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Roundtable Debate: Controversies in the Management of the Septic Patient – Desperately Seeking Consensus

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Commentary

Roundtable debate: Controversies in the management of the septic patient – desperately seeking consensus

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Abstract

Despite continuous advances in technologic and pharmacologic management, the mortality rate from septic shock remains high. Care of patients with sepsis includes measures to support the circulatory system and treat the underlying infection. There is a substantial body of knowledge indicating that fluid resuscitation, vasopressors, and antibiotics accomplish these goals. Recent clinical trials have provided new information on the addition of individual adjuvant therapies. Consensus on how current therapies should be prescribed is lacking. We present the reasoning and preferences of a group of intensivists who met to discuss the management of an actual case. The focus is on management, with emphasis on the criteria by which treatment decisions are made. It is clear from the discussion that there are areas where there is agreement and areas where opinions diverge. This presentation is intended to show how experienced intensivists apply clinical science to their practice of critical care medicine.

Keywords sepsis, septic shock, resuscitation, pneumonia

Introduction

Despite continuous advances in technologic and pharmacologic management, the mortality rate from septic shock remains high. Each year in the USA there are an estimated 400,000 cases of sepsis, resulting in more than 100,000 deaths annually [1]. The hemodynamic derangements of septic shock are characterized by arterial hypotension, peripheral vasodilatation, hypovolemia from capillary leakage, and the development of myocardial depression. An excessive inflammatory response typifies the initial stages of infection and contributes to the progression

to organ failure. Progression to septic shock represents failure of the circulatory system to maintain adequate delivery of oxygen and other nutrients to tissues, causing cellular and then organ dysfunction (Task force of the American College of Critical Care Medicine and Society of Critical Care Medicine [2]). The ultimate goals of therapy for shock are to restore effective tissue perfusion, to normalize cellular metabolism, and to preserve and restore tissue function.

Care of patients with sepsis includes measures to support the circulatory system and treat the underlying infection.

ACTH = adrenocorticotropic hormone; CAP = community-acquired pneumonia; CVP = central venous pressure; DIC = disseminated intravascular coagulation; ED = emergency department; FiO₂ = fractional inspired oxygen; ICU = intensive care unit; MAP = mean arterial pressure; PA = pulmonary artery; PCO₂ = partial carbon dioxide tension; PO₂ = partial oxygen tension; scVO₂ = central venous oxygenation.

Although there is a substantial body of knowledge indicating that fluid resuscitation, vasopressors, and antibiotics accomplish these goals, consensus on how they should be prescribed is lacking. Recent clinical trials have provided new information on the addition of individual adjuvant therapies, including adrenal supplementation therapy, tight glucose control, and drotrecogin alpha (activated) to standard therapies. These therapies are effective with statistical certainty in their respective study populations, but they do not provide insights into potential synergistic or antagonistic interactions, making it challenging to determine which combination of treatments, if any, is best for a given patient. It is the reasoning that clinicians use to process this information and synthesize individual care plans that is the focus of this commentary.

We present the reasoning and preferences of a group of intensivists who met to discuss the management of an actual case. Throughout this presentation, the focus is on management, with emphasis on the points of discussion of the criteria by which treatment decision are made. It is clear from the discussion that there are areas where there is agreement and areas where opinions diverge. Participants support their opinions with literature citations and provide a perspective on how clinical practice can be distinct from participation in a clinical trial.

Case presentation part 1

The patient is a 56-year-old male who awoke the morning of admission with nausea, shortness of breath, and diaphoresis. Over the previous 2 days he had noted a productive cough, associated with midline chest pain, shaking chills, and three to four episodes of watery diarrhea. He had no abdominal pain and no swelling or pain in the legs. Over the past 3 months he had lost 30 lb (approximately 13.6 kg) in weight and he had recently sought medical attention for left shoulder pain. A bone scan was reportedly negative. He had no known drug allergies and took no medications. Family history was unremarkable. He was a former smoker, of less than 20 pack-years, having stopped about 3 years previously, and he denied alcohol or illicit drug use. He had worked as a dry cleaner for the past 30 years.

Physical examination in the emergency department (ED) revealed a temperature of 97°F (36.1°C), a heart rate of 180 beats/min, and blood pressure of 120/60 mmHg. His respirations were labored at 26 breaths/min, and oxygen saturation was 89% on 4 l nasal cannulae oxygen. During the examination he had an episode of coffee ground emesis. He was put on a nonrebreather mask, and his oxygen saturation increased to 98%. Breath sounds were diminished in the right upper lung zones. His stool was hemocult positive. Initial laboratory study findings are summarized in Table 1.

Dr A As we stand at the bedside, reviewing the admission laboratory findings and waiting impatiently for a chest

Table 1

| Initial laboratory values | |
|------------------------------|---|
| Parameter | Value |
| Potassium | 3.5 mmol/l |
| Chloride | 99 mmol/l |
| Carbon dioxide | 19.9 mmol/l |
| BUN | 26 mg/dl |
| Creatinine | 1.9 mg/dl |
| Glucose | 89 mg/dl |
| Hematocrit | 43.7% |
| Platelet count | 137,000 mm ³ |
| Bands | 18% |
| PT/INR | 14.8 s/1.4 |
| PTT | 48.9 s |
| D-dimer | >1000 ng/ml |
| PH | 7.32 |
| PO ₂ | 101 mmHg |
| P _{CO} ₂ | 27 mmHg |
| ECG | Narrow complex tachycardia with 2–3 mm ST-segment depressions in leads V ₃ –V ₅ |

BUN, blood urea nitrogen; INR, international normalized ratio; P_{CO}₂, partial carbon dioxide tension; PO₂, partial oxygen tension; PT, prothrombin time; PTT, partial thromboplastin time.

radiograph, let us try and put these findings together. First of all, this patient presents with an acute illness with fever, chills, a cough that is productive of purulent sputum, and 3 days of watery diarrhea. At first thought this sounds like community-acquired pneumonia (CAP), possibly with an atypical pathogen. Perhaps the diarrhea is a red herring. Weight loss and left shoulder pain in a 53-year-old former smoker raises concern for lung cancer with possible postobstructive pneumonia, and we shall look for signs of volume loss or chest wall metastasis on the chest radiograph. This patient also has evidence of severe sepsis, with a left shift, and tachycardia. He has signs of impending organ failures with renal dysfunction, a creatinine level of 1.9 mg/dl, metabolic acidosis, a coagulopathy with an elevated prothrombin time and D-dimer, and low platelets that could signal early disseminated intravascular coagulation (DIC). He has respiratory failure, with an A–a gradient over 500. He is probably hemoconcentrated, and clinically we would expect him to be hypovolemic from diarrhea, high insensible losses, and poor oral intake. My immediate therapeutic concern is the tachycardia, the nature of the cardiac rhythm, and the possibility of myocardial ischemia.

Dr D I might disagree with you that this patient has severe sepsis. What if, after 2 or 3 l saline, his blood pressure, heart

rate, and creatinine normalize? I think this illustrates one of the greatest triage challenges in this area, and that is differentiating infection with sepsis from another very common scenario – infection with dehydration and hypovolemia. I think the most important point is not to confuse sepsis with hypovolemia from any cause, including hemorrhage.

Dr B The first steps in the care of patients like this should be very systematic. Once the tachycardia was assessed and assuming the chest radiograph confirms pneumonia, I would initiate prompt antibiotic therapy based on the most likely type(s) of infection; ensure adequate hemodynamic and respiratory support; try to identify the source of infection; identify and ascertain the extent of his organ dysfunction; and, based on that, develop an overall treatment plan.

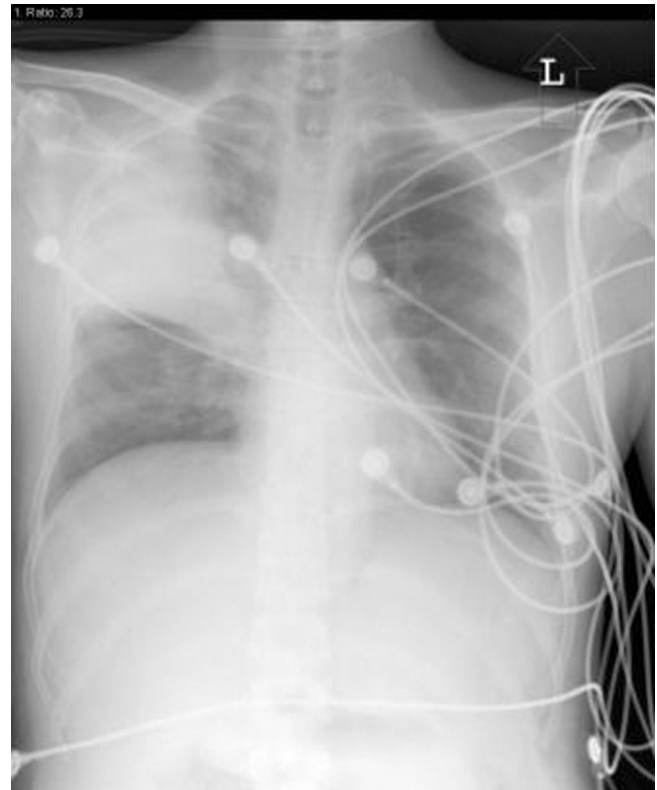
Dr C I agree – we need to treat this suspected infection. Although a chest radiograph is not initially available, there is a strong clinical suspicion for pneumonia, as a source of major infection, and empiric antibiotic coverage should be started. When the differential diagnosis includes a central nervous system infection, there is never a question in regard to early antibiotic coverage, and in fact antibiotics are started within a window of 6–8 hours. Data for most infections, especially pneumonia, have the same window of opportunity in regard to mortality. Animal models of septic shock also indicate that mortality can directly relate to time delay in antibiotics. If there is any delay in the work up, including a delay in obtaining a chest radiograph, then empiric treatment for CAP with ceftriaxone and azithromycin should be initiated.

Case presentation part 2

The patient was given 2 l of normal saline and a chest radiograph was obtained. He was given a total of 18 mg adenosine with no response; and then 2.5 mg intravenous verapamil in three doses, with a decrease in heart rate to 110 beats/min. Atrial fibrillation was diagnosed. His blood pressure fell with these interventions. The chest radiograph showed a dense opacity in the right-upper lobe with patchy opacities in the right-lower lobe, the lingula, and left-upper lobe. There were no clear air bronchograms or lateral shift to suggest lobar collapse (Fig. 1).

Dr B There are now additional diagnostic data available, and clinically important interventions have been done that raise important considerations. The additional radiographic information addresses the concerns raised about the 30 lb weight loss and any chronic process that may be acutely infected. There is no clear evidence of an endobronchial lesion or airway obstruction. This, along with the history of a recent negative bone scan, makes cancer less likely. Active tuberculosis is possible, and sputum should be sent for appropriate studies. With the complaint of midsternal pleuritic chest pain, there is concern of pericardial involvement. However, there are no suggestive changes on the ECG, and the heart size looks normal, somewhat narrow,

Figure 1



Initial radiograph showing a right-upper lobe opacity and opacities in the right-lower, lingula, and left-upper lobes.

and probably under-filled, which is consistent with hypovolemia.

Dr A Do we need to consider any other diagnostic tests for CAP in a patient with severe sepsis?

Dr C It can be very helpful in cases like this to have blood and sputum cultures. It is usually possible to get a set of blood cultures in patients like this, prior to starting antibiotics. Although they do not have a high yield, they can play an important role in the treatment of the infection by identifying possible sources and unusual or resistant organisms. They can also help to identify high-risk patients.

Dr B The purist's goal is to try to establish a bacteriologic diagnosis, but the realization is that one must initially treat broadly because no single test has the sensitivity and specificity to allow one to treat narrowly. Regardless, the coverage we use includes coverage for almost every possible bacteriologic pathogen. Knowing that this patient is from the community, we do not need to consider double Gram-negative coverage, even in a septic patient. If a patient is from the community but has recently been hospitalized, is immunosuppressed, is being treated with steroids, or has

structural lung disease, such as bronchiectasis, then we would consider alternative or additional antibiotic coverage to cover for *Pseudomonas* spp. or other resistant Gram-negative rods. For the time being there is no indication to change either the azithromycin or ceftriaxone. I agree that to try to obtain a bacteriologic diagnosis, we use blood, urine and sputum cultures, if available, and might perform bronchoscopy once the patient is hemodynamically stable.

Dr C Getting back to the ECG, the patient has a narrow complex tachycardia with a rate of 190 beats/min with 2–3 mm ST-segment depressions across the precordium. Should the heart rate be directly controlled? Could the patient be having a myocardial infarction or is he simply volume depleted? I am concerned about using adenosine before adequately addressing the patient's volume status. The initial approach should be to volume replete him aggressively and see whether the hemodynamics improve, and then address any persistent tachycardia only after he is volume replete. In this case, rate controlling agents may not be the first line of therapy, given a strong suspicion for sepsis. One question that comes up is, what if he is ischemic and you start volume resuscitating him? Is he going to go into heart failure? Does that matter? This should not be an issue. If the need arises then support him with invasive or noninvasive ventilation and get him through this. Regardless of the cause of the tachycardia, fluid load this patient.

Dr A Would there be any indication to treat him for an acute coronary syndrome with aspirin or heparin at this point? Would there be a problem with starting heparin in this man if one felt he truly had a coronary basis of ischemia versus demand ischemia? It is likely that this represents demand related ischemia, as opposed to an unstable coronary syndrome. This is a 55-year-old man. The ECG shows a narrow complex tachycardia at 190 beats/min with ST-segment depressions in V_3 – V_5 . Creatine phosphokinase and troponin levels were all initially normal. Is there a down side to giving aspirin? Aspirin is not going to be of much value, if you think this is demand-related ischemia. It does complicate the decision making for drotrecogin alpha (activated) should he develop severe sepsis. There is also the concern that he is having gastrointestinal bleeding. There is reluctance to go after his ischemia in a big way until we get his rate controlled. If ECG changes persist after control of heart rate, then we might consider aspirin. If heparin is started then it can easily be discontinued.

Dr B I agree that aspirin may complicate the decision making, should you want to give a new agent like drotrecogin alpha (activated). Patients receiving aspirin or other antiplatelet agents were excluded from the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial, and so its safety in the presence of antiplatelet agents is unclear. If you think the patient is more at risk for death from severe sepsis than from demand ischemia, then

your attention should be directed toward the interventions that are most likely to give the patient benefit. Because this patient had no prior history of coronary disease, and because demand related ischemia is more likely than an acute coronary syndrome that may benefit from aspirin, the risk/benefit moves one step toward sepsis interventions rather than acute myocardial infarction interventions. Coronary flow is upregulated in sepsis [3–5]. It is actually unusual for patients to develop myocardial ischemia.

Case presentation part 3

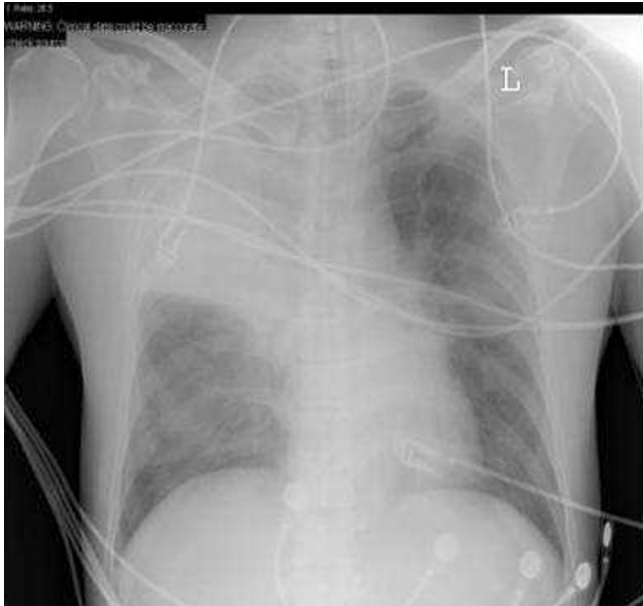
The patient was admitted to the general medical floor. He was still tachycardic at 110 beats/min in sinus rhythm, and ST-segment changes had resolved. He was described as being cold and clammy. His systolic blood pressure was now in the 90s. He was given an additional 3 l normal saline, resulting in a blood pressure of 110/60 mmHg. He was increasingly tired, and his breathing became more labored. He received ceftriaxone and azithromycin. The patient subsequently required orotracheal intubation with a #8 endotracheal tube. He was given fentanyl, propofol, and midazolam for intubation. Eight hours after presenting in the ED, he was transferred to the intensive care unit (ICU). A chest radiograph following intubation showed progression of the right-upper lobe process. The heart rate was 106 beats/min, and blood pressure was 94/47 mmHg with a mean arterial pressure (MAP) of 60 mmHg. Oxygen saturations were 96% on 100% oxygen. An additional 3 l normal saline was given, for a total of about 6.5 l (Fig. 2).

Dr A What is interesting in this case is that, in the ED, when you have someone who already has single organ failure and some borderline findings that make you suspect he is on his way to multiorgan failure, should this patient automatically be an ICU admission? We argue this frequently because, if you volume resuscitate this patient in the ED and he turns around in the ED, the tachycardia goes away, the ST segments normalize, his respiratory distress gets better, and he either goes to an ICU or a regular floor bed. This becomes a very important triage question. This patient is a great example of someone who has the potential to crash very hard, and if you intervene right away with early therapy you may be able to reverse at least what we see as early organ dysfunction and prevent multiorgan failure. This man could have gone straight to the ICU, and we could have figured all this out there, rather than try to get him floor ready. The other thing is that if you send him to the ICU, he could spend 24 hours there and then be ready to go to the floor; instead he ended up coming to the ICU for a week.

Case presentation part 4

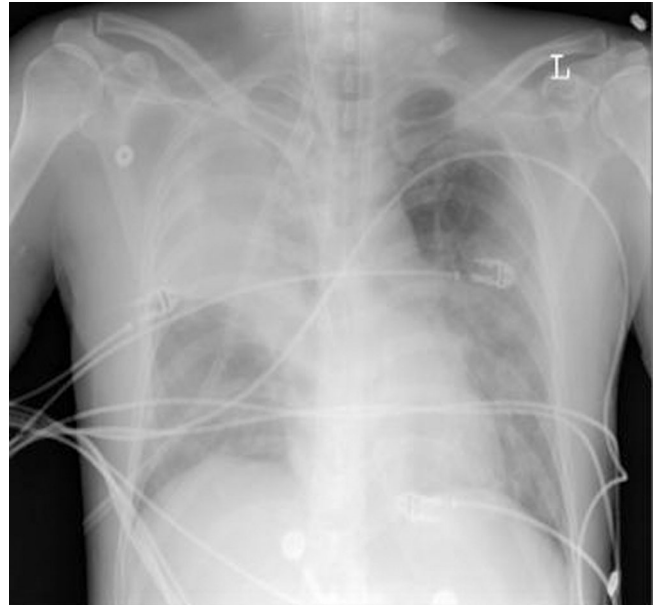
Two hours later, the patient was agitated on the ventilator and had frequent high peak airway pressure alarms; the oxygen saturations were stable. The blood pressure had been trending downward, with systolic in the high 70s, MAP in the 50s, and urine output under 20 cc/hour. His sodium

Figure 2



Postintubation radiograph showing progression of the right-upper lobe opacity.

Figure 3



Radiograph showing progressive involvement of both lungs.

was 137 mmol/l, potassium 3.2 mmol/l, chloride 118 mmol/l, carbon dioxide 17.8 mmol/l, blood urea nitrogen 18 mg/dl, and creatinine 1.1 mg/dl, the latter representing an improvement. The glucose was 170 mg/dl, phosphate was down to 1.4 mg/dl, and albumin was 1.3 g/dl. The white cell count was 6500/mm³ with 15% bands; platelets were 56,000/mm³. The hematocrit was down to 28.4%. Cardiac enzymes were within normal limits. The arterial blood gases on 50% inspired fractional oxygen (FiO₂) were as follows: pH 7.46, partial carbon dioxide tension (PCO₂) 24 mmHg, and partial oxygen tension (PO₂) 99 mmHg. Central venous pressure (CVP) was 14 cmH₂O. Central venous PO₂ was 39 mmHg. Lactate was 5.6 mg/dl. Norepinephrine (noradrenaline) was being started (Fig. 3).

Dr D Resuscitation is clearly ongoing, and appropriate end-points have not yet been reached. The patient is hypotensive, in spite of 8–10 l crystalloid. He has not received any blood, and pressors are being started. He was just intubated and heavily sedated. The chest radiograph needs to be checked for anything that could have a negative hemodynamic impact, such as a pneumothorax or other mechanical reasons for shock.

Dr A How do we judge the completeness of his volume resuscitation?

Dr B Clinical indices should be the first guide to the appropriateness of volume resuscitation. Clinical markers that were originally deranged can be followed, looking for

improvement. Regardless, many of these patients may go on to develop organ failure. A threshold is often reached at which volume is given to the point that the presumption is that the patient is intravascularly replete. How is that point defined in the patient with organ failure? It depends, in part, on the age of the patient and cardiac function. If the patient is young or left ventricular function is known from a previous echocardiogram, then a central venous line with CVP and central venous oxygenation (scVO₂) monitoring may be adequate. Alternatively, if cardiac function is not known or there is a suspicion of compromise, especially in an elderly patient, or if a large volume of fluid has been given without improvement, then invasive monitoring with a pulmonary artery (PA) line would be a consideration. When do you decide that enough fluid has been given? When is it time to hang a pressor or an inotrope? Initial volume resuscitation should be between 8 and 10 l, but after that how do you decide if that is enough or if are they leaking into the third space?

Dr A Adequacy of volume resuscitation is a big picture issue, and I never rely on a single variable. Multiple parameters are considered, including the hemodynamic measurements of heart rate, blood pressure, urine output, skin perfusion, and mentation. If these measures do not improve with aggressive volume expansion, then a PA line is considered. This suggests that it takes an experienced intensivist to judge fluid requirements. How does the resident or nonintensivist do it? As part of the protocol for early goal-directed therapy, pressors are used to keep the MAP about 60 or the systolic

pressure above 90. Fluids are given to raise the CVP to between 10 and 12. The central venous oxygen saturation is pushed up with dobutamine and/or red cells. If these goals are not achieved within a reasonable time frame, then consider what additional information can be obtained from the PA catheter. The reason why the PA catheter trials have been so inconclusive is because there have been such varying goals or protocols associated with their use. If we could figure out the best protocol to resuscitate people, then we might be able to use the PA line as a guide and perhaps show benefit over non-PA-guided protocols.

Dr D This raises the question as to when pressors should be started. The preference is not to hang vasopressors early in the resuscitation. If the patient is not adequately volume resuscitated, then splanchnic blood flow could be compromised by pressors. Conversely, we cannot allow a patient to remain hypotensive while striving to achieve volume resuscitation goals. Although the preference is to refrain from giving vasopressors before adequate volume resuscitation, sometimes we have to maintain an adequate blood pressure. In patients who are on pressors, should target goals be adjusted? It is likely that a higher central venous pressure is required in patients who are on pressors. A patient who has a CVP of 12 or 15, but who requires significant doses of vasopressors to maintain adequate MAP, might really need a CVP of 25.

Dr B When resuscitating a septic patient, there is a need, if we have not achieved our therapeutic goal, to double check the status of the left ventricle. We should not make an assumption in the septic patient that left ventricular function is normal. Many of these patients, perhaps even this one, have pulmonary vascular alterations in which there is a disconnect between the left and right side. They can have elevated CVPs in the presence of a low wedge. In this setting the PA catheter may give us additional useful information that CVP does not. An important point is not to fall into the trap of searching for the one best number. There is no one best number. Generally, there is a lot of information being generated for each patient, and it is important to look at all this information, especially the stroke volume or cardiac output for given CVP or wedge values, and how all these variables change, or do not change, after fluid boluses. Noninvasive estimates of preload and cardiac function can also be obtained. We all want to be reassured that we have given enough, but not too much, volume. If more fluid is given, and whatever index of cardiac function is being followed does not change, then we're probably close to adequate fluid resuscitation. That said, we have no idea whether this is the right construct, even though we all seem to agree on it. It may be that a strategy that favors norepinephrine, vasopressin, and/or inotropes allowing for less fluid resuscitation produces better outcomes than one that favors aggressive fluid resuscitation aimed at optimizing cardiac output and minimizing vasopressors. One recent

study of elective surgical patients [6] showed superior outcomes with a severely restricted perioperative fluid management strategy. We need much better studies in this area.

Case presentation part 5

He received over 10 l isotonic crystalloid, and his initial CVP was around 6 mmHg. He received additional volume as a combination of crystalloid and colloid; the resulting CVP was 15 mmHg.

Dr A Is it possible to be more efficient in the resuscitation? Do colloids make a difference in resuscitation?

Dr D Colloids make a difference in the sense that we can volume resuscitate much more quickly. We also add oncotic pressure, which hopefully keeps more crystalloid intravascularly, and the total volume of fluid is less. If the issue is one of timing, then the more aggressively you achieve your end-diastolic volume goals, the better.

Dr C Inadequate preload in sepsis and septic shock is multifactorial and can be related to venodilation, fever and fluid losses, and diffuse capillary leak. Vascular dysfunction presumably results from damage to underlying endothelium and likely results in compromised endothelial barrier function. Larger colloids are more likely to stay in the intravascular space. This, in combination with widespread inflammatory activation, explains one of the challenges of fluid therapy – capillary leak and formation of edema. This also plays a role in the requirement for large volume resuscitation. Restoration of adequate circulatory volume is necessary to permit adequate tissue perfusion, but it may not be sufficient on its own to correct microvascular abnormalities associated with sepsis.

Dr A The literature does not support a benefit of one colloid over the other, or colloids over crystalloids. So the question is, you know you can give 10 l crystalloid or you can give 2.5 l colloid, so why wouldn't you just give 2.5 l? It is faster, with the same gauge intravenous line. Many intensivists would generally use 100% crystalloid, and many of us would look for reasons to give blood. If the hemoglobin is below 10, then packed red blood cells would be reasonable.

Dr B For the most part I would use crystalloid as a first-line agent. Some of us would consider using both starch and blood, depending on the hemoglobin. As far as a specific approach, once I have reached a point where the patient has received over 6–10 l crystalloid, there is a desire to give something that is going to stay intravascular and provide more volume expansion with less total volume. At this point, I would start using colloid and, especially knowing his hemoglobin is where it is, I would probably give him starch. The bottom line is that most of us agree that the quantity and timing of whatever you pick is much more important than the fluid you pick.

Dr A Would anybody transfuse this patient with a hematocrit of 28.4?

Dr C Knowing he has a hematocrit that was 43 when he came in is important. He has had close to 10 l of crystalloid. Based on the protocol of Rivers and coworkers [7], initial volume resuscitation was given to get the CVP to 8–12. $scVO_2$ is then examined. If the $scVO_2$ is under 70, then either dobutamine or red cells (to get to a hematocrit of 30) are given to achieve a $scVO_2$ above 70%. It is not entirely clear why the patients assigned to early goal-directed therapy in the Rivers study did better. The data suggest that it was not necessarily because they got blood but rather the timing of how much fluid they received. At the end of 72 hours, both groups received the same amount of fluid but it was frontloaded in the early goal-directed therapy group, potentially having only to do with the aggressiveness of resuscitation. However, the protocol group did receive more blood (64% versus 16% transfused) during the first 6 hours.

Dr B There are several studies that show that packed red blood cells may not increase oxygen utilization in sepsis. It is believed their main benefit in a situation like this is as a colloid – one that is very expensive, is of limited supply, and may have a variety of infection risks.

Dr A Should we treat this patient with empiric steroids?

Dr D The best current evidence with which to answer this question comes from the randomized controlled trial conducted by Annane and coworkers [8]. A prior trial suggested that failure to augment serum cortisol by 9 $\mu\text{g}/\text{dl}$ after high-dose adrenocorticotrophic hormone (ACTH) was a bad prognostic sign and was independent of the pre-ACTH stimulated cortisol value [9]. The subsequent randomized controlled trial by Annane and coworkers showed benefit from steroids in the ACTH nonresponder patients only. Therefore, a random cortisol without cosyntropin may not help you decide whether to treat relative adrenal insufficiency. On the practical side, in many institutions cortisol results are not available for 2 days. If that were the case, then I would draw a pre- and post-ACTH cortisol and begin hydrocortisone 50 mg every 6 hours until the cortisol results return. I think we all would withdraw steroids if the serum cortisol increased by more than 9 $\mu\text{g}/\text{dl}$ following ACTH.

Dr A According to the study by Annane and coworkers [8], if the baseline cortisol goes from 55 to 61, then the patient must be treated because they have relative adrenal insufficiency. An argument could be made that if the baseline cortisol is 55, then the patient may not benefit from additional steroids. Of the 299 patients who were studied and the 229 who were said to be adrenally insufficient, we do not know what fraction of those patients truly had a baseline cortisol of 55. In the patients who had an elevated cortisol to start with,

it is unclear whether there is really any benefit in steroid replacement.

Dr D A cosyntropin stimulation test is easy and safe and is the only clear way, at the present time, to distinguish patients who appear to have an insufficient adrenal response. Because the random cortisol is not a reliable index, the best approach would be to treat the patient with steroid replacement therapy, pending the results of the cosyntropin stimulation test, and withdraw steroids, once those results show a normal response. This assumes that patients who respond are not harmed by 2 days of steroids.

Case presentation part 6

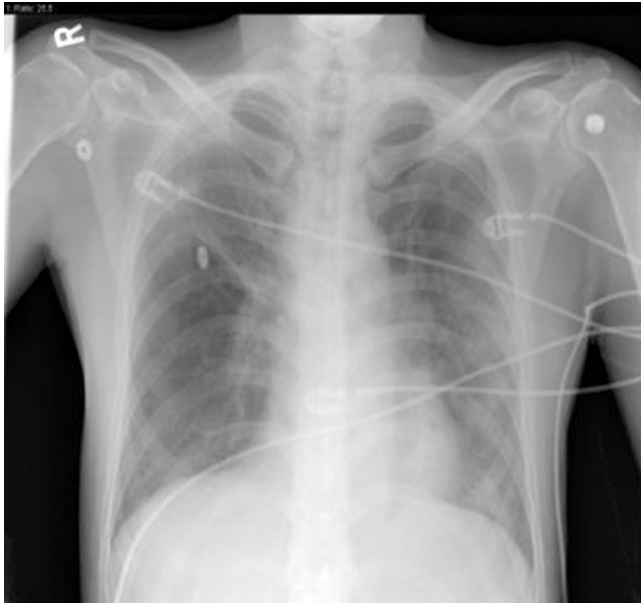
Two hours later the sodium was 135 mmol/l, potassium 4.5 mmol/l, chloride 94 mmol/l, carbon dioxide 17 mmol/l, blood urea nitrogen 21 mg/dl, creatinine 1.8 mg/dl, and glucose 153 mg/dl. An arterial blood gas on 60% F_{iO_2} revealed pH 7.33, PCO_2 34 mmHg, and PO_2 70 mmHg, with a central venous oxygen saturation of 66%. The white blood cell count was 32,000/mm³ with 32% bands. The platelets had dropped to 28,000/mm³, and the international normalized ratio was 1.8, with a prothrombin time of 19.5 s and a partial thromboplastin time of 50 s. Urine output had increased to 40 cc/hour.

Dr A Should this patient be treated with drotrecogin alpha (activated)?

Dr B This patient has septic shock, organ injury, coagulopathy, and signs of DIC. His platelets are 28,000, which is below the 30,000 cutoff used in the PROWESS trial [10], but I think this may be exactly the kind of patient who should receive Drotrecogin alpha (activated). In the PROWESS trial DIC was part of the enrollment criteria. Actually, in the subgroup analysis, the DIC patients did better. If there is concern with the platelet count, we can either give platelets if this man had a lot of incisions or previously showed bleeding or forget about the platelet count, give the drotrecogin alpha (activated), and watch him expectantly.

Dr D My understanding of the mechanisms by which this drug works tells me that drotrecogin alpha (activated) works by reversing the underlying pathophysiology in sepsis, and if you can improve this patient rapidly in the first 24 hours with standard therapies, then he is likely to have a better mortality. If you can't, then an intervention with a drug like drotrecogin alpha (activated) makes sense [11]. The data make a case for early treatment in all respects. Early intervention of almost anything is better than later intervention. Given what we know of the sepsis cascade, the further it rolls on the worse it gets. For most of us who have been sepsis investigators for a long time, the generalized expectation is that the earlier we intervene the better the chances that one can interrupt the sepsis cascade, and so on.

Figure 4



Radiograph showing generalized improvement.

Case presentation part 7

Over the next 48 hours the findings on chest radiography improved. A chest computed tomography scan was done and did not reveal an endobronchial lesion. By day 3 the patient was off pressors. Urine output was up and the Fio_2 is down. The patient was awake, alert, and responsive. On the third hospital day he was extubated. The white count was $14,000/\text{mm}^3$ without bands. The platelets and prothrombin time normalized, and the creatinine was normalizing (Fig. 4).

Dr A The next question is whether he is clearly getting better. Do we keep the patient in the ICU to complete the full course of drotrecogin alpha (activated) or send him to the floor? Those are two different questions: do we have to complete the full 96-hour infusion and do we keep a patient who no longer requires ICU level care in the unit to complete the treatment?

Dr D Here is a man who is off the vent; renal failure and hypotension are resolved. If someone meets every other criterion for leaving the ICU – except for the fact they are receiving drotrecogin alpha (activated) – do you send him out of the ICU on drotrecogin alpha (activated) or stop the infusion early to send him out to the medical floor? If he is this stable, then I would stop the infusion and send him out. I think most would agree that you wouldn't keep the patient in the ICU solely to keep him on drotrecogin alfa (activated) if he is no longer critically ill. However, the much more common question is if he were still intubated, off pressors, looking much better, and one was thinking about extubating, 72 hours into the course, would one continue drotrecogin alpha (activated)? In that case I feel compelled to continue

the drug. We don't raise that same question with antibiotics, and in that scenario he would continue to receive antibiotics for the next 7–10 days.

Summary

The analysis and commentary of the care provided to this patient with severe sepsis and septic shock highlight the challenges in assessing and managing critically ill patients. The participants provided their perspectives on the recognition of physiological instability and the definition of severe sepsis and septic shock; at what point a patient should be admitted to the ICU; the importance of early goal-directed resuscitation therapy and the choice of resuscitation fluid; when to consider intravascular monitoring; the use of low-dose corticosteroids and drotrecogin-alpha; and at what point an improving patient should leave the ICU (Table 2).

In this case, the assessment of the patient begins with recognition of the signs and symptoms of a serious infection. The participants agreed not only that antibiotic treatment should be given within 8 hours of presentation but also that combination therapy for CAP was appropriate. It was agreed that cultures of blood, urine, and sputum are indicated but should not delay the initiation of antibiotic therapy. Diagnostic bronchoscopy was not recommended while the patient was hemodynamically unstable.

Patients often present with tachycardia and electrocardiographic abnormalities that may reflect sepsis, infection with vasodilation and hypovolemia (so-called ineffective arterial circulation), or cardiac ischemia. Distinguishing sepsis and an ineffective circulation from an acute coronary syndrome can be challenging. All of the participants agreed that, regardless, the most important effort should be directed toward restoring adequate intravascular volume. Resolution of tachycardia and increased urine flow with fluid resuscitation would suggest that hypovolemia and sepsis were the problems. Although there were differences of opinion regarding the timing of CVP or PA catheter placement, all were in agreement that a CVP or pulmonary capillary wedge pressure in the single digits was inappropriate for this patient. Furthermore, all agreed that the adequacy of volume resuscitation was best determined from cumulative data, including serial hemodynamic measurements, measurements of arterial and central venous oxygenation, and the response to volume infusion.

Both the availability and potential risks (although small) of transfusion of red blood cells made their use more restricted. The group agreed that patients with a hematocrit of less than 30 and a mixed or central venous oxygen saturation of less than 70% might benefit from red cell transfusion. Additionally, everyone agreed that patients who are not likely to be harmed by 2 days of steroid replacement with hydrocortisone and fludrocortisone, but continued treatment with steroids should be guided by the results of a

Table 2**Summary of the views of the participants on alternative approaches to these therapeutic options for a man with circulatory failure in the context of a community-acquired pneumonia**

| Would you manage this patient with ... | Dr AW | Dr NW | Dr TT | Dr CL | Dr AL | Dr ML | Dr NH | Dr SN | Dr SH | Dr HC |
|--|--|--|--|--|--------------------------------------|--|--|--------------------------------------|--------------------------------------|-------|
| Early empiric antibiotics (ceftriaxone and azithromycin) | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree |
| Early volume resuscitation | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree |
| Colloid | Yes, in combination with crystalloid | No | No | No | Yes, in combination with crystalloid | No | No | Yes, in combination with crystalloid | Yes, in combination with crystalloid | No |
| Crystalloid | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Lactated Ringers | Agree |
| Packed red blood cells | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | No |
| Dobutamine | Agree | Agree | Agree | No | Agree | Agree | Agree | Agree | Agree | No |
| Empiric steroids | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree |
| Cosyntropin test | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree |
| DC steroids if cortisol change >9 | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree |
| Line for CVP monitoring | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree |
| PA Catheter | If persistent hypotension and oliguria with CVP >12 cmH ₂ O | If persistent hypotension and oliguria with CVP >12 cmH ₂ O | If persistent hypotension and oliguria with CVP >12 cmH ₂ O | If persistent hypotension and oliguria with CVP >12 cmH ₂ O | No | If persistent hypotension and oliguria with CVP >12 cmH ₂ O | If persistent hypotension and oliguria with CVP >12 cmH ₂ O | Agree | No | No |
| Drotrecogin alpha (activated) | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree | Agree |

CVP₁, central venous pressure.

cosyntropin stimulation test. All of the participants agreed that this patient with severe sepsis and no contraindications should be treated with drotrecogin-alpha (activated).

Conclusion

The Blue Ginger Group has prepared this synthesis of opinion on the optimal treatment of a specific case of severe sepsis in order to share how experienced critical care providers treat their patients. This presentation is not intended to advocate particular treatment algorithms but rather to show how experienced intensivists apply clinical science to their practice of critical care medicine. Applying information provided by clinical trials to practice requires synthetic reasoning, judgment, and knowledge about the patient as well as those patients included in the studies. Even more important than the specific details of this analysis is that we need more high-quality clinical trial data to clarify which treatments or combinations of treatments best help individual patients with severe sepsis.

Competing interests

The author(s) declare that they have no competing interests.

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