The Golden Hours: Diagnosis and Treatment of Sepsis
in an Emergent Care Setting

By: Jane Dueck

Summer Work Experience & Training Program – May to August, 2010

The Pas, Manitoba

Supervisors: Dr. Richard Kostyk and Dr. Marie Noel
Introduction

During the early stages of my time in The Pas, I was shadowing Dr. Marie Noel when she realized that one of her patients on the medical ward had likely developed sepsis. After entering the new orders for diagnostic tests and empiric antibiotic therapy into the patient’s chart, she explained to me the diagnostic criteria for sepsis and the importance of acting while the patient was still in the “golden hours” of the condition. She also expressed some concern that sepsis was not being diagnosed promptly or appropriately in the emergency department, and that treatment was being delayed due to lack of awareness of the diagnostic criteria.

It has been shown that there is often great variability in management of sepsis in emergency departments around the world, and that many physicians do not follow the widely-accepted guidelines (1). With this project, I am attempting to answer the following questions pertaining to this issue. First, is sepsis being diagnosed correctly (based on the SIRS criteria) in the emergency department of The Pas Health Complex? Second, are the appropriate treatments being administered within the “golden hours” following the patient’s admission?

SIRS and sepsis

The systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock are defined and classified along a continuum of graded severity. Where the patient falls on this continuum is a determinant of their mortality, with sepsis having the best prognosis (10% to 15% mortality) and septic shock having the worst (43% to 54% mortality) (2).

SIRS describes a dysregulated systemic inflammatory response that can occur following a wide variety of physiological insults, and it is characterized by the presence of at least two of the following: temperature greater than 38.5°C or less than 35°C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 breaths per minute, and white blood cell (WBC)
count of greater than $12 \times 10^9$ cells/L. SIRS can result from non-infectious conditions, which is important to keep in mind when distinguishing it from sepsis (3, 4).

When SIRS results from a suspected or confirmed infectious process (such as a urinary tract or respiratory infection), it is called sepsis (2). Therefore, in order to make the diagnosis of sepsis, the patient must meet the SIRS criteria, plus have a proven or clinically suspected site of infection. Since sepsis is a systemic condition, clinical presentation can be very variable and may also be nonspecific, with the patient complaining of general malaise, dizziness, altered mental status, or weakness (4). When attempting to determine the site of infection, examining the patient for clinical features of localized infection (cough in respiratory infection or flank pain in UTI) can be of use (4).

Severe sepsis is the next step on the continuum, defined as sepsis plus at least one of the following: mottled skin, capillary refill time greater than 3 seconds, urine output 0.5 mL/kg for at least one hour, lactate $> 2$ mmol/L, abrupt change in mental status, abnormal EEG findings, platelet count $<100,000$ platelets/mL, disseminated intravascular coagulation, acute lung injury or ARDS, or cardiac dysfunction as measured by echocardiogram or ECG. The mortality rate for severe sepsis ranges from 17% to 20% (2).

Septic shock has an even higher mortality rate than severe sepsis, and is defined as severe sepsis plus one or both of the following: systemic mean blood pressure less than 60 mmHg (unless the patient’s baseline blood pressure is hypertensive) despite adequate fluid resuscitation, or maintaining the systemic mean blood pressure greater than 60 mmHg requires dopamine $>5$ mcg/kg/min, norepinephrine $<0.25$ mcg/kg/min, or epinephrine $<0.25$ mcg/kg/min despite adequate fluid resuscitation. Septic shock can also be refractory, requiring even more dopamine, norepinephrine, or epinephrine in addition to fluid resuscitation in order to stabilize the patient (3).
At the most severe end of the spectrum is multiple organ dysfunction. This refers to altered or decreased organ function such that the patient cannot maintain homeostasis without medical intervention. The organ dysfunction can be primary, resulting from and directly attributable to a given physiological insult, or secondary, when it is a consequence of the host’s response to the insult. (3)

In the United States, sepsis is now the 10th leading cause of death (2), and is among the most common reasons for admission to intensive care units throughout the world (4). Mortality increases with the severity of the disease and where the patient falls on the sepsis spectrum. Other factors which affect mortality include the host’s response (failure to develop a fever is associated with increased fatality rates, as is leukopenia (3,4), any underlying disease states, the patient’s age, site of infection, and the microorganism causing the infection. For example, MRSA is more common in The Pas, which appeared to play a role in the physicians’ choices of antibiotics for septic patients. Interestingly, the presence or absence of a positive blood culture does not appear to influence the patient’s outcome, and as many as 50% of patients will not demonstrate a positive blood culture at the time of diagnosis (2,3).

There have been many publications over the years describing appropriate treatments and interventions for septic patients. Perhaps the most ambitious and far-reaching of these has been the Surviving Sepsis Campaign, which proposed a series of treatment ‘bundles’ to be applied to patients at different stages of the sepsis continuum.

*The Surviving Sepsis Campaign*

The Surviving Sepsis Campaign ( SSC) was published by an international conference of 55 experts operating out of 11 different organizations, and consists of a set of guidelines for clinicians caring for septic patients, and improving outcomes for patients diagnosed with sepsis or septic shock (5). The original guidelines were published in 2001; updated versions were
The guidelines were developed based on extensive review of evidence-based literature, and the quality of the evidence was judged by predefined criteria using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria, which is a system for grading the strengths of clinical practice recommendations. The GRADE criteria evaluate the quality of the evidence, assess the risks vs. benefits of the recommendation in question, and examine the burdens and costs for each recommendation. Evidence is classified as high-quality (grade A), moderate quality (grade B), low quality (grade C), and very low quality (grade D). The treatment recommendations in this paper are taken from the SSC recommendations.

Several authors have evaluated the SSC guidelines. Vincent and Marshall express their support of the SSC’s methods and recommendations, although they advise a degree of caution in following the exact letter of the guidelines. They state that it is the clinician’s prerogative to make decisions for individual patients which may go against the SSC guidelines, and also remind the reader that the guidelines are not legally binding standards of practice (6).

Additionally, there have been studies which show the mortality benefits of applying the SSC protocols. Ferrer et al. evaluated four therapeutic goals and four treatments outlined in the SSC publication, and their outcome measure was hospital mortality. They concluded that achievement of the SSC’s treatment goals was associated with better survival, although they identified several patient factors such as age and gender which also had a significant impact on their mortality in spite of the treatments given (7). Castellanos-Ortega and his colleagues also examined the SSC protocols in terms of mortality and length of hospital stay for patients with septic shock; they determined that implementation of the SSC guidelines were associated with shorter hospital stays and significant decreases in mortality (8).
Treatments for sepsis

Many authors liken sepsis to emergent conditions such as acute myocardial infarction, stroke, and polytrauma when discussing the importance of speed in treatment (4,5,9). However, these same authors admit that unlike stroke, trauma, and AMI, the signs of sepsis are often very subtle and difficult to detect. Identification of the patient during the early “golden hours” shortly after their arrival in the hospital and early initiation of treatment are linked to more promising prognoses, whereas failure to act within the “golden hours” can result in the patient’s progression to organ failure (4). The SSC expresses the importance of beginning treatment within six hours of admission for patients with sepsis, and within the first hour following admission for patients with septic shock (5). Six hours will be the operating definition of the “golden hours” of sepsis for the purposes of this paper.

Early goal-directed therapy is the phrase that has been coined to describe the constellation of interventions designed to improve the condition of the septic patient, and the key to initiating therapy is rapid recognition of the septic patient and prompt mobilization of frontline health care providers (4).

The SSC and other authors outline many different treatments suitable for septic patients. The SSC in particular outlines eighteen different types of interventions, ranging from initial hemodynamic resuscitation to stress ulcer and DVT prophylaxes (5). For the purposes of this project, I will examine only a few of the most important early interventions.

One of the first things that the SSC recommends is obtaining blood, urine, or other cultures in order to confirm the site of infection and identify the responsible pathogens. These cultures should ideally be obtained before antibiotic therapy is initiated, although the SSC guidelines stress that empiric antibiotic therapy should not be significantly delayed if the cultures cannot be drawn promptly (5). In addition to blood cultures, the SSC recommends that imaging
studies should also be performed to identify or confirm a potential source of infection, although caution should be exercised when transporting patients off-unit and placing them into imaging devices inside which the patient’s status is difficult to monitor (5).

Another important early intervention is source control, including removal of any infected object (such as a catheter) if possible, and antibiotic therapy. Source control involves identifying the site of infection within the first six hours following presentation, and attempting to neutralize the source of infection by debriding necrotic tissue, removing infected catheters or venous lines, draining abscesses, etc. The techniques offering the least harm to the patient should be employed when implementing source control measures. The initial empiric therapy should include antibiotics to cover all likely pathogens, and should be directed at the presumed source of the infection. Treatment must take into account complex issues such as any drug intolerances, the clinical presentation of the patient, the likely pathogens, and any antibiotics that the patient has used recently. Recently used antibiotics should be avoided if possible. The antibiotic regimen should be reassessed daily to avoid toxicity or resistance, and should certainly be re-evaluated once the results from the cultures are in. The duration of therapy should be 7-10 days, and if the patient’s illness is caused by a non-infectious cause, antibiotic therapy should be stopped to minimize the risk that the patient will be infected with a resistant pathogen or suffer from drug toxicity (5). Antibiotic therapy has been identified by several authors as being of the utmost importance in septic patients, with delays in administration of intravenous antibiotics being strongly linked to increases in mortality (4,10,11).

Equal in importance to diagnosis and early administration of antibiotics is volume resuscitation by fluid challenge. The SSC does not recommend crystalloids over colloids or vice versa, although this is an area of some contention among experts (4). According to Raghavan et al., the most commonly-used fluid for volume resuscitation is 0.9% NaCl (normal saline). Fluid
challenge is different from simple fluid administration in that in fluid challenge, large volumes are administered under a short period of time under close supervision to evaluate the patient’s response (4). Naturally, such aggressive techniques may not be appropriate for patients with underlying health conditions such as heart failure, although for otherwise healthy patients it is recommended that fluid challenge techniques are applied for as long as the hemodynamic improvement (in terms of blood pressure, heart rate, urine output, etc.) continues. The SSC recommends that fluid challenge be started with at least 1000 mL of crystalloids or 300-500 mL of colloids over 30 minutes, depending on the patient’s initial hemodynamic status (5).

The SSC’s other recommendations concern vasopressors, inotropes, corticosteroids, recombinant human activated protein C, packed red cells and other blood products, mechanical ventilation, sedation, and several other interventions (5). However, many of these are guidelines for patients suffering from severe sepsis or septic shock, and are less relevant for the patient with ‘basic’ sepsis. Due to time and space constraints of this project, it was not possible to examine all possible interventions, so I will not discuss them further here.

Methods

Unfortunately, the medical records computer system in The Pas is not capable of pulling up a list of patients who were admitted or discharged with a specific diagnosis (i.e., sepsis). So, in order to obtain my sample of patients for this project, I had to ask the hospital staff to generate from memory a list of patients who had recently been diagnosed with sepsis. The final list of potential subjects consisted of thirty-three names from a period of about two years; however, not all of these patients were suitable, for several reasons.

Inevitably, there were a few patients on the list who were never given a diagnosis of sepsis—that is, their names were included on the list in error. There were also several patients who developed their sepsis while they were on the ward; these patients were excluded because
this project is examining patients who present to the emergency department with sepsis. Third, I decided to exclude the neonatal and pediatric patients, since the guidelines for treatment of these groups are different from adults. Lastly, a few of the patients who may have been appropriate to include in the project had to be excluded due to technical issues such as illegible handwriting or the relevant forms not being included with the chart.

The final list of patients who met the criteria I was looking at consisted of twelve names, with dates of admission since July 2008. All were adult patients, and all had presented to the emergency department and received a diagnosis of sepsis at some point during that presentation.

The following data was collected for each patient:

- Identifying information: date and time of presentation to the ER, Health Record number, age, and entrance complaint
- Vital signs and SIRS measures: temperature, heart rate, respiratory rate, WBC count, blood pressure, and oxygen saturation
- Diagnosis: the diagnosis the attending physician reported on the ER form, as well as any suspicions about a site of infection
- Diagnostic tests: which tests were ordered, and the time at which they were performed
- Treatments: which antibiotics, fluids, or other treatments were given, and the times at which they were provided

The resulting data was analyzed as follows. First, the patient’s SIRS measures (respiratory rate, heart rate, temperature, and WBC count) were examined, and note was made of whether or not the patient met the SIRS criteria. Record was also kept of any clinical suspicion or confirmation of a site of infection, and of the diagnosis the patient received. These measures
were then used to determine if (a) the patient met the criteria for a diagnosis of sepsis, and (b) if the diagnosis of sepsis was correctly made based on the patient’s characteristics.

Additional notes were made of the diagnostic tests ordered by the attending physician, and the time at which they were performed. The purpose of this was twofold. First, I wanted to see if the appropriate panel of tests were being ordered in a timely manner, and second, I wanted to see if blood cultures and urine samples were taken before or after antibiotics were given.

I also recorded any treatments the patient received, focussing primarily on antibiotics (which antibiotics were prescribed, and how long it took for treatment to be started), and fluids (how much fluid was given, at what speed, and how long it took for fluids to be administered). I also made note of any other treatments the patients received, such as analgesics or anti-nausea agents, although that information is only of incidental value for this project.

Results

Diagnosis

Of the twelve patients, nine received a diagnosis of sepsis in the emergency room, while the other three were diagnosed later, after admission (and after the six-hour timeframe recommended by the SSC had elapsed). Eight out of the twelve patients met the sepsis criteria (SIRS measures plus a proven or clinically suspected site of infection), while four did not. The following table illustrates the breakdown of patients.

<table>
<thead>
<tr>
<th></th>
<th>Met sepsis criteria</th>
<th>Did not meet sepsis criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Not diagnosed</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

At this point, it is worth noting that for three out of the four patients who did not meet the sepsis criteria but were diagnosed as having sepsis, their respiratory rate was not taken by the triage nurse or any other members of the healthcare team. It is possible that the addition of a
significant respiratory rate (>20 breaths/minute) to their data could have changed the category they fell into from not meeting the sepsis criteria to meeting the criteria, and so their diagnosis of sepsis might actually have been appropriate.

*Diagnostic tests*

Of the twelve patients whose emergency room records I reviewed, six had blood cultures drawn and nine had urine cultures taken. All blood cultures were taken before antibiotic therapy was initiated. There was one patient whose sepsis was due to a septic arthritis of the knee; his joint aspiration for culture and sensitivity was also done before antibiotics were started. Speaking from my own experience working in The Pas emergency department, the laboratory technicians always responded very promptly to requests for blood and other samples to be taken, and all of the patients I reviewed had their blood samples drawn within an hour of admission to the ER. Urine samples, however, often took longer to obtain.

With regards to the imaging studies recommended by the SSC, six of the twelve patients were given x-rays (five chest, one knee). No additional imaging studies were ordered.

All patients had a CBC ordered, and four had a very thorough panel of tests ordered, including liver function, renal function, electrolytes, blood glucose, and others.

*Treatment: Antibiotics*

Of the nine patients who were diagnosed with sepsis, all received antibiotics in the emergency room. The average time from admission to onset of antibiotic treatment was two hours and seven minutes; the longest delay was two hours and forty minutes, the shortest wait was fifty minutes. Since the SSC recommends that antibiotic treatment begins sooner than 6 hours after admission, this is acceptable; but there is likely still some room for improvement.
With regards to the antibiotics that were prescribed, piperacillin-tazobactam, ceftriaxone, and vancomycin were the most popular choices, although there were also many others that were prescribed, making it difficult to make generalizations about antibiotic preferences.

*Treatment: Fluid support*

Of the nine patients who were diagnosed with sepsis, seven out of nine were given fluids in the emergency room. The amount of fluid given to patients varied widely, from as little as 500 mL to as much as 9 L (over several hours), but the most commonly-administered fluid was normal saline, usually given in 1000 mL boluses with each bolus being delivered over the course of an hour.

*Discussion*

*Issues for diagnosis*

The factor which distinguishes sepsis from SIRS is a proven or clinically suspected site of infection. While most patients who were diagnosed with sepsis had a confirmed or suspected infection (UTIs were the most common), there was one patient diagnosed with sepsis who met the SIRS criteria (37.1°C, HR 103, RR not taken, and WBC $25.2 \times 10^9$) but had in fact suffered a drug overdose, with all blood and urine cultures coming back negative for infection, and no clinical suspicions of infection were noted in the chart. Although this was an isolated case, it does hint that perhaps the criteria for SIRS and sepsis are not fully understood among some practitioners.

Another issue is that, as previously mentioned, several of the patients (seven out of the total twelve) did not have their respiratory rate taken by the triage nurse. Since respiratory rate makes up one fourth of the SIRS criteria, excluding it puts the attending physician at a disadvantage when it comes to making the diagnosis of sepsis.
The most important diagnostic issue, however, is the three patients who met the sepsis criteria but were not diagnosed with sepsis in the emergency room. While two of these patients were treated with fluids and antibiotics, the third was not, despite the identification of a site of infection. This suggests a lack of familiarity with the SIRS/sepsis criteria, and identifies an area where improvement is needed, in terms of diagnosing sepsis within the six hours following presentation and beginning treatment promptly upon diagnosis.

**Issues for treatment**

As mentioned above, the average time to the initiation of antibiotic therapy was two hours and seven minutes, which falls within the six-hour time frame recommended by the SSC. Additionally, most patients did receive initial broad-spectrum coverage, with antibiotics such as piperacillin-tazobactam, ceftriaxone, and vancomycin being popular initial choices.

While fluids were administered in almost all cases, and several patients received total volumes in excess of 5 litres, the aggressive fluid challenge techniques outlined in the SSC guidelines were not applied. There was great variability in the amounts of fluid administered; with patients receiving as little as 500 mL in some cases and as much as 10 L in others. It is possible that clinical variation in each patient’s hemodynamic status and underlying health conditions guided the attending physician’s decisions for volume resuscitation; however, it does not seem like aggressive fluid challenge techniques (high-volume boluses over short periods of time) were implemented in any of the cases. The most common initial fluid prescription was for a 1000 mL bolus over one hour; recall that the SSC recommendation is for the same or even greater volume over half the time.
Limitations

The major limitation of my project was the means by which patients were selected. Due to the necessity of getting a list of sepsis patients from nurses and other healthcare staff, rather than using the medical records computer system to pull up a list of all patients who received that diagnosis, there is a regrettably high likelihood of selection bias. Additionally, as I mentioned briefly in the results section, the respiratory rate was not taken in triage for 7 out of the 12 patients. Since this value is an important piece of the SIRS criteria, its exclusion from over half of the charts may have skewed the data, masking patients who would have actually met the SIRS/sepsis criteria with the addition of one more significant vital sign.

A less tangible limitation of this project is that there is no way of objectively recording how much of a role the attending physician’s clinical instinct played in their diagnosis. As discussed previously, a knowledge of the patient’s risk factors and past medical history (knowledge that is quite common in a smaller centre such as The Pas), as well as a career’s-worth of experience and well-developed clinical judgement, may have given the attending physician other reasons for diagnosing sepsis in a patient who did not meet the SIRS/sepsis criteria at that point in time.

Recommendations

I have mentioned that several authors liken sepsis to CVA and myocardial infarction when discussing the importance of rapid diagnosis and treatment. There are definitive protocols set out for the treatment of CVA and AMI in the emergency room, so my major recommendation is the addition of a protocol for treatment of septic patients to the emergency room. Familiarizing emergency room staff (both nurses and doctors) with the sepsis criteria, appropriate diagnostic tests to order, and the important treatment modalities will likely go a long way towards streamlining and hastening the diagnosis and treatment of septic patients.
Castellanos-Ortega et al. implemented a successful hospital-wide quality improvement program for septic patients by distributing posters and pocket cards throughout various departments and offering continuing education lectures on the diagnosis and treatment of sepsis to hospital staff (8).

Larger centres have experienced some success by implementing multidisciplinary sepsis teams who screen for sepsis and manage septic patients throughout the hospital, as well as identifying barriers to care and providing a consistent level of response (4). It is difficult to say whether or not this would be useful or appropriate in a smaller centre such as The Pas, although it is at least worth mentioning briefly here.

Additionally, as I have mentioned, the respiratory rate was not taken for over half of the patients whose charts I reviewed. In addition to being a valuable piece of information in the diagnosis of septic patients, the respiratory rate can be helpful in other clinical scenarios, such as the interpretation of blood gas results. It is my belief that more stringent insistence on a complete set of vital signs for each patient would assist not only in the diagnosis of sepsis, but also provide a more complete clinical picture for any emergency room staff who see the patient after triage.

Conclusions

In spite of the small sample size, I believe it is possible to draw some conclusions from the data generated by this project. First, the staff of The Pas emergency room are identifying some patients with sepsis and initiating treatment of those patients in a timely manner, taking advantage of the “golden hours” of the septic patient’s presentation. However, there were also patients who were misdiagnosed as being septic, and patients who were septic but were not diagnosed by the attending physician in the ER. This seems to indicate that perhaps the SIRS/sepsis criteria are not the determining factors in the diagnoses of many patients. With
regards to the treatments administered by the staff in The Pas Health Complex emergency department, the principles of antibiotic therapy, source identification, and source control outlined in the SSC recommendations appear to be being followed. However, volume resuscitation by fluid administration was not implemented as aggressively as the SSC guidelines recommended, despite the fact that several of the patients did indeed receive large volumes of fluid.

As I suggested in my recommendations, additional training and information on the definition of SIRS versus sepsis and recognition of these two related but separate conditions, along with knowledge of the SSC recommendations for treatment, would likely assist emergency department staff in making the correct diagnosis and rapidly initiating treatment of this very serious and life-threatening condition.


