. Clinical features of right-sided infective endocarditis occurring in non-drug users. *J Korean Med Sci*. 2014;29:776–781.
24. Ramadan FB, Beanlands DS, Burwash IG. Isolated pulmonic valve endocarditis in healthy hearts: a case report and review of the literature. *Can J Cardiol*. 2000;16:1282–1288.
25. Pellicelli AM, Pino P, Terranova A, et al. Eustachian valve endocarditis: a rare localization of right side endocarditis. A case report and review of the literature. *Cardiovasc Ultrasound*. 2005;3:30.
26. Wilson LE, Thomas DL, Astemborski J, et al. Prospective study of infective endocarditis among injection drug users. *J Infect Dis*. 2002;185:1761–1766.
27. Dressler FA, Roberts WC. Infective endocarditis in opiate addicts: analysis of 80 cases studied at necropsy. *Am J Cardiol*. 1989;63:1240–1257.
28. Zijlstra F, Fioretti P, Roelandt JR. Echocardiographic demonstration of free wall vegetative endocarditis complicated by a pulmonary embolism in a patient with ventricular septal defect. *Br Heart J*. 1986;55:497–499.
29. Pons-Lladó G, Carreras F, Borrás X, et al. Findings on Doppler echocardiography in asymptomatic intravenous heroin users. *Am J Cardiol*. 1992;69:238–241.
30. Fernandez Guerrero ML, Gonzalez et al. Endocarditis caused by *Staphylococcus aureus*: a reappraisal of the epidemiologic, clinical, and pathologic manifestations with analysis of factors determining outcome. *Medicine (Baltimore)*. 2009;88:1–22.
31. Cannon N, Cobbs C. Infective endocarditis in drug addicts. In: Kaye D, ed. *Infective Endocarditis*. 1st ed. Baltimore: University Park Press; 1976:111–127.
32. Sullam PM, Drake TA, Sande MA. Pathogenesis of endocarditis. *Am J Med*. 1985;78:110–115.
33. Tuazon CU, Sheagren JN. Increased rate of carriage of *Staphylococcus aureus* among narcotic addicts. *J Infect Dis*. 1974;129:725–727.
34. Smit J, Korup E, Schönheyder HC. Infections associated with permanent pacemakers and implanted cardioverter-defibrillator devices. A 10-year regional study in Denmark. *Scand J Infect Dis*. 2010;42:658–664.
35. DiNubile MJ. Abbreviated therapy for right-sided *Staphylococcus aureus* endocarditis in injecting drug users: the time has come? *Eur J Clin Microbiol Infect Dis*. 1994;13:533–534.
36. Abraham J, Mansour C, Veledar E, et al. *Staphylococcus aureus* bacteremia and endocarditis: the Grady Memorial Hospital experience with methicillin-sensitive *S. aureus* and methicillin-resistant *S. aureus* bacteremia. *Am Heart J*. 2004;147:536–539.
37. Banks T, Fletcher R, Ali N. Infective endocarditis in heroin addicts. *Am J Med*. 1973;55:444–451.
38. Boucher HW, Sakoulas G. Perspectives on daptomycin resistance, with emphasis on resistance in *Staphylococcus aureus*. *Clin Infect Dis*. 2007;45:601–608.
39. Carbon C. Experimental endocarditis: a review of its relevance to human endocarditis. *J Antimicrob Chemother*. 1993;31(suppl D):71–85.
40. Klevens RM, Morrison MA, Nadle J, et al; Active Bacterial Core surveillance (ABCs) MRSA Investigators. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA*. 2007;298:1763–1771.
41. Haque NZ, Davis SL, Manierski CL, et al. Infective endocarditis caused by USA300 methicillin-resistant *Staphylococcus aureus* (MRSA). *Int J Antimicrob Agents*. 2007;30:72–77.
42. Townell NJ, Munckhof WJ, Nimmo G, et al. Community-associated methicillin-resistant *Staphylococcus aureus* endocarditis “down under”: case series and literature review. *Scand J Infect Dis*. 2012;44:536–540.
43. Hiramatsu K. Vancomycin resistance in staphylococci. *Drug Resist Updat*. 1998;1:135–150.
44. Howden BP, Davies JK, Johnson PD, et al. Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. *Clin Microbiol Rev*. 2010;23:99–139.
45. Gonzalez-Ruiz A, Beiras-Fernandez A, Lehmkuhl H, et al. Clinical experience with daptomycin in Europe: the first 2.5 years. *J Antimicrob Chemother*. 2011;66:912–919.
46. Hagihara M, Umemura T, Mori T, et al. Daptomycin approved in Japan for the treatment of methicillin-resistant *Staphylococcus aureus*. *Ther Clin Risk Manag*. 2012;8:79–86.
47. Lefort A, Mainardi JL, Seltou-Suty C, et al. *Streptococcus pneumoniae* endocarditis in adults. A multicenter study in France in the era of penicillin resistance (1991–1998). The Pneumococcal Endocarditis Study Group. *Medicine (Baltimore)*. 2000;79:327–337.
48. Shekar R, Rice TW, Zierdt CH, et al. Outbreak of endocarditis caused by *Pseudomonas aeruginosa* serotype O11 among pentazocine and tripeleonnamine abusers in Chicago. *J Infect Dis*. 1985;151:203–8.
49. Bisbe J, Miro JM, Latorre X, et al. Disseminated candidiasis in addicts who use brown heroin: report of 83 cases and review. *Clin Infect Dis*. 1992;15:910–923.
50. Miró JM, Puig de la Bellacasa J, Odds FC, et al. Systemic candidiasis in Spanish heroin addicts: a possible source of infection. *J Infect Dis*. 1987;156:857–858.
51. Kalokhe AS, Roupael N, El Chami MF, et al. *Aspergillus endocarditis*: a review of the literature. *Int J Infect Dis*. 2010;14:e1040–e1047.
52. Kothari A, Pillai BS, Bhan A. Pacing lead endocarditis due to *Aspergillus fumigatus*. *Indian J Med Microbiol*. 2010;28:72–73.
53. Clayton JJ, Baig W, Reynolds GW, et al. Endocarditis caused by propionibacterium species: a report of three cases and a review of clinical features and diagnostic difficulties. *J Med Microbiol*. 2006;55:981–7.
54. Noel W, Hammoudi N, Wegorowska E, et al. Pacemaker endocarditis caused by *Propionibacterium acnes*: a case report. *Heart Lung*. 2012;41:e21–e23.
55. Zedtwitz-Liebenstein K, Gabriel H, Graninger W. Pacemaker endocarditis due to *Propionibacterium acnes*. *Infection*. 2003;31:184–185.
56. Chua AG, Ding J, Schoch PE, et al. Pacemaker-induced endocarditis due to *propionibacterium acnes*. *Clin Infect Dis*. 1998;27:1541–1542.
57. Alexiou C, Langley SM, Stafford H, et al. Surgery for active culture-positive endocarditis: determinants of early and late outcome. *Ann Thorac Surg*. 2000;69:1448–1454.
58. Reisberg BE. Infective endocarditis in the narcotic addict. *Prog Cardiovasc Dis*. 1979;22:193–204.
59. Sheagren J. Endocarditis complicating parenteral drug abuse. *Curr Clin Top Infect Dis*. 1981;2:211–33.
60. Cherubin CE, Sapira JD. The medical complications of drug addiction and the medical assessment of the intravenous drug user: 25 years later. *Ann Intern Med*. 1993;119:1017–1028.
61. Aguado JM, Arjona R, Ugarte P. Septic pulmonary emboli. A rare cause of bilateral pneumothorax in drug abusers. *Chest*. 1990;98:1302–1304.
62. Horstkotte D, Follath F, Gutschik E, et al; Task Force Members on Infective Endocarditis of the European Society of Cardiology; ESC Committee for Practice Guidelines (CPG); Document Reviewers. Guidelines on prevention, diagnosis and treatment of infective endocarditis executive summary; the task force on infective endocarditis of the European society of cardiology. *Eur Heart J*. 2004;25:267–276.
63. Starakis I, Mazokopakis EE. Injecting illicit substances epidemic and infective endocarditis. *Infect Disord Drug Targets*. 2010;10:22–26.
64. Houpiakian P, Raoult D. Blood culture-negative endocarditis in a reference center: etiologic diagnosis of 348 cases. *Medicine (Baltimore)*. 2005;84:162–173.
65. Raoult D, Casalta JP, Richet H, et al. Contribution of systematic serological testing in diagnosis of infective endocarditis. *J Clin Microbiol*. 2005;43:5238–5242.
66. Baddour LM, Epstein AE, Erickson CC, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee; Council on Cardiovascular Disease in Young; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Nursing; Council on Clinical Cardiology; Interdisciplinary Council on Quality of Care; American Heart Association. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation*. 2010;121:458–477.
67. Palepu A, Cheung SS, Montessori V, et al. Factors other than the Duke criteria associated with infective endocarditis among injection drug users. *Clin Invest Med*. 2002;25:118–125.
68. San Román JA, Vilacosta I. Role of transesophageal echocardiography in right-sided endocarditis. *Echocardiography*. 1995;12:669–672.
69. San Román JA, Vilacosta I, López J, et al. Role of transthoracic and transesophageal echocardiography in right-sided endocarditis: one echocardiographic modality does not fit all. *J Am Soc Echocardiogr*. 2012;25:807–814.
70. Ginzton LE, Siegel RJ, Criley JM. Natural history of tricuspid valve endocarditis: a two dimensional echocardiographic study. *Am J Cardiol*. 1982;49:1853–1859.
71. Berger M, Delfin LA, Jelveh M, et al. Two-dimensional echocardiographic findings in right-sided infective endocarditis. *Circulation*. 1980;61:855–861.
72. San Román JA, Vilacosta I, Zamorano JL, et al. Transesophageal echocardiography in right-sided endocarditis. *J Am Coll Cardiol*. 1993;21:1226–1230.
73. Helwig FC. The frequency of anomalous reticula in the right atrium of the human heart “Chiari network”: report of eight cases. *Am J Pathol*. 1932;8:73–80.7.

74. Vilacosta I, San Roman JA, Roca V. Eustachian valve endocarditis. *Br Heart J*. 1990;64:340–341.
75. San Román JA, Vilacosta I, Sarriá C, et al. Eustachian valve endocarditis: Is it worth searching for? *Am Heart J*. 2001;142:1037–1040.
76. Grammes JA, Schulze CM, Al-Bataineh M, et al. Percutaneous pacemaker and implantable cardioverter-defibrillator lead extraction in 100 patients with intracardiac vegetations defined by transesophageal echocardiogram. *J Am Coll Cardiol*. 2010;55:886–894.
77. Vilacosta I, Sarriá C, San Román JA, et al. Usefulness of transesophageal echocardiography for diagnosis of infected transvenous permanent pacemakers. *Circulation*. 1994;89:2684–2687.
78. Victor F, De Place C, Camus C, et al. Pacemaker lead infection: echocardiographic features, management, and outcome. *Heart*. 1999;81:82–87.
79. Xie J, Liu S, Yang J, et al. Inaccuracy of transthoracic echocardiography for the identification of right-sided vegetation in patients with no history of intravenous drug abuse or cardiac device insertion. *J Int Med Res*. 2014;42:837–848.
80. Bruun NE, Habib G, Thuny F, et al. Cardiac imaging in infective endocarditis. *Eur Heart J*. 2014;35:624–632.
81. Naqvi TZ, Rafie R, Ghalichi M. Real-time 3D TEE for the diagnosis of right-sided endocarditis in patients with prosthetic devices. *JACC Cardiovasc Imaging*. 2010;3:325–327.
82. Kestler M, Muñoz P, Rodríguez-Créixems M, et al; Group for the Management of Infectious Endocarditis (GAME). Role of (18)F-FDG PET in patients with infective endocarditis. *J Nucl Med*. 2014;55:1093–1098.
83. Kouijzer IJ, Vos FJ, Janssen MJ, et al. The value of 18F-FDG PET/CT in diagnosing infective endocarditis. *Eur J Nucl Med Mol Imaging*. 2013;40:1102–1107.
84. Hecht SR, Berger M. Right-sided endocarditis in intravenous drug users. Prognostic features in 102 episodes. *Ann Intern Med*. 1992;117:560–566.
85. Martín-Dávila P, Navas E, Fortún J, et al. Analysis of mortality and risk factors associated with native valve endocarditis in drug users: the importance of vegetation size. *Am Heart J*. 2005;150:1099–1106.
86. Bonow RO, Carabello BA, Chatterjee K, et al; 2006 Writing Committee Members; American College of Cardiology/American Heart Association Task Force. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2008;118:e523–e661.
87. Ribera E, Miró JM, Cortés E, et al. Influence of human immunodeficiency virus 1 infection and degree of immunosuppression in the clinical characteristics and outcome of infective endocarditis in intravenous drug users. *Arch Intern Med*. 1998;158:2043–2050.
88. Habib G, Hoen B, Tornos P, et al; ESC Committee for Practice Guidelines. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J*. 2009;30:2369–2413.
89. Crane LR, Levine DP, Zervos MJ, et al. Bacteremia in narcotic addicts at the Detroit medical center. I. microbiology, epidemiology, risk factors, and empiric therapy. *Rev Infect Dis*. 1986;8:364–373.
90. Chan Tompkins NH, Harnicar SJ. Prescribing trends with daptomycin (cubicin) for the treatment of Gram-positive infections. *P T*. 2008;33:282–288.
91. Chambers HF, Miller RT, Newman MD. Right-sided *Staphylococcus aureus* endocarditis in intravenous drug abusers: two-week combination therapy. *Ann Intern Med*. 1988;109:619–624.
92. Korzeniowski O, Sande MA. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts: a prospective study. *Ann Intern Med*. 1982;97:496–503.
93. Falagas ME, Matthaiou DK, Bliziotis IA. Aminoglycosides in combination with a β -lactam for the treatment of bacterial endocarditis: authors' response. *J Antimicrob Chemother*. 2006;57:639–647.
94. Abrams B, Sklaver A, Hoffman T, et al. Single or combination therapy of staphylococcal endocarditis in intravenous drug abusers. *Ann Intern Med*. 1979;90:789–791.
95. Miller MH, Wexler MA, Steigbigel NH. Single and combination antibiotic therapy of *Staphylococcus aureus* experimental endocarditis: emergence of gentamicin-resistant mutants. *Antimicrob Agents Chemother*. 1978;14:336–343.
96. Cosgrove SE, Vigliani GA, Fowler VG Jr, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis*. 2009;48:713–721.
97. Bayer AS, Murray BE. Initial low-dose aminoglycosides in *Staphylococcus aureus* bacteremia: good science, urban legend, or just plain toxic? *Clin Infect Dis*. 2009;48:722–724.
98. Baddour LM, Wilson WR, Bayer AS, et al; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease; Council on Cardiovascular Disease in the Young; Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia; American Heart Association; Infectious Diseases Society of America. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation*. 2005;111:e394–e434.
99. Geraci JE, Wilson WR. Vancomycin therapy for infective endocarditis. *Rev Infect Dis*. 1981;3(suppl):S250–S258.
100. Eliopoulos GM. Antimicrobial agents for treatment of serious infections caused by resistant *Staphylococcus aureus* and enterococci. *Eur J Clin Microbiol Infect Dis*. 2005;24:826–831.
101. Wilson AP, Gaya H. Treatment of endocarditis with teicoplanin: a retrospective analysis of 104 cases. *J Antimicrob Chemother*. 1996;38:507–521.
102. Gentry CA, Rodvold KA, Novak RM, et al. Retrospective evaluation of the therapies for *Staphylococcus aureus* endocarditis. *Pharmacotherapy*. 1997;17:990–997.
103. Charles PG, Ward PB, Johnson PD, et al. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus*. *Clin Infect Dis*. 2004;38:448–451.
104. Moore CL, Osaki-Kiyari P, Haque NZ, et al. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant *Staphylococcus aureus* with a high vancomycin minimum inhibitory concentration: a case-control study. *Clin Infect Dis*. 2012;54:51–58.
105. Fowler VG Jr, Boucher HW, Corey GR, et al; *S. aureus* Endocarditis and Bacteremia Study Group. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355:653–665.
106. McCalla C, Smyth DS, Robinson DA, et al. Microbiological and genotypic analysis of methicillin-resistant *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2008;52:3441–3443.
107. Rehm SJ, Boucher H, Levine D, et al. Daptomycin versus vancomycin plus gentamicin for treatment of bacteraemia and endocarditis due to *Staphylococcus aureus*: subset analysis of patients infected with methicillin-resistant isolates. *J Antimicrob Chemother*. 2008;62:1413–1421.
108. Levine DP, Lamp KC. Daptomycin in the treatment of patients with infective endocarditis: experience from a registry. *Am J Med*. 2007;120(10 suppl 1):S28–S33.
109. Dohmen PM, Guleri A, Capone A, et al. Daptomycin for the treatment of infective endocarditis: results from a European registry. *J Antimicrob Chemother*. 2013;68:936–942.
110. Smith J, Claeys K, Barber K, et al. High-dose daptomycin therapy for staphylococcal endocarditis and when to apply it. *Current Infect Dis Rep*. 2014;16:429.
111. Drees M, Boucher H. New agents for *Staphylococcus aureus* endocarditis. *Curr Opin Infect Dis*. 2006;19:544–550.
112. Souli M, Pontikis K, Chrysosouli Z, et al. Successful treatment of right-sided prosthetic valve endocarditis due to methicillin-resistant teicoplanin-hetero-resistant *Staphylococcus aureus* with linezolid. *Eur J Clin Microbiol Infect Dis*. 2005;24:760–762.
113. Moss R, Munt B. Injection drug use and right sided endocarditis. *Heart*. 2003;89:577–581.
114. DiNubile MJ. Short-course antibiotic therapy for right-sided endocarditis caused by *Staphylococcus aureus* in injection drug users. *Ann Intern Med*. 1994;121:873–876.
115. Torres-Tortosa M, de Cueto M, Vergara A, et al. Prospective evaluation of a two-week course of intravenous antibiotics in intravenous drug addicts with infective endocarditis. Grupo de Estudio de Enfermedades Infecciosas de la Provincia de Cádiz. *Eur J Clin Microbiol Infect Dis*. 1994;13:559–564.
116. Espinosa FJ, Valdés M, Martín-Luengo F, et al. [Right endocarditis caused by *Staphylococcus aureus* in parenteral drug addicts: evaluation of a combined therapeutic scheme for 2 weeks versus conventional treatment]. *Enferm Infecc Microbiol Clin*. 1993;11:235–240.

117. Ribera E, Gómez-Jimenez J, Cortes E, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided *Staphylococcus aureus* endocarditis. A randomized, controlled trial. *Ann Intern Med.* 1996;125:969–974.
118. Musci M, Siniawski H, Pasic M, et al. Surgical treatment of right-sided active infective endocarditis with or without involvement of the left heart: 20-year single center experience. *Eur J Cardiothorac Surg.* 2007;32:118–125.
119. Bayer AS, Bolger AF, Taubert KA, et al. Diagnosis and management of infective endocarditis and its complications. *Circulation.* 1998;98:2936–2948.
120. Akinosoglou K, Apostolakis E, Koutsogiannis N, et al. Right-sided infective endocarditis: surgical management. *Eur J Cardiothorac Surg.* 2012;42:470–479.
121. Okonta KE, Adamu YB. What size of vegetation is an indication for surgery in endocarditis? *Interact Cardiovasc Thorac Surg.* 2012;15:1052–1056.
122. Heldman A. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. *Am J Med.* 1996;1:68.
123. Dworkin R, Sande M, Lee B, et al. Treatment of right-sided *Staphylococcus aureus* endocarditis in intravenous drug users with ciprofloxacin and rifampicin. *Lancet.* 1989;334:1071–1073.
124. Nathani N, Iles P, Elliott TS. Successful treatment of MRSA native valve endocarditis with oral linezolid therapy: a case report. *J Infect.* 2005;51:e213–e215.
125. Wilkoff BL, Love CJ, Byrd CL, et al; Heart Rhythm Society; American Heart Association. Transvenous lead extraction: Heart Rhythm Society expert consensus on facilities, training, indications, and patient management: this document was endorsed by the American Heart Association (AHA). *Heart Rhythm.* 2009;6:1085–1104.
126. Viganego F, O'Donoghue S, Eldadah Z, et al. Effect of early diagnosis and treatment with percutaneous lead extraction on survival in patients with cardiac device infections. *Am J Cardiol.* 2012;109:1466–1471.
127. Chen LY, Huang CH, Kuo SC, et al. High-dose daptomycin and fosfomycin treatment of a patient with endocarditis caused by daptomycin-nonsusceptible *Staphylococcus aureus*: case report. *BMC Infect Dis.* 2011;11:152.
128. Marcos LA, Camins BC. Successful treatment of vancomycin-intermediate *Staphylococcus aureus* pacemaker lead infective endocarditis with telavancin. *Antimicrob Agents Chemother.* 2010;54:5376–5378.
129. Arbulu A, Holmes RJ, Asfaw I. Surgical treatment of intractable right-sided infective endocarditis in drug addicts: 25 years experience. *J Heart Valve Dis.* 1993;2:129–137; discussion 138.
130. Arbulu A, Holmes RJ, Asfaw I. Tricuspid valvectomy without replacement. Twenty years' experience. *J Thorac Cardiovasc Surg.* 1991;102:917–922.