Septic Shock: A Race against Time

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Septic shock is a life threatening condition that is not always responsive to proper antibiotic therapy and vasopressors, thereby leading to the rapid decline and death of the patient. We report a case of a 28-year-old female admitted to the intensive care unit (ICU) with group A streptococcal (GAS) community acquired pneumonia (CAP). Within hours of her admission she developed severe septic shock with severe global myocardial dysfunction. Profound septic and cardiogenic shock did not respond to high dose vasopressors, and as a last resort and desperate measure to keep the patient alive, extracorporeal support was initiated with veno-arterial extracorporeal membrane oxygenation (VA-ECMO).

PATIENT DESCRIPTION

A 28-year-old female arrived to the emergency department with complaints of severe weakness and general malaise over the past few days. The patient also complained of cough with purulent sputum that turned rust colored during those days. On arrival, the patient was tachypneic and hypoxic with peripheral hypoperfusion. Measured blood pressure was 100/60 mm/Hg. A chest X-ray was performed, which showed large opacities in the middle and upper lobes on the right lung [Figure 1]. The clinical and radiologic finding supported a diagnosis of right community acquired pneumonia (CAP). Antibiotic therapy with third generation cephalosporin was initiated, and the patient was admitted to the ICU for further medical care due to the severe clinical presentation with impending septic shock.

At the time of ICU admission, the patient's sequential organ failure assessment (SOFA) score was 9 (score range 0 and > 14 points) and APACHE II index score of 16 (score range between 0 and > 34). The vital signs of the patient were temperature of 39°C, blood pressure 95/50 mm/Hg, sinus rhythm of 130, and respiratory rate of 31 with oxygen saturation of 93% on oxygen reservoir mask at 15 liters/min O_2 support. Due to respiratory failure, the patient required immediate intubation. The patient was ventilated with a positive end-expiratory pressure (PEEP) of 8 cmH_2O, driving pressure of 15 cmH_2O, and a fraction of inspired oxygen (FiO_2) of 40%. However, the patient rapidly deteriorated and required PEEP of 13 cmH_2O, driving pressure of 18 cmH_2O, and FiO_2 60%. The patient's blood gas analysis demonstrated a severe metabolic acidosis with lactate levels of 6 mmol/L (normal range 0.5–1.8 mg/dl) and pH of 7.12. Sputum culture stain and direct microscopy examination demonstrated gram positive diplococci. Blood cultures were pending. The patient received empiric therapy according to the infectious disease specialist with ceftriaxone 2 grams once a day, azithromycin 500 mg once a day, vancomycin 1 gram twice a day (antibiotic cover for possible resistant pneumococcal and staphylococcal infections), and oseltamivir 75 mg twice a day. Viral respiratory polymerase chain reaction panel was negative for H1N1, Influenza A and B. The oseltamivir was discontinued.

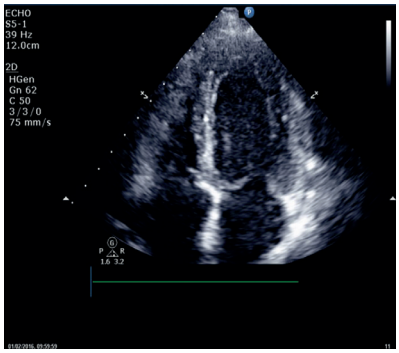
Within the next few hours the patient's condition deteriorated requiring FiO_2 of 80–100% with increasing driving pressures. Therapy with inhaled nitric oxide (NO) at a dose of 10 ppm was added. Due to increasing hemodynamic instability, advanced hemodynamic monitoring with pulse contour cardiac output analysis (PiCCO) was initiated. Initial measurements demonstrated near normal cardiac output with cardiac index (CI) of 3.5 $L/min/m^2$ (normal range at rest is 2.6–4.2 $L/min/m^2$). After initial resuscitation with fluids and vasopressors, patient's condition stabilized and after implementing recruitment maneuvers with lung protective ventilation, FiO_2 decreased to 40%. However, a few hours later, the patient became highly unstable, requiring noradrenaline at a dose of 0.8 µg/kg/min combined with adrenaline at a dose of 0.08 µg/kg/min and vasopressin at a dose of 0.03 iu/min. At this time, only 5 hours after her ICU admission, cardiac output deteriorated significantly, with a measured CI of less than1 $L/min/m^2$. The patient was anuric. Laboratory blood tests showed acute renal failure and lactic acidosis. An emergency echocardiogram was performed, which demonstrated severe global hypokinesia, ejection fraction < 25%, and sinus rhythm [Figure 1].

Due to the patient's rapidly deteriorating condition, with refractory septic shock requiring high doses of vasopressors and manifestations of very low cardiac output, extracorporeal support was considered. The patient was placed on a peripheral femoro-femoral VA-ECMO

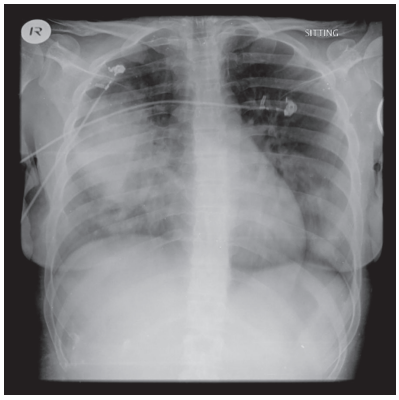
as a last resort salvage therapy. Although VA-ECMO is not indicated for septic shock therapy, there were several case communications indicating this therapy may be beneficial in refractory septic shock as a lifesaving therapy. After initializing VA-ECMO at a flow of 3 liters per minute, the patient's condition improved with increased blood pressure and cardiac output. Due to the ongoing metabolic acidosis and oliguria the patient began continuous renal replacement therapy (CRRT). The patient was placed on lung protective ventilation protocol with PEEP 7 cmH_2O, driving pressure of 12 cmH_2O, and FiO_2 40%.

Figure 1. Right side pneumonia and cardiac index measurment during the septic and cardiogenic shock

[A] Chest X-ray with large opacities in the mid and top lobes on the right. The finding support right sided pneumonia



[B] Echocardiogram at the time of septic and cardiogenic shock, demonstrating severe global hypokinesia, ejection fraction < 25% and sinus rhythm



One day after connecting the patient to VA-ECMO, blood cultures results returned positive for *Streptococcus pyogenes*, group A *Streptococcus* (GAS). The antibiotic therapy was changed according to antibiogram (the pathogen was susceptible to all antibiotics) and infectious disease specialist consult to penicillin G. Clindamycin was added to treat high suspicion of clinical toxic shock syndrome. Adjuvant therapy with intravenous immunoglobulins (IVIG) was added, as it is recommended in sepsis guidelines in refractory septic shock, at a cumulative dose of 60 g (1 gram/kg/day) at the first day of therapy and 30 g for 2 more days (3-day protocol) in addition to high dose steroids.

Due to the risk of developing a cerebrovascular ischemia the neurological condition of the patient was repeatedly checked and sedation was stopped. After the third day, the patient's condition started to improve. The acidosis resolved, noradrenaline dosage was reduced and the cardiac index started to improve allowing flow reduction of the VA-ECMO. CI continued to increase and dobutamine was added to the treatment reaching cardiac index of 3.5 $L/min/m^2$. Due to clinical improvement, the patient no longer needed VA-ECMO support and was weaned off VA-ECMO after 3 days (total of 53 hours).

The patient continued to improve. Vasopressor and inotropic therapy was stopped. After recovering from severe refractory septic and cardiogenic shock with GAS, the patient developed ventilator associated pneumonia (VAP) complicated with empyema (according to the literature 5–10% of nosocomial pneumonia progress to empyema), which required two chest tube insertions and eventually pleural decortication by video assisted thoracoscopy (VATS).

Because of the prolonged mechanical ventilation and severe muscle weakness the patient underwent tracheostomy and developed hospital acquired pneumonia (HAP) on the left. Blood and sputum cultures were negative for bacterial ethiology. Fungal infection was suspected due topositive galatomannan in the sputum. After 2 weeks of broad spectrum antibiotics and antifungal therapy the patient improved and underwent decanulation. A few days later, the patient was discharged to her home for further rehabilitation.

COMMENT

Septic shock is a life threatening condition involving hemodynamic instability, organ dysfunction, and signs of hypoperfusion requiring rapid intervention. Infection source control, proper antibiotics therapy, and stabilization of the patient with vasopressors and fluids are the main treatment options. Invasive disease with GAS is rare and affects all age groups, with a higher incidence in children and those over the age of 50 years regardless of associated co-morbidities. Pneumonia is an uncommon manifestation of GAS infection, which manifests with bacteremia (80% of cases) and complications such as pleural effusion and empyema [1].

VA-ECMO utilizes both a centrifugal, continuous flow pump, and a membrane oxygenator that facilitate carbon dioxide and oxygen exchange with a full biventricular cardiopulmonary support. VA-ECMO patients are mechanically ventilated with lung protective ventilation protocol. The VA-ECMO mitigates the hypoxia and hypercarbia [2].

VA-ECMO in adults causes vasodilation and improves cardiac output; however, peripheral VA-ECMO returns the blood via the arterial catheter in retrograde flow to the aorta causing an increase in after load of the left heart leading to increase cardiac oxygen consumption. It is indicated in several clinical conditions (cardiac arrest, cardiogenic shock, severe acute congestive heart failure, myocarditis) in addition to hemodynamic findings of cardiac index < 1.8, central venous pressure > 20 cmH_2O, wedge pressure > 18, systolic blood pressure < 80 with two inotropic agents support, distal signs of low perfusion, and cardiac wall motion abnormality [2,3]. Complications of VA-ECMO use are bleeding; thrombosis of circuit; incomplete retrograde oxygenation leading to cerebral,

coronary, and upper extremity hypoxia, infection, and gas embolism; and pulmonary edema due to congestive heart failure [3].

In our ICU we used echocardiography in conjunction with $PiCCO_2$ to further evaluate the cardiac function and the volemic state of the patient. In this patient, the rapid deterioration followed by a rapid recovery of the cardiac function excluded primary cardiac disease. The findings in the echocardiography excludes pulmonary embolism as the trigger for shock and global dysfunction of the heart.

We conducted a literature search for the use of VA-ECMO in septic shock adult patients. The information available is scarce. There are several reports in the literature regarding infection leading to severe cardioplegia with a severe global cardiac dysfunction requiring VA-ECMO. In a retrospective observational study, 14 patients received rescue therapy of VA-ECMO due to cardiac failure secondary to septic shock. Ten patients survived with reported good quality of life [1]. In another study, 52 patients who had been diagnosed with septic shock and cardiovascular collapse were placed on VA-ECMO. Eight patients (15%) survived and were discharged. It was observed that all patients above age of 60 years (38%) died, suggesting that age over 60 years should be considered as a contraindication for VA-ECMO therapy [4].

We found a similar case report of a 29-year-old patient diagnosed with influenza H1N1 viral infection who presented with cardiovascular failure and was placed on VA-ECMO as a salvage therapy and survived [5]. We believe that criteria for VA-ECMO in septic shock should be further expanded to define and identify the patients who might benefit from VA-ECMO therapy in a refractory septic shock condition.

CONCLUSIONS

The patient we presented in our case report had a rare presentation of CAP followed by invasive GAS disease, manifesting as a rapidly life threatening deteriorating condition, with severe refractory septic and cardiogenic shock, driving us to have the decision of placing the patient on VA-ECMO as a last resort option and salvage therapy. Despite the scarce data available, we believe that VA-ECMO is an optional therapeutic intervention and should be used more often in a rapidly deteriorating refractory septic shock patient with severe cardiac dysfunction.

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**Simplicity of life, even the barest, is not a misery,
but the very foundation of refinement.**

William Morris (1834–896), British textile designer, poet, novelist, translator and socialist activist associated with the British Arts and Crafts Movement

Capsule

SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans

Turner and colleagues demonstrated that in patients who experienced mild infections (n=77), serum anti-SARS-CoV-2 spike (S) antibodies declined rapidly in the first 4 months after infection and then more gradually over the following 7 months, remaining detectable at least 11 months after infection. Anti-S antibody titers correlated with the frequency of S-specific bone marrow plasma cells (BMPCs) obtained from bone marrow aspirates of 18 severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) convalescent patients 7 to 8 months after infection. S-specific BMPCs were not detected in aspirates from 11 healthy subjects with no history of SARS-CoV-2 infection. The authors demonstrate that S-binding BMPCs are quiescent, indicating that they are part of a long-lived compartment. Consistently, circulating resting memory B cells directed against the S protein were detected in the convalescent individuals. Overall, they show that SARS-CoV-2 infection induces a robust antigen-specific, long-lived humoral immune response in humans.

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