

Neutropenic patient with fever and abdominal pain

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Dr. Hallie Metz: Today's case is that of a 49-year-old woman who presented to the Emergency Department (ED) by ambulance for respiratory distress. The patient was diagnosed with precursor B-cell type Acute Lymphocytic Leukemia 6 months prior to presentation, had undergone her third cycle of aggressive chemotherapy 10 days prior to presentation. She had a history of febrile neutropenia and line infections after past rounds of chemotherapy. The morning of the patient's arrival to the ED, she complained of some vague abdominal pain, had a few episodes of vomiting, and a low grade temperature. She was referred into the ED for evaluation by the Hematology Oncology Fellow on call that morning.

Dr. Richard Wolfe: This patient seems to have a very significant medical history and seemingly has the potential to be critically ill. What did she look like on arrival to the ED?

Dr. Metz: Upon arrival by ambulance, the patient appeared to be an overweight woman clearly in distress. Her vital signs were: temperature 40°C rectally, pulse rate 124, blood pressure 122/86, respiratory rate 36, and oxygen saturation 94% RA. She was markedly confused, tachypneic and had an increased work of breathing. She responded to voice but was unable to verbalize or follow commands. Examination of the head included eyes held wide open, pupils equal and reactive, extra-ocular muscles intact. Her heart rate was a regular rhythm although tachycardic and without appreciable murmurs. Her lung

examination revealed tachypnea, abdominal respirations, and poor air movement diffusely although grossly clear to auscultation bilaterally. Her abdomen was soft but distended. Tenderness to palpation was impossible to ascertain secondary to her altered mental status. She had palpable distal pulses and minimal appreciable peripheral edema. Her neurological exam included being alert but not oriented to self, place, or time. She did not follow commands or withdraw from pain although she would turn her head in response to voices although this action appeared nonpurposeful.

Dr. Wolfe: Can you describe your initial clinical impression and diagnostic plan?

Dr. Metz: Secondary to her recent medical history, rapid change in mental status from the morning when she was able to converse with family, and her respiratory distress, this patient raised concerns for severe systemic infection, of abdominal or respiratory origin, and airway compromise. Our initial thoughts were to place the patient on continuous monitor, establish a definitive airway, gain appropriate intravenous access, obtain lab work, and start broad spectrum antibiotic therapy. After the patient was stabilized, the plan was to obtain various CAT scans as follows:

- Head, secondary to altered mental status and hypercoagulability secondary to malignancy, to evaluate for mass or acute intracranial bleed,
- Chest, secondary to respiratory distress and hypercoagulability, to evaluate for mass, pulmonary embolism, pleural effusions,
- Abdomen, secondary to abdominal distention, complaints of abdominal pain and vomiting, and recent chemotherapy to evaluate for mass and other intraabdominal pathology.

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Dr. Amy Hurwitz: Can you describe the immediate assessment and establishment of a definitive airway?

Dr. Metz: An emergency airway cart had been prepared prior to the patient's arrival secondary to the Emergency Radio conversation between the Advanced Life Support team and the ED staff. She was placed in a supine position and pre-oxygenated with a non-rebreather oxygen mask with an oxygen saturation of 100%. With an Attending Physician, two ED nurses, two ED residents, and a Respiratory Therapist present in the room, 20 mg of IV Etomidate followed by 120 mg of IV Succinylcholine were administered for sedation and paralysis through a 16 gauge peripheral IV. A 7.5 Endotracheal tube was passed through the vocal chords with one attempt. Tube placement was confirmed with oxcolorimetry, auscultation, and visualization of bilateral chest rise with ventilation. Verced, 2 mg IV, was given for sedation.

Dr. Carlo Rosen: This patient was quite tachypneic on arrival. What was her ventilatory status after intubation?

Dr. Metz: Despite her significant respiratory distress upon arrival, the patient was over-breathing the ventilator and required 10 mg IV vecuronium for continued paralysis.

Dr. Leon Sanchez: Medications used during endotracheal intubation in critically ill patients can sometimes have undesirable effects on hemodynamics. What were the patient's vital signs at this time?

Dr. Metz: Initially following sedation, intubation, and mechanical ventilation, the patient's blood pressure fell slightly from an approximate systolic blood pressure of 120 to 94/64. However, within minutes, her systolic blood pressure fell further to measurements in the 80 s. During this time, peripheral Levophed was started for vasopressor activity to restore adequate blood pressure and organ perfusion. A central venous line was being placed in the patient's right femoral vein under ultrasound guidance secondary to weak peripheral pulses and body habitus.

Dr. Nathan Shapiro: Considering the presumed diagnosis of septic shock, do you consider placing a "sepsis line"?

Dr. Metz: The utility of a "sepsis line" for monitoring central venous pressure (CVP) was discussed and considered. However, the patient's blood pressure was falling rapidly, reaching a systolic bloody pressure nadir of 68, and as she had had multiple central lines in the past, she had multiple scars at both internal jugular sites. It was decided to place a central venous line in the groin for rapidity of access.

Dr. Shapiro: It is understandable that you wanted to gain access quickly, but can you briefly discuss Early Goal Directed Therapy (EGDT) in the resuscitation of septic patients in the ED?

Dr. Metz: It has been well shown that patient's in both the ED and the Intensive Care Unit have improved outcomes and reduced mortality when EGDT is applied to the management of severe sepsis at earlier stages of disease. Sepsis involves increased oxygen demand, dysfunction of oxygen extraction, and overall myocardial depression. The resuscitation of septic patients should begin as soon as the syndrome is recognized and should not be delayed until they reach the intensive care unit [18]. When early therapy is not comprehensive, the progression to severe disease has often already occurred by the time patients arrive to the Intensive Care Unit [5, 13, 15]. Caring aggressively for these patients after that point can be completely inactive and even harmful [12].

The first stage of comprehensive resuscitation of septic patients takes place within the first 6 h of care. This care primarily occurs in the ED. The goals during this initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol:

Central venous pressure (CVP): 8–12 mm Hg (Although in mechanically ventilated patients, a higher target CVP of 12–15 mm Hg is recommended to account for the increased intrathoracic pressure

Mean arterial pressure \geq 65 mm Hg

Urine output \geq 0.5 mL \times kg⁻¹ \times h⁻¹

Central venous (superior vena cava), or

mixed venous oxygen saturation \geq 70% (ScvO₂) [2]

These goals are initially approached with fluid resuscitation with crystalloid or colloid infusion. If the goal of CVP 8–12 mmHg is not met by fluid administration without the correlation to central venous oxygenation saturation $>$ 70% within this first stage, than packed red blood cells should be administered with or without the addition of dobutamine [11].

At least two sets of blood cultures should be drawn, or one from each vascular access site, and presumably appropriate antibiotics started based on the suspected source of infection. Antibiotics, usually broad spectrum, should be started within the first hour of diagnosis of severe sepsis [2]. Diagnostic studies, such as xrays or CT scans, should be obtained to help identify the source if and when the patient is stable for transport.

Dr. Wolfe: Can you discuss measuring oxygen saturation and the septic patient in the ED?

Dr. Metz: The early stages of sepsis are accompanied by circulatory insufficiency creating an imbalance between tissue oxygen supply and demand, leading to global hypoperfusion and shock. Increases in oxygen extraction or decreases in the central venous saturation (ScvO₂) or mixed

venous saturation (SvO₂) implies falling venous oxyhemoglobin saturation [11, 13] which is associated with increased morbidity or mortality if unrecognized and can occur when a patient is displaying normal vital signs [15]. Early hemodynamic assessment on the basis of physical finding, vital signs, CVP, and urinary output often fails to detect the systemic tissue hypoperfusion and hypoxia of septic patients [18]. It has been shown to be a more definitive resuscitation strategy to use certain end points, such as SvO₂, as clinical markers for achieving the EDGT goals.

SvO₂, monitored at the level of the pulmonary artery, has been shown to be a surrogate for monitoring cardiac index as a target of hemodynamic therapy in the resuscitation of septic patients and for quantifying the severity of global hypoxia [3, 4]. SvO₂ gives an estimate of the oxygen saturation of blood returning to the right side of the heart which indirectly correlates with tissue oxygen extraction as well as the balance between systemic oxygen delivery and demand [3, 13].

Dr. Tibbles: There had been controversy over the use of ScvO₂ versus SvO₂ in monitoring the septic patient. How do the two numerical values compare?

Dr. Metz: There continues to be debate over the equivalency of SvO₂ and ScvO₂ in certain ranges of oxygen saturation, namely the normal to high ranges. However, these values are typically found in the later stages of sepsis and in patients already in the intensive care unit [13]. In the ED, the important issue is whether there is clinical correlation in the lower ranges where the information is more relevant. Although the range of critical values of SvO₂ (<65%) and ScvO₂ (<70%) differ, they have both been shown to be pathologically equivalent and if measured, are associated with high mortality [4, 8, 18]. When it is impractical to insert a pulmonary artery catheter, as it often is in the ED, SvO₂, can be reliably measured in the central circulation [16] at the level of the superior vena cava (ScvO₂).

In a randomized, controlled study of over 260 patients where the control group did not receive EGDT, the EGDT group received more intravenous fluid, red cell transfusions, and inotropic therapy during the first 6 h. The goal of 70% or higher for central venous oxygen saturation was met by 60% of the patients in the control group but in the EGDT group, the goal was met in over 94% of patients [18]. Meaning that the patients in the standard therapy, or control group, had a significantly lower central venous oxygen saturation than those in the EGDT group within the first 6 h of resuscitation. However, during the next 66 h of care, the control group received more transfusions, vasopressors, and required more mechanical ventilation and pulmonary artery catheterization implying that they were

under-resuscitated initially. During this time period, the control group had higher heart rates, lower mean arterial pressures, but similar CVPs when compared to the EGDT group. The control group also had a significantly higher in-hospital mortality at 28 days and a higher rate of sudden cardiac death than the EGDT group [18].

Dr. Tibbles: Is it necessary to monitoring ScvO₂ through a “sepsis line” if the patient is being treated accordingly?

Dr. Metz: The problem with monitoring CVP is that it is a pressure management alone and does not refer to volume. A pressure-volume discrepancy may still exist even in the setting of a CVP above the critical level. Significant hypovolemia may be present with normal to increased CVP secondary to impaired ventricular response [9, 13]. Ten to 15% of patients with a near-normal systemic blood pressure will continue to have significant myocardial depression requiring inotropic support [10, 11, 14]. Normal blood pressure readings may lead to inadequate fluid resuscitation.

The measurement of ScvO₂ as a surrogate of the oxygen supply/demand balance, therefore, is necessary part of the EGDT protocol. This may be done through specialized central venous catheters or intermittent sampling and measuring of central venous blood [17]. However, catheters through “sepsis” lines give a continuous measurement of oxygen balance which theoretically would be more useful.

Dr. Wolfe: What implications do you think this had for the future of the management of the septic patient in the ED?

Dr. Metz: The incidence of sepsis and septic shock in elderly persons is substantially higher than in the younger population. The projected growth of the elderly population in the United States will increase the incidence of septic patients approximately 1.5 percent per year. The estimated cases per year in 2010 and 2020 are over 900,000 and 1 million respectively and estimated cost per year is almost 20 million dollars [5, 21].

Dr. Hurwitz: What were your plans for this patient at this point?

Dr. Metz: Her blood pressure responded to the vasopressor activity of the Levophed. She was given a total of 9 liters of crystalloid to maintain and CVP above 9. The lab work showed neutropenia and secondary to the fever and hypotension, the patient was given intravenous broad spectrum antibiotics including Zosyn, Vancomycin and Capsfungin, under the direction of the Hematology/Oncology Service. When she was hemodynamically stabilized on Levophed, various CAT scans were performed as indicated above and reported as “Diffuse pneumatosis along the ascending, transverse, and descending colon with dilatation of the

ascending and transverse colon, mucosal wall thickening, lack of enhancement, mesenteric and portal venous gas. These findings are consistent with ischemic bowel.” Free air and free fluid and bibasilar pulmonary opacities likely indicating aspiration pneumonia were also visualized in the abdominal cavity. No pulmonary embolism was identified.

Dr. Hurwitz: What are the implications of neutropenic colitis?

Dr. Metz: Neutropenic colitis, a severe necrotizing enteropathy, is a well documented and life-threatening complication of aggressive chemotherapy mainly for lymphoproliferative and hematologic malignancies [1, 6, 8, 19, 20].

It initially was thought to primarily associated with high-dose chemotherapy but newer studies show ischemic colitis after standard dose regimens as well. It is primarily seen in hematologic malignancies but there are case reports of ischemic colitis with neutropenia in solid tumor malignancies as well. The mortality rate can be as high as 21%. It can have disastrous outcomes, such as perforation and intra-abdominal sepsis, but often resolves with withdraw of chemotherapeutic agents and supportive care [1, 6, 19, 20].

Dr. Sanchez: What was the clinical course of this patient?

Dr. Metz: The surgical service was consulted and after much discussion with the next of kin regarding prognosis and survival, the patient was taken the operating room for an exploratory laparotomy under the assumption of ischemic bowel. In the operating room, she was found to have necrotic bowel from the cecum to the left lower quadrant without perforation. A total abdominal colectomy was performed and initially the abdomen was packed and left open. She returned to the operating room 3 days later for washout. An ileostomy and gastrojejunostomy were performed at that time. She remained on mechanical ventilation for a few weeks and had to return to the operating room another time for wound dehiscence, tracheostomy placement, and fat necrosis. However, she was eventually weaned off of mechanical ventilation, and discharged to a rehabilitation facility 2 months after initial presentation.

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