No Right Answer

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Foreword
Information about a real patient is presented in stages (boldface type) to an expert clinician (Dr Adler), who responds to the information, sharing his reasoning with the reader (regular type). A discussion by the authors follows.

Patient presentation: Mr H is a 61-year-old man with a medical history significant for hypertension, hyperlipidemia, and benign prostatic hyperplasia who was admitted to the medical service with a chief complaint of fevers. Eleven years before presentation, the patient underwent a prostate biopsy for a rapidly rising prostate-specific antigen, and there was no evidence for malignancy. The biopsy was complicated by septicemia, which was treated with antibiotics. Four months before admission, the patient presented to the urology clinic with worsening urinary retention, and the decision was made to proceed to transurethral resection of the prostate. A preoperative workup was significant only for a urine culture growing 1000 colonies of enterococcus, and no antimicrobial treatment was given. He underwent a technically successful transurethral resection of the prostate and was discharged home the next day after passing a voiding trial.

Two days after being discharged, the patient had fevers to 102°F and was readmitted to the hospital. He was found to have an Enterococcus faecalis urinary tract infection and was treated with 1 day of intravenous cefepime before being discharged the next day on a 7-day course of amoxicillin–clavulanic acid. On the day after discharge, blood cultures that were drawn on admission grew E faecalis with the same susceptibility pattern cultured from the urine, but there was no alteration in the treatment plan. The patient’s fevers resolved.

One month before admission, the patient presented to an outside emergency department with decreased exercise capacity, pleuritic back pain, and malaise. Computed tomography of the chest with contrast identified a right upper-lobe consolidation (Figure 1), and a 10-day course of levofloxacin was prescribed for presumed community-acquired pneumonia. His fever improved, but his shortness of breath progressed, and he became symptomatic with even minimal exertion. On the day of admission, he developed a fever of 101°F and went to the emergency department for further care.

On presentation to our hospital, the patient’s physical examination revealed a temperature of 101.1°F, heart rate of 140 bpm and regular, blood pressure of 141/74 mm Hg, respiratory rate of 18 breaths per minute, and oxygen saturation of 93% on room air. The neck veins were elevated to 10 cm H2O with prominent a and v waves. The carotid upstrokes and volumes were normal. The lungs were clear to auscultation. The point of maximal impulse was displaced laterally. There was a normal-sounding S1 and a physiologically split S2. A grade II/IV decrescendo diastolic murmur was loudest at the left upper sternal border and could be heard equally well supine and upright. There was no S3. Peripheral pulses were normal. There was trace ankle edema. He denied any history of intravenous drug use.

The ECG showed sinus tachycardia at a rate of 126 bpm, a normal axis, and right atrial enlargement (Figure 2).

Dr Adler: The patient’s history of bacteremia, progressive dyspnea on exertion, fevers, and new heart murmur are highly suggestive of infective endocarditis (IE) with important valvular destruction. His history of sepsis after prostate biopsy and the growth of enterococci in his urine before and after the transurethral resection of his prostate add to the concern for endocarditis. Typical organisms involved in subacute IE are the viridans group streptococci, enterococcus, and coagulase-negative staphylococcus.1 Given the patient’s history of genitourinary tract instrumentation and known enterococcal bacteremia, enterococcus is the most likely culprit organism in this case. A previous case-control study of enterococcal IE showed that the risk of developing enterococcal bacteremia is 3 to 6 times higher with E faecalis than with E faecium bacteremia.2 In addition, this same study estimated that the rate of development of IE after enterococcal bacteremia could be as high as 5.7% even in patients with native valves. Although no optimum length of therapy for enterococcal bacteremia is known, it is our practice to treat with intravenous antibiotics until blood cultures clear before transitioning to oral antibiotics. In general, we would also strongly consider transthoracic and usually transesophageal echocardiography before changing to oral antibiotics.

The patient’s diastolic decrescendo murmur in the left upper sternal border and evidence of right-sided volume overload are consistent with pulmonary insufficiency and suggest...
IE involving the pulmonary valve. The episode of pleuritic back pain with a right upper-lobe consolidation 1 month before admission was likely a septic embolic event, further implicating the right-sided heart valves.

Given the patient’s presentation, with fever and dyspnea, blood cultures should be drawn and broad-spectrum bactericidal intravenous antibiotics started. An echocardiogram should be obtained to confirm our clinical suspicion and to determine the degree of regurgitation, right ventricular dysfunction, and presence and size of vegetations. Given the high suspicion for endocarditis, it would be reasonable to proceed with a step-wise approach with transthoracic and then transesophageal echocardiography. These tests will confirm the diagnosis, determine which valves are involved, and evaluate for an intracardiac abscess or penetrating lesion for potential surgical planning.

**Patient presentation (continued):** Blood cultures were drawn, and the patient was started on cefepime, vancomycin, and levofloxacin. Four of 4 blood cultures grew ampicillin-sensitive enterococcus within 14 hours of being drawn, and the patient was switched to ampicillin and weight-based gentamicin. The susceptibility pattern was identical to the blood and urine cultures drawn 4 months before the present admission.

A transthoracic echocardiogram showed a large mobile echodensity on the pulmonary valve that prolapsed into the right ventricle during systole with associated severe pulmonary regurgitation (Figure 3A and 3B). There was moderate right ventricular dilatation with normal systolic function. The left ventricular ejection fraction was 65%, and there were no other valvular abnormalities. A transesophageal echocardiogram showed a 2.6-cm vegetation on the pulmonary valve, moderate to severe regurgitation, and no patent foramen ovale (Figure 4A and 4B). En bloc 3-dimensional reconstructions of the valve were suggestive of a bicuspid configuration. The tricuspid, mitral, and aortic valves had no vegetations.

**Dr Adler:** I became involved in the case at this point as the cardiology consultant. This was a patient who had a large vegetation, significant regurgitation, easily precipitated dyspnea on exertion, right ventricular dilatation, and a likely septic embolization to his lungs. I felt that the patient was at high risk for adverse events should medical therapy alone be pursued. However, there is little good evidence to guide therapeutic decisions in right-sided endocarditis.

In the Early Surgery Versus Conventional Treatment in Infective Endocarditis (EASE) trial, there was a significant decrease in the composite end point of death and embolic events at 6 weeks in patients with left-sided endocarditis with large vegetations and important valvular destruction who were randomized to early surgical versus conventional treatment (3% versus 23%, respectively). The benefit of early operation was driven primarily by a reduction in systemic embolic events, with no patients in the surgical arm and 21% in the

![Figure 1.](http://circ.ahajournals.org/)

**Figure 1.** Computed tomography scan of the chest with intravenous contrast showing a right upper-lobe consolidation consistent with septic embolization.

![Figure 2.](http://circ.ahajournals.org/)

**Figure 2.** ECG showing sinus tachycardia at a rate of 126 bpm, a normal axis, and right atrial enlargement. This ECG does not meet the criteria for right ventricular hypertrophy.
medical therapy arm having an embolic event within the first 6 weeks. However, as with many other prospective studies of endocarditis management, this trial specifically excluded patients with right-sided endocarditis.

As a result of the patient’s high risk for an adverse outcome with medical therapy alone and his otherwise excellent health, we felt that he would be likely to benefit from pulmonary valve replacement. At this point, coronary angiography should be performed to determine whether there is significant coronary artery disease. If there is, the patient would benefit from concurrent coronary artery bypass grafting to avoid the risks of a repeat sternotomy.

**Patient presentation (continued):** Coronary angiography showed a right-dominant system with no obstructive disease. The patient was taken to the operating room on the fourth hospital day. The patient was cannulated for bypass via a median sternotomy. A transverse incision was made in the pulmonary artery that revealed a large ball-like vegetation on the pulmonic valve. The valve and the vegetation were resected. Pathological evaluation showed a bicuspid valve and soft, tan, lobulated excrescences that were 4.0×0.9 cm in aggregate (Figure 5). A 25-mm bovine pericardial valve was sutured into the pulmonic position, and the pulmonary artery was closed with a patch of autologous pericardium.

The patient tolerated the operation well, and he was discharged on the fifth postoperative day with a plan to complete 6 weeks of gentamicin and ampicillin and 3 months of anticoagulation with warfarin. The patient developed mild acute kidney injury after 4 weeks that resolved with cessation of gentamicin. Ampicillin was stopped 4 days short of 6 weeks because of significant eosinophilia. At his last evaluation, the patient felt nearly back to normal and had full return of his exercise capacity.

**Discussion**

Although the precise incidence of IE is not known, it is estimated that there are 10,000 to 15,000 cases annually in the United States. Of these cases, ≈5% to 10% involve the right-sided heart valves. An even smaller proportion of all cases of IE, ≈1.5 to 2.0%, are isolated to the pulmonic valve. The highest-risk group for right-sided endocarditis has long been recognized as intravenous drug users; however, patients with pre-existing valvular disease, patients with congenital heart disease, and those with intracardiac devices are also at increased risk. The clinical manifestations of right-sided IE are similar to those of left-sided IE, including fever, malaise, and immune complications. Cardiac complications include valvular regurgitation, electric conduction abnormalities, and heart failure. Additionally, right-sided IE may result in septic embolization to the lungs, causing pulmonary infarction and pulmonary hypertension.

Systemic embolization can also be observed in right-sided endocarditis, with intrapulmonary shunting and septal defects being implicated as the causes of the embolization of right-sided IE into the systemic circulation. Therefore, peripheral stigmata of endocarditis, including Roth spots, Janeway lesions, and Osler nodes, may be observed. Cardiac auscultation may reveal a diastolic murmur, usually at the left upper sternal border and sometimes more pronounced in the supine position, signifying pulmonic valve regurgitation.
The mainstay of therapy for IE is antimicrobial therapy, and the choice and length of therapy are greatly dependent on the organisms involved. Bactericidal agents are used when possible, and multiple agents such as a β-lactam and an aminoglycoside are often used in combination to reduce the risk of treatment failure. Typical treatment courses are 2 to 6 weeks of total therapy, and there are no data to suggest that antimicrobial therapy for pulmonary valve IE should deviate from these currently established guidelines.

In addition to antimicrobial treatment, surgical valve replacement is commonly used in IE for patients at high risk of treatment failure. It is clear that patients with hemodynamic compromise, heart failure, or conduction block warrant early surgery, but guidelines have been mixed with regard to other indications for early surgery. The American College of Cardiology and American Heart Association 2006 guidelines recommend early surgery with a Class IIa indication in patients with recurrent emboli and persistent vegetation despite antimicrobial therapy. The European Society of Cardiology 2009 guidelines go further by recommending early surgery for patients with isolated, very large vegetations (defined as >1.5 cm in diameter). A summary of both groups’ recommendations with regard to indications for surgery is given in Table 1. Moreover, the EASE trial demonstrated that the composite end point of all-cause mortality, embolic events, and recurrent infection was significantly reduced by early surgery in patients with left-sided vegetations >1 cm in diameter. The EASE trial required evidence of severe stenosis or regurgitation and excluded patients who presented with moderate to severe heart failure.

The major caveat with the current guidelines and essentially all of the clinical trial data available is that patients with right-sided IE are excluded. Historically, both tricuspid IE and pulmonary valve IE are managed conservatively with antimicrobial therapy, and surgery is not undertaken unless there is indication of severe right-sided heart failure, paravalvular abscess, or ongoing devastating pulmonary embolization. The decision to perform valve replacement surgery on a patient with right-sided IE is also historically a difficult one because of the high prevalence of intravenous drug use in this population and the risk for recurrent infection related to poor treatment compliance, which would be particularly deleterious in the presence of a new prosthetic valve.

Because of the rarity of the disorder, we retrospectively reviewed our experience with pulmonary valve IE from 2000 to 2014 at 2 teaching hospitals in Boston, MA (Brigham and Women’s Hospital and Massachusetts General Hospital). Data on all patients admitted were obtained through the Research Patient Data Registry, a computerized registry that serves as a central data warehouse for all inpatient and outpatient records at Partners HealthCare sites. Approval for the study was granted by the Partners Human Research Committee.

![Figure 5](http://circ.ahajournals.org/)

**Figure 5.** Pathology showing 2 tan lobulated excrescences resected from the pulmonary valve consistent with vegetations.

### Table 1. Summary of Indications for Surgery for IE Based on American College of Cardiology/American Heart Association 2014 Practice Guidelines and European Society of Cardiology 2009 Guidelines

<table>
<thead>
<tr>
<th>Indication</th>
<th>Class of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure/valve function</td>
<td></td>
</tr>
<tr>
<td>Valve dysfunction leading to heart failure</td>
<td>Class I*†</td>
</tr>
<tr>
<td>Severe aortic or mitral regurgitation (no heart failure)</td>
<td>Class IIa†</td>
</tr>
<tr>
<td>Uncontrolled infection</td>
<td></td>
</tr>
<tr>
<td>Highly resistant organisms (fungi)</td>
<td>Class I*†</td>
</tr>
<tr>
<td>Locally advanced infection: perivalvular abscess, heart block, fistula formation</td>
<td>Class I*†</td>
</tr>
<tr>
<td>Persistently positive blood cultures (or fever) after &gt;5–7 d of appropriate antibiotic therapy</td>
<td>Class I*†</td>
</tr>
<tr>
<td>Prevention of embolization</td>
<td></td>
</tr>
<tr>
<td>Aortic or mitral valve vegetation (&gt;10 mm) with ≥1 embolic episode despite appropriate antibiotic therapy</td>
<td>Class I†</td>
</tr>
<tr>
<td>Recurrent emboli and persistent vegetation despite appropriate antibiotic therapy</td>
<td>Class IIA*</td>
</tr>
<tr>
<td>Isolated very large vegetation (&gt;15 mm)</td>
<td>Class IIB†</td>
</tr>
<tr>
<td>Mobile vegetations &gt;10 mm with or without embolization</td>
<td>Class IIB*</td>
</tr>
</tbody>
</table>

IE indicates infective endocarditis.

*Recommendation based on American College of Cardiology/American Heart Association 2014 practice guidelines.

†Recommendation based on European Society of Cardiology 2009 guidelines.
Table 2. Clinical Characteristics of Patients With Isolated Pulmonary Valve Endocarditis at our Institution (n=7)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n</td>
<td>7</td>
</tr>
<tr>
<td>Age, y Mean (range)</td>
<td>40.7 (24–61)</td>
</tr>
<tr>
<td>Congenital heart disease, n</td>
<td>5</td>
</tr>
<tr>
<td>Artificial pulmonary valve, n</td>
<td>3</td>
</tr>
<tr>
<td>History of intravenous drug use, n</td>
<td>1</td>
</tr>
<tr>
<td>Intracardiac device, n</td>
<td>2</td>
</tr>
<tr>
<td>Size of vegetation, cm</td>
<td>1.3 (range, 0.5–2.6)</td>
</tr>
<tr>
<td>Septic pulmonary embolization on presentation, n</td>
<td>3</td>
</tr>
<tr>
<td>Microbiology, n</td>
<td></td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td>3</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus coagulase-negative</td>
<td>1</td>
</tr>
<tr>
<td>Bartonella</td>
<td>1</td>
</tr>
</tbody>
</table>

Treatment and outcomes

| Follow-up, d Mean (range)                  | 1289 (4-3131) |
| Length of antimicrobial therapy, wk Mean   | 6.85 (6–10)   |
| Mortality at 90 d, n                       | 0              |
| Progressive heart failure after treatment, n | 2              |
| Microbial recurrence, n                    | 0              |

1. Three patients had tetralogy of Fallot; 1 patient had a ventricular septal; and 1 patient had a bicuspid pulmonary valve.
2. Both patients had implantable cardioverter-defibrillators.
3. One patient had surgery early, and 3 patients had surgery after completion of antibiotics.

Four of the patients underwent surgery, with 1 patient going to surgery within the first week of diagnosis (the presented case) and 3 going to surgery after the completion of antibiotics. Two patients developed progressive heart failure, and none had a microbiological recurrence. All 7 patients are currently alive.

These clinical characteristics are similar to those documented in a study of 27 patients with isolated pulmonary valve IE by Bindra et al21 from 1986 to 1998. Notably, the majority of patients had predisposing factors, including underlying cardiac disease, intravenous drug use, or intracardiac catheters. One of these patients underwent surgery, and the mortality rate was 15%. In the Bindra et al study, 48% of patients had Staphylococcus aureus IE, which may have driven the increase in mortality rate compared with the 7 cases presented here.

Some retrospective data suggest that there are certain risk factors for increased mortality in right-sided IE. In a review, vegetations >2 cm were associated with a significantly higher risk of mortality (33% versus 1.3%) in patients with tricuspid valve IE.22 It has not been established whether the specific organism affects mortality rate in right-sided IE as it does in left-sided IE, but the type of organism is likely another factor that can be considered when deciding on the timing of surgery.16

Because of the overall lack of data, it remains unclear exactly how to approach the question of surgery in pulmonary valve IE. Using the limited data available for right-sided endocarditis and making inferences based on guidelines established largely for left-sided endocarditis, we propose several indications for the surgical management of right-sided endocarditis (Table 3).

The lack of prospective data on outcomes in these patients is a major obstacle, and although randomized, controlled trials would be helpful, the rarity of the entity will make the conduct of a trial quite difficult. Perhaps more can be learned from the broad analysis of national registry data.

Disclosures

None.

References

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