

# A Multidisciplinary Approach to *Staphylococcus aureus* Triple-Valve Infective Endocarditis With Multi-Organ Involvement

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## Abstract

Multivalvular endocarditis is a rare and potentially fatal complication that can occur in people who inject drugs. Currently, there are few cases that have been studied or reported in literature. A complication of this manifestation that worsens prognosis and treatment is the distribution of septic emboli throughout the body which highlights the dissemination of the infection. There are no specific guidelines on the treatment of multivalvular endocarditis, but its complexity can present challenges in administering medical and surgical treatment. In this case of a 37-year-old man with infective endocarditis of 3 valves, a comprehensive work-up found septic emboli in the lungs, kidneys, ribs, spine, and brain with ophthalmologic involvement that resulted in visual impairment. This case highlights important complications that can occur with septic emboli and management of these issues using a multidisciplinary approach including the treatment of substance use disorder.

## Keywords

triple-valve infective endocarditis, *Staphylococcus aureus*, septic emboli, multivalvular endocarditis, people who inject drugs

## Introduction

Infective endocarditis (IE) is a pathology characterized by inflammation of the endocardium due to infection. *Staphylococci* and *Streptococci* are responsible for approximately 80% of all IE cases.<sup>1</sup> Common bacterial causes of IE include viridans streptococci, *Streptococcus gallolyticus*, *Staphylococcus aureus*, coagulase-negative staphylococci, HACEK organisms (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*), and *Enterococci* (third most common after *Staphylococci* and *Streptococci* species).

Risk factors most frequently associated with the development of IE include cardiac injury, prior cardiac surgery, and poor dental hygiene. Injection drug use (IDU) is responsible for 10% of all IE cases. The incidence rate of IE in people who inject drugs (PWID) is estimated to be 2% to 5%.<sup>2</sup> Most cases of IE are left sided; however, PWID can have tricuspid valve involvement.<sup>3</sup> Approximately 86% of IE cases in PWID are right sided, of which 90% involve the tricuspid valve.<sup>4</sup>

The pathogenesis of IE in PWID is believed to be caused by recurrent valvular damage from intravenous particulates. Endocardial injury is a foundation for platelet aggregation and thrombus formation leading to vegetations. Intravenous

bacteria then colonize the vegetations leading to IE. Patients with IE typically present with fevers, chills, malaise, generalized weakness, and anorexia. Physical examination in IE can widely vary, though findings such as Osler nodes, Janeway lesions, new or changed heart murmurs, arthralgias, or numerous other symptoms of embolic disease can suggest IE. Tachypnea and tachycardia can also be noted on physical examination. A dermatologic examination can be useful in cases of IE due to the possible presence of Janeway lesions and Osler nodes, although they are estimated to be seen in less than 10% of all cases. Furthermore, the use of Duke Criteria as a clinical tool to determine the likelihood of IE can also support the diagnosis.<sup>4</sup> An electrocardiogram along with CBC (complete blood count) with a differential should

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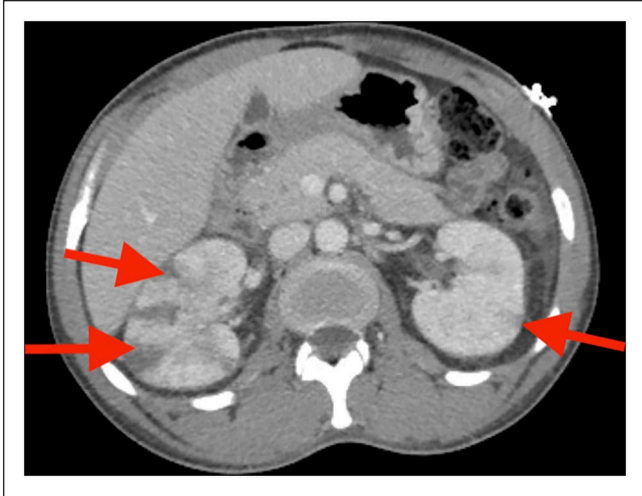
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**Figure 1.** CT abdomen and pelvis with and without IV contrast showing acute bilateral renal infarcts (red arrows) with bilateral pyelonephritis.

be obtained to rule out possible conduction abnormalities or ST changes and leukocytosis, respectively. An X-ray and computed tomography (CT) of the chest can also be obtained to assess for any other complications.<sup>5</sup>

Infective endocarditis can have complications that lead to poor prognosis. Approximately one-third of patients with IE will develop heart failure symptoms. Other complications such as intracardiac abscesses and arrhythmias are less common. Extracardiac complications including septic emboli can lead to pulmonary, neurologic, gastrointestinal, and renal pathologies.<sup>5</sup>

## Case Presentation

A 37-year-old man with a medical history significant for previously treated hepatitis C (HCV) with ledipasvir/sofosbuvir and IDU with methamphetamine presented to the emergency department (ED) with complaints of generalized weakness, neck stiffness, right knee pain, and confusion for 1 week. Vital signs on admission were blood pressure 128/31 mmHg, heart rate 128 beats per minute, respiratory rate 31 breaths per minute, 94% on room air, and temperature of 39.1°C. On physical examination, he was orientated to situation and location, but not to date. The patient had bilateral wrist pain on palpation and neck stiffness upon flexion. “Track marks” were not well seen, but nontender hemorrhagic macular lesions were noticed on his palms and suspected to be early Janeway lesions.

An initial CT of the head did not find acute pathology, though his CT of the abdomen and pelvis was significant for acute bilateral renal infarcts with bilateral pyelonephritis, worrisome for septic emboli (Figure 1). Computed tomography angiography of the chest showed multiple pulmonary nodules with central cavitation suggesting septic pulmonary emboli (Figure 2), along with abscess and osteomyelitis

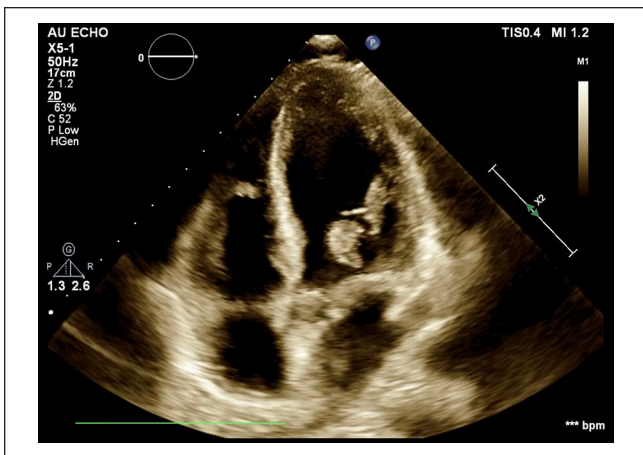


**Figure 2.** CT chest angiography displaying multiple pulmonary nodules with central cavitation suggesting septic pulmonary emboli (red arrows).

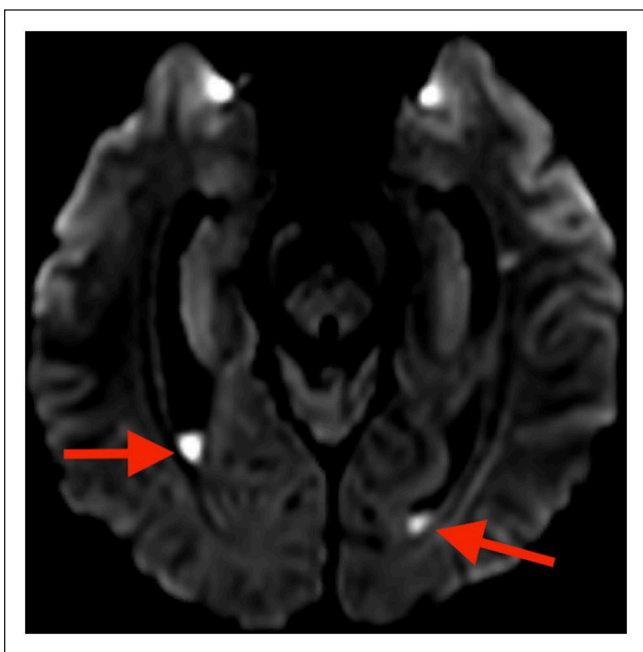
involving the distal right first rib at the costochondral junction extending between the right first and second ribs. Laboratory studies were remarkable for white blood cell (WBC) 47,100/mm<sup>3</sup>, hemoglobin 13.1 g/dL, platelets 143,000/mm<sup>3</sup>, sodium 127 mEq/L, chloride 88 mEq/L, blood urea nitrogen (BUN) 42 mg/dL, creatinine 1.87 mg/dL, glucose 165 mg/dL, aspartate transaminase 203 U/L, alanine transaminase 139 U/L, alkaline phosphatase 233 U/L, total bilirubin 6.6 mg/dL, and lactic acid 5.2 mmol/L, and he screened HIV-negative. Two sets of blood cultures returned positive for methicillin-sensitive *Staphylococcus aureus* (MSSA). He was initially started on empiric antibiotics with vancomycin and cefepime and de-escalated to cefazolin by the hospitalist team.

Infectious disease (ID) service was consulted on hospital day 2 for management of MSSA bacteremia and high clinical suspicion for IE. Infectious disease service recommended to change from cefazolin to nafcillin to target his MSSA bacteremia and for better central nervous system (CNS) penetration given concerns for possible meningitis. He had an acute kidney injury that worsened over the next week. Transthoracic echocardiogram (TTE) revealed masses on 3 heart valves—a moderate sized vegetation (1.51 × 0.87 cm) on the pulmonic valve, a large and mobile vegetation (1.37 × 0.66 cm) on the posterior leaflet of the tricuspid valve, and a large mass (2.5 × 0.89 cm) on the anterior mitral valve (Figure 3). Mild regurgitation was observed in each affected valve. Hepatitis C antibody returned positive with an RNA viral load of 5,677,448 copies IU/mL, supporting an HCV re-infection. The patient was educated to abstain from IDU, avoid sharing needles, and follow-up with gastroenterology for outpatient treatment of HCV.

A magnetic resonance imaging (MRI) of the brain without IV contrast showed multiple acute infarctions compatible with septic emboli, as well as restriction of fluid diffusion in the occipital horns of lateral ventricles compatible with ventriculitis (Figure 4). Magnetic resonance imaging of the cervical spine without IV contrast also revealed discitis/osteomyelitis at C6-C7 level with a prevertebral fluid collection at C1-C4 concerning for epidural abscess (Figure 5). A

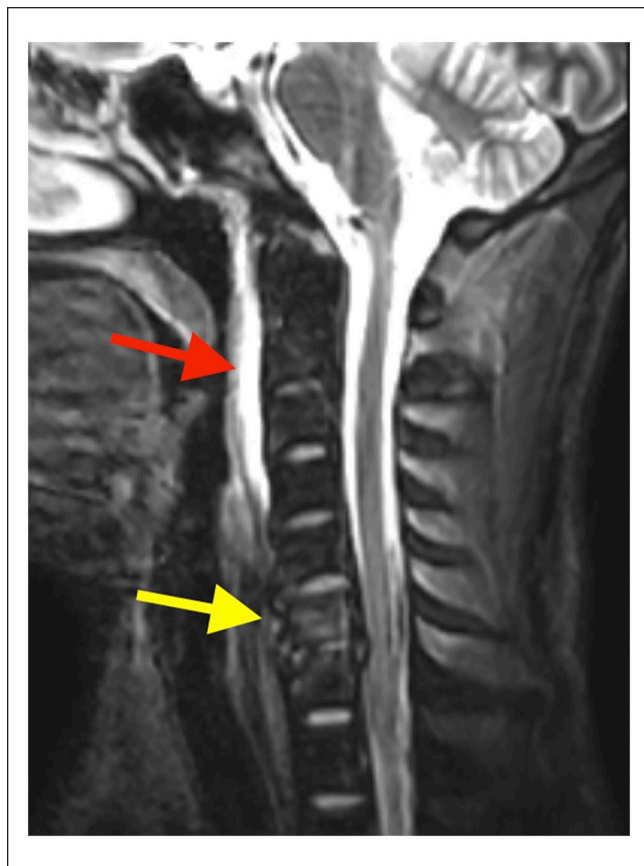


**Figure 3.** TTE showing vegetations on pulmonic, mitral, and tricuspid valves.



**Figure 4.** MRI brain without IV contrast, using DWI (diffusion-weighted imaging) sequence, highlighting multiple acute infarctions compatible with septic emboli (red arrows).

lumbar puncture (LP) was later performed; cerebrospinal fluid (CSF) analysis revealed a negative gram stain. The cell count was 1,010 WBC, 44 red blood cell (RBC), with 98 neutrophils, and an opening pressure of 15 cm H<sub>2</sub>O. Cerebrospinal fluid protein was elevated at 86 mg/dL, with a normal glucose of 56 mg/dL. Infectious disease service also recommended to obtain a transesophageal echocardiogram (TEE) for better valve visualization and to exclude perivalvular abscess. Given the findings of his head MRI, both neurology and neurosurgery services were consulted, and advised against acute intervention due to the patient’s active MSSA bacteremia. Cardiothoracic surgery (CTS) was also consulted given his



**Figure 5.** MRI cervical spine without IV contrast, using STIR (Short-TI inversion recovery) sequence, revealing discitis/osteomyelitis at C6-C7 level (yellow arrow) with a prevertebral fluid collection at C1-C4 (red arrow) concerning for epidural abscess.

multivalvular endocarditis and suggested medical management with prolonged antimicrobial therapy. From a CTS perspective, the patient would not be a surgical candidate until he had complete resolution of all foci of his MSSA infection and complications from his septic emboli.

As his cognition improved, the patient reported decreased vision in his right eye. Ophthalmology was consulted on hospital day 3 and the patient was diagnosed with endogenous endophthalmitis of the right eye and chorioretinitis of the left eye. Vitreous tap and injection with intravitreal vancomycin and ceftazidime were performed in his right eye; vitreous samples were sent for bacterial and fungal cultures with no subsequent growth. The patient’s vision improved over the next 14 days after administration of vancomycin eye drops along with systemic nafcillin therapy.

Repeat blood cultures were obtained until clearance of his bacteremia on hospital day 11. Infectious disease service recommended to complete a 6-week course of nafcillin to address his MSSA IE. On hospital day 15, a CT chest without IV contrast was ordered to reassess the patient’s rib osteomyelitis. Computed tomography imaging confirmed new cavitary pulmonary nodules consistent with septic emboli and



progression of erosive changes involving the medial right first rib. On hospital day 17, CTS was reconsulted for surgical evaluation of his rib osteomyelitis and underwent debridement of his right first and second ribs. On hospital day 24, the patient was evaluated by neuroradiology and had a cerebral angiogram performed, which showed no evidence of mycotic aneurysm or vascular malformations.

He completed a 4-week course of nafcillin on hospital day 35 and developed intolerable infusion reactions with excruciating burning pain. The patient refused nafcillin but consented to changing antibiotics. Central nervous system penetration was deemed less important after completing 4 weeks of therapy, so he was switched to cefazolin for 2 additional weeks.

The patient was discharged home on hospital day 51 after 6 weeks of IV antibiotics from negative blood cultures. He was transitioned to oral cephalexin 1 g twice daily for an additional 4 weeks given his disseminated MSSA infection and presence of cervical osteomyelitis. He was seen by specialists in addiction medicine both during his hospitalization and as an outpatient. The patient attended outpatient behavioral therapy and counseling sessions at his local mental health facility. On follow-up appointments with ID, CTS, cardiology, and gastroenterology, he reported abstinence from further drug use, resolution of his generalized weakness and pain, as well as vision improvement. Cardiothoracic surgery and cardiology repeated a TTE in 3 months to assess his vegetations and to plan for heart valve repair while gastroenterology prepared to initiate HCV treatment.

Unfortunately, the patient relapsed in his methamphetamine use after 4½ months post discharge. He was readmitted with *Streptococcus mitis* bacteremia, septic shock, acute respiratory distress syndrome, liver failure, and severe thrombocytopenia. Repeat TTE showed multiple new large vegetations on the anterior, septal, and posterior leaflets of the tricuspid valve, large vegetation on the aortic valve, and an anterior mitral valve leaflet perforation with a large vegetation. Cardiothoracic surgery concluded his surgical risk for mortality was prohibitive. On hospital day 8, his family elected to transition to comfort care measures and the patient passed away peacefully.

## Discussion

Our patient was found to have multivalvular endocarditis involving the tricuspid, pulmonic, and mitral valves secondary to MSSA. Published literature on multivalvular endocarditis is limited, with only a few cases.

Multivalvular endocarditis is an uncommon form of IE, comprising 12% to 30% of cases.<sup>6</sup> Current evidence and guidelines focus more on immediate medical and cardiac surgical interventions, with less on the management of extensive septic emboli. In addition, not as much emphasis has been placed on behavioral interventions that may help reduce further high-risk activities and re-infection. These limitations will only become more apparent as incidence increases,

with the cases of IE rising from 478,000 in 1990 to 1,090,530 in 2019.<sup>7</sup> On a PubMed search of the word “multivalvular endocarditis,” 57 publications were found with the earliest in 2013. One retrospective analysis found that patients with multivalvular endocarditis had a higher incidence of heart failure (42.7% vs 52.9%,  $P < .001$ ), surgical necessity (67.7% vs 85.1%,  $P < .001$ ), and in-hospital mortality (26.9% vs 34.3%,  $P < .001$ ) when compared with patients with single-valve IE.<sup>6</sup> Our patient did require surgical debridement for osteomyelitis and abscess involving his first and second ribs but was otherwise medically managed for his other infectious sequelae. He clinically improved without life-threatening complications and was discharged after completing his 6-week antibiotic treatment.

One unique finding in this case was endogenous endophthalmitis in the right eye and chorioretinitis in the left eye. One previous retrospective case review in 1986 of 72 cases of metastatic endophthalmitis found that only 10 cases were secondary to IE.<sup>8</sup> Of these cases, the majority were found to have endophthalmitis in both eyes. In another study in 2015 analyzing risk factors of patients with *Staphylococcus aureus* bacteremia (SAB) ocular infections, IE was found to be present in patients with SAB ocular infections compared with patients with SAB without ocular involvement (18% vs 2%;  $P < .001$ ).<sup>9</sup> When our patient experienced loss of vision in the right eye, it was recommended by ophthalmology to switch systemic antibiotic treatment from nafcillin to cefazolin for better vitreous penetration. The decision was made to prioritize CNS penetration given his MRI findings of multiple brain infarcts and cerebral septic emboli and he was continued on nafcillin. He received additional therapy with intravitreal vancomycin and ceftazidime injections and vancomycin eye drops for 14 days. Furthermore, combination MSSA therapy was deferred given increased risk of adverse events and lack of clinical support; daptomycin and vancomycin are reserved for highly beta-lactam allergic patients and have poorer outcomes in treating MSSA bacteremia compared with beta-lactam agents.<sup>10,11</sup>

Due to the burden of disease, a multidisciplinary approach was needed for this care with surgical specialties, neurology, ophthalmology, and addiction medicine. Although the patient completed antibiotic therapy for 10 total weeks, the vegetations on his valves still posed a risk for embolism. Cardiothoracic surgery was consulted but deemed that the operation was risky in the acute setting given his multiple comorbidities and extensive disseminated disease. People who inject drug with IE tend to be younger with lower surgical risk; however, an important concern in surgical treatment is the likelihood of IE recurrence due to relapse of substance use.<sup>12</sup> Due to this population's higher incidence of smoking, alcoholism, and HIV, there is a higher probability of acute liver failure during surgery.<sup>12</sup> The American Association for Thoracic Surgery released question-based guidelines in 2016 for how to approach surgical management of IE.<sup>12</sup> Factors such as severe heart failure, severe valve dysfunction, systemic embolization, and sepsis resistant to antibiotic

treatment for 5 to 7 days can influence surgical decisions. This patient initially responded well to medical management with intravenous and oral antibiotics for 10 weeks. Unfortunately, he relapsed in his sobriety 4½ months later and was unable to receive his heart valve surgery.

Maintaining sobriety in PWID with IE is also imperative to prevent worsening of prognosis and relapse of infection. One retrospective study compared the 24-month survival in patients with IE due to IDU who received comprehensive addiction treatment (psychosocial consultation and medication management) with patients who only received partial addiction treatment. It was discovered that all active drug users who obtained comprehensive addiction treatment (n = 20) survived past 24 months.<sup>13</sup> On the other hand, out of the 28 active drug users who received little to no treatment for addiction, 7 did not survive.<sup>13</sup> The American Heart Association sponsored a statement emphasizing the importance of managing substance abuse disorder in PWID with IE, highlighting inpatient and outpatient management strategies as well as linkage to care.<sup>14</sup> Barriers to treatment for substance use disorder have been extensively studied and factors such as lack of specially trained personnel and treatment facilities are a common obstacle.<sup>14,15</sup> Medical providers and institutions should be aware of the benefits of more comprehensive care in managing IE in PWID and take steps to improve utilization and access in substance use disorder treatment.

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### Ethics Approval

Our institution does not require ethical approval for reporting individual cases.

### Informed Consent

Verbal and written informed consent was obtained from the patient for their anonymized information to be published.

### Prior Presentation of Abstract

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