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Case Study

Unique Considerations in the Management of Early Sepsis in Orthotopic Heart Transplant Recipients: A Case Study

Schantz O and Mukherji J*

Loyola University Medical Center, Maywood, IL, USA

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1. Abstract

Orthotopic heart transplant (OHT) recipients are immune-compromised patients and are at a significantly increased risk for developing infections.

Sepsis is life-threatening, and without early detection and treatment it can lead to a dysregulated systemic inflammatory response with acute organ dysfunction. However, the clinical profile of OHT recipients with sepsis is different as these patients tend to have less fever and leukocytosis. Their presentation may not provoke clinical suspicion of sepsis as they may have diminished symp-toms and attenuated clinical and radiologic findings.

The management of sepsis in these patients are similar to non-transplanted patients. It relies main-ly on early recognition and treatment, including appropriate administration of antibiotics, resus-citation with intravenous fluids, and vasoactive drugs. The infusion of fluid however needs to be closely monitored because elevated filling pressures including central venous pressure levels can reflect fluid overload, right ventricular dysfunction and be a precursor to cardiogenic shock.

Other aspects, which need attention, include managing immunosuppressive therapies in the presence of overt or suspected sepsis. Often dose reduction or removal of immunosuppressive medications is done arbitrarily, as there are no guidelines endorsed to modify the host immunological response. Evidence also points to reduced allograft function and patient survival in the presence of infections. Given the challenges in immune-compromised patients it is likely that early sepsis in OHT patients will have worse outcomes than non-transplanted septic patients.

2. Introduction

Sepsis in OHT recipients with coexisting cardiac dysfunction is a devastating condition carrying as high as a 90% mortality rate [1]. The immediate post-operative period after OHT presents a particularly vulnerable period during which multiple competing physiologic insults including the effects of cardiopulmonary bypass, cardiac dysfunction due to cold ischemia, and profound immunosuppression cripple the physiologic reserves critical to overcoming sepsis.

Treating early sepsis after OHT surgery presents a host of diagnostic and management challenges which need to be addressed on an individual basis. For example, the severely neutropenic patient following antithymocyte globulin therapy (ATG) will have a defective innate immune response making the individ-ual vulnerable to many conventional and opportunistic pathogens.

OHT recipients, like other solid organ transplant (SOT) patients, lack adaptive immunity, making them susceptible to pathogens that can only be countered by an effective cellular immune response. Allograft rejection in the setting of infection is also a confounding diagnostic factor. Often, it is difficult to make an accurate and early diagnosis of sepsis as signs of inflammation may be trivial in the immune-suppressed state. Covering these patients with empiric antimicrobial agents is often lifesaving but selection of appropriate therapy in an era of progressive antibiotic resistance can add to the difficulty.

Current treatment strategies developed in non-cardiothoracic surgery patients, especially related to liberal crystalloid administration, can prove detrimental in the setting of preexisting low cardiac output heart failure. We present a case of fulminant sep-

***Corresponding Author (s):** *Jayanta Mukherji, Loyola University Medical Center, Maywood, IL, USA, E-mail: jmukher@lumc.edu; oliver.schantz@lumc.edu; Michelle.busse@luhs.org*

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sis after cardiac transplantation and review the unique considerations in this patient population.

3. Case Study

A 62-year-old male with long-standing heart failure due to ischemic cardiomyopathy underwent orthotopic heart transplantation. His preoperative workup revealed a severely reduced ejection fraction (EF) of 20%, left ventricular enlargement, and global hypokinesis.

His medical conditions included paroxysmal atrial fibrillation, type 2 diabetes mellitus, and chronic kidney disease.

In the months prior to his transplantation, he had been hospitalized for methicillin-susceptible Staphylococcus aureus (MSSA) bacteremia and was maintained on chronic suppressive oral doxycycline. Immediate preoperative chemistries were notable for a degree of acute kidney injury (creatinine 2.37 mg/dl) and hepatic injury (AST 335 IU/L, ALT 481 IU/L) thought to be due to de-compensated heart failure.

He underwent an uneventful orthotopic heart transplantation with intra-operative trans-esophageal echocardiogram demonstrating good allograft function (EF 65%, normal right and left ventricular function).

In the intensive care unit (ICU) his underlying condition began to deteriorate after 48 hours of initial stability. He needed multiple inotrope and pressors for circulatory support. Dobutamine (3-5 mcg/kg/min), epinephrine (0.08- 0.12 mcg/kg/min), and norepinephrine (0.06-0.12 mcg/kg/min) infusions were titrated with pulmonary artery catheter monitoring to stabilize his cardiac index (CI) above 2.0 and mean arterial pressure (MAP) at or greater than 65 mmHg. He remained on mechanical ventilator support with stable oxygenation and gas exchange.

Immunosuppressants (methylprednisone, mycophenolate mofetil and tacrolimus) and immunoprophylactic drugs were used according to protocol.

On post-operative day 3 chest roentgenography revealed worsening right lower lobe pulmonary infiltrates. Findings of persistently elevated white blood cell count (24,000/ml) raised concern for developing pulmonary infection. Bronchoalveolar lavage (BAL), blood, and urine cultures were sent and he was started on iv van-comycin, cefepime, and metronidazole.

Despite antibiotic therapy his pulmonary function, including oxygenation, worsened placing increasing strain on his right ventricle. By post-operative day 4 he was in right ventricle (RV) failure with a central venous pressure (CVP) exceeding 25 mmHg and severely hypokinetic and dilated RV on bedside TTE. In-haled epoprostenol, used as a pulmonary vasodilator, along with escalation of epinephrine infusion (greater than 0.2 mcg/kg/min) did not provide benefit. His renal function declined precipitous-ly culminating in an uric renal failure necessitating continuous venovenous hemofiltration (CVVH) and fluid removal of 75 to 100ml/hr as tolerated. Despite IV fluid restriction and fluid removal with CVVHD, his cardiogenic shock state persisted, manifesting signs of multi-organ failure.

Hepatic failure with elevated transaminases (AST 5287, ALT 2021, INR > 2, total bilirubin > 5) was treated with vitamin K and FFP transfusions. Hypoglycemia, unrelated to insulin use, was treated with 10% dextrose infusion.

Both BAL and several blood cultures grew gram-negative rods with eventual speciation of Klebsiella pneumoniae. He was already on broad spectrum antibiotic coverage and his central line and hemodialysis catheter insertion sites were changed. His overwhelming infection resulted in significant leukopenia (WBC < 500/ml) on the 5^{th} post-operative day at which time immunosuppressive medications were held. Blood lactate progressively trended from 2 mg/dl up to 10 mg/dl as further evidence of his combined septic and cardiogenic shock.

The patient was returned to the operating room for placement of a venoarterial extracorporeal membrane oxygenation (VA-EC-MO). No heparin was needed as he remained severely coagulo-pathic with spontaneous bleeding from multiple sites. His ongoing bleeding and anemia did not resolve despite multiple massive blood product transfusions. After discussion with his family, care was electively withdrawn on post-operative day 9.

4. Discussion

Sepsis is an insidious clinical entity resulting in significant morbidity and mortality. Sepsis has recently been re-characterized as "life-threatening organ dysfunction caused by a dysregulated host response to infection" by the Third International Consensus Definitions for Sepsis and Septic Shock [1, 2]. Despite increased recognition and efforts to improve clinical outcomes, mortality is still reported to be as high as 25-30% or 40-50% in septic shock [3] even in the absence of heart failure. Pre-existing organ dysfunction has been shown to be a significant risk factor for early death in patients with septic shock [4]. Patients presenting for heart transplant often have preexisting renal, hepatic, pulmonary, and metabolic dysfunction which predispose them to further complications during the post-operative period. Given the central role of the cardiopulmonary system in the physiologic response to sepsis, characterized by a high cardiac output (CO) and increased ventilatory demand, patients who develop sepsis after heart transplantation are often unable to meet systemic demand and quickly manifest signs and symptoms of septic shock and cardiopulmonary failure.

Recognition of sepsis after heart transplantation can be confounded by preexisting hemodynamic disturbance, altered immune responses, and coexisting organ dysfunction. The systemic inflammatory response syndrome (SIRS) has been one of the most widely used screening criteria for detecting impending sep-sis. Two or more disturbances in thermal regulation (>38 or < 36 deg C), heart rate (> 90 BPM), respiratory function (RR > 20 or PaCO2 < 32), and abnormal WBC (> 12,000 or < 4,000 or > 10% band forms) are considered indicative of a significant inflammatory response and developing sepsis. Due to the effects of immunosuppressants, heart transplant recipients may not manifest with fever or leukocytosis until overwhelming infection is already established. In a series of immunosuppressed renal trans-plant recipients, one in six patients failed to manifest more than one SIRS criteria in the context of severe sepsis [5]. Additionally, the transplanted heart is autonomically isolated and maintenance of an intrinsic rate greater than 90 BPM is often desired. Recognition of impending sepsis in these patients requires a high degree of clinical suspicion and close attention to subtle changes in multiple physiologic parameters without reliance on the wide perturbations demonstrated in non-transplant patients.

Lactic acidosis is a widely documented finding in septic shock and indicator of cellular dysfunction [2]. Recent publications have called into question the pathophysiologic significance of lactate but its role as a biomarker remain sound [6]. Despite its clear association with sepsis, elevated plasma lactate can be seen with other clinical conditions including hepatic dysfunction and cardiogenic shock, both commonly encountered in heart trans-plant recipients. Elevated lactate as an indicator of tissue hypo-perfusion is often found in severe decompensated cardiogenic shock associated with depressed cardiac output. Interpretation of lactate levels can be difficult during low CO. Jha and Hittalmani have noted a paradoxical improvement in CO with worsening lactic acidosis may herald developing sepsis in these patients [1]. Nevertheless, plasma lactate remains a useful prognostic indica-tor and marker of recovery [2].

Routine imaging and culture data help to identify infection and tailor therapy but have unique caveats in transplant recipients. Imaging studies often provide evidence of developing infection but may be confounded by other clinical entities and are reliant on an intact inflammatory response to manifest demonstrable roentgenographic findings. Bafi et al. noted decreased findings on imaging studies as a common issue in transplant recipients [7]. Infiltrates on chest roentgenography can represent infection but are also found with pulmonary edema, ARDS, tacrolimus-pneumonitis, and aspiration. High resolution computerized to-mography can be especially useful to delineate between infectious vs. noninfectious conditions and guide therapy [7]. Routine cultures help to narrow antibiotic choice but can take days to provide actionable results and may not identify atypical organisms. Additionally, pre-transplant, patients have often received broad-spectrum antibiotics and have a higher incidence of culture negative sepsis [1]. Due to potential issues with each test, identification of an infectious source in transplant recipients is often dependent on multiple imaging modalities and microbiologic studies.

Appropriate antibiotic therapy remains the single most important modifiable factor determining patient outcome. Early studies have demonstrated a 12% increase in mortality for each hour of delay [8]. Consideration of pathogenic organisms must take into account the pre-transplant condition of the recipient, knowledge of the donor, and hospital course [7]. Studies in transplant recipients have demonstrated a wide array of culpable organisms involved in post-transplant bacteremia and sepsis [9,10]. Offending organisms range from typical gram positive (Staph, Strep, and Enterococcus spp) and gram negative (E. coli, Klebsiella spp, Serratia spp) infections to uncommon infections involving fungi (candida, pneumocystis) and systemic viral infections (CMV, HSV) [9,10,1]. Initiation of broad-spectrum antibiotic therapy must factor in the wide range of possible organisms responsible for sepsis in SOT recipients. Reciprocally, antibiotic therapy must be narrowed as soon as the offending organism and its sensitivities are identified to avoid potential drug interactions with immunosuppressive medications. Tacrolimus has been associated with significant nephrotoxicity which can be augmented with concomitant antibiotic therapy. Aminoglycosides, rifampin, vancomycin, fluconazole, and macrolides have clinically significant interactions with tacrolimus that must be taken into consideration [11].

Currently there is no consensus on the management of immunosuppressive therapies during sepsis. In a retrospective study of 190 heart transplants with postoperative sepsis and interval suspension of immunosuppressive therapy, only one case of acute rejection was identified suggesting the relative safety of withholding immunosuppression during episodes of infection [12]. On the other hand, others have demonstrated increased mortality and graft failure in renal transplant recipients after withdrawal of immunosuppression [7]. Despite conflicting evidence, most authors recommend at least a reduction in the intensity of immunosuppressive therapy during periods of sepsis [7]. Alternatively, glucocorticoids remain an attractive option in the management of sepsis as well as preventing acute rejection in this context. There is a risk for opportunistic infections, regardless of transplant time, during therapy for allograft rejection with periods of excessive immunosuppression [14].

Management of hemodynamics and resuscitation in sepsis has

been extensively studied. Proponents of early goal directed therapy (EGDT) have led to the prevailing practice of administering multiple liters of crystalloid to patients with septic shock despite uncertainties into the specific beneficial endpoints of EGDT [13]. Excessive fluid administration can result in increased endothelial permeability, tissue edema, and organ (including graft) dysfunction. Using a fluid challenge to assess the hemodynamic state after each intervention helps rationalize the fluid administration. Unfortunately, CVP is not helpful in predicting the hemodynamic response to a fluid challenge. Elevated CVP can produce microcirculatory blood flow impairment and exacerbate acute kidney injury [15].

After heart and lung transplantation, protocolized fluid administration has been noted to be particularly harmful [1]. Excessive fluid administration in the setting of cardiac dysfunction can promote pulmonary edema, right ventricular strain, liver congestion, and exacerbation of cardiac edema leading to further reductions in systolic and diastolic performance [1]. Elevations in CVP in the setting of low cardiac output can further compromise perfusion pressure, oxygen delivery, and consequently organ function. Dynamic indices of fluid responsiveness, such as pulse pressure variation, have been suggested to be of value in limiting the negative consequences of "over-resuscitation" while optimizing cardiac performance [7]. Conversely, maintenance of mean arterial pressure (MAP) has been emphasized to promote perfusion to vital organs and reduce organ failure, especially in transplanted organs [7]. Emphasis on inotropic support and vasopressors has thus been given greater consideration in heart transplant recipients than in other populations [1]. Transplanted organs lack auto-regulatory mechanisms to respond to periods of altered hemodynamics. The combined effects of depressed SVR (diastolic pressure) and propensity for fluid loading during sepsis both result in unfavorable changes to coronary perfusion pressure (aortic diastolic pressure minus LVEDP). Reductions in perfusion pressure and consequently oxygen delivery can rapidly propagate circulatory collapse. This highlights the importance of maintaining adequate systemic blood pressure while optimizing the administration crystalloid. In this sense, echocardiographic evaluation is invaluable to guide clinical decision-making.

5. Summary

The management of sepsis after heart transplantation requires consideration of the unique physiology encountered during the post-transplant period. Attenuated inflammatory responses can mask clinical findings making diagnosis difficult. Heightened awareness to subtle changes in physiologic state are required to identify early sepsis. Early identification is critical to starting appropriate antibiotics before multi-organ failure ensues. Immunosuppressive medications predispose to infection and temporary reduction during sepsis is considered prudent. Due to pre-existing cardiac dysfunction, care must be taken to optimize hemodynamic parameters while avoiding detrimental effects on the heart. Although antibiotic therapy was instituted early, our case demonstrates the precarious situation faced by the heart transplant recipient immediately after transplantation.

Key points on early sepsis in OHT recipients
Immunosuppressive drug regimens that are used to prevent allograft rejection predispose OHT recipients to an increased incidence and spectrum of infections
Bloodstream infections (BSIs) remain a major cause of mortality after transplantation
Infection can lead to a dysregulated systemic inflammatory response with acute organ dysfunction (severe sepsis) and hypotension that is refractory to fluid resuscitation (septic shock)
Increased awareness and early effective management of patients with severe sepsis have improved
The mortality remains higher than 40% to 50% when shock is present (7)
Current management relies on early recognition and treatment, including appropriate admin-istration of antibiotics with source control measures, as well as resuscitation with intravenous fluids and vasoactive drugs

Risk factors for developing infections in OHT recipients
Preoperative factors
Evidence of decompensated heart failure with preexisting hepatic and or renal dysfunction
Advanced age, poor nutritional status,
Receiving treatment for underlying infection such as pneumonia, urinary tract infection at the time of undergoing transplant or prior colonization with antimicrobial-resistant pathogens.
Donor-derived infections (antibiotics may be started empirically if infection in donor suspected while awaiting donor cultures)
Intraoperative factors
Intraoperative complications, bleeding or prolonged procedure
Postoperative factors
Immunosuppressive drugs
Central lines, hemodialysis catheters, Infected tract from drivelines in ventricular assisted devices, infected pacemaker wires not removed.
Prolonged intubation, aspiration
Allograft (cardiac) dysfunction
Viral coinfection?

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