Sepsis

Chapter 2

Current Dilemmas in Diagnosing Sepsis

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Abbreviations: APACHE : Acute Physiology, Age, Chronic Health Evaluation; CMS: The Centers for Medicare and Medicaid; HIPAA : Health Insurance Portability and Accountability Act; ICD-10-CM : International Classification of Diseases, 10th Revision, Clinical Modification; ICU : Intensive care unit; NIS : Healthcare Cost and Utilization Project Nationwide Inpatient Samples; qSOFA : Quick Sequential Organ Failure Assessment; SEP-1 : Early Management Bundle, Severe Sepsis/Septic Shock; SIRS : Systemic inflammatory response syndrome; Sepsis-3 : The Third International Consensus Definitions for Sepsis and Septic Shock; SOFA : Sequential Organ Failure Assessment

1. Introduction

The concept of systemic inflammatory response syndrome (SIRS) was first adopted in 1991 by the American College of Chest Physicians and the Society of Critical Care Medicine to aid in the early detection of sepsis [1]. The pathophysiology surrounding SIRS was described as the poor regulation of inflammatory mediators, which led to tissue injury, followed by multiple organ dysfunction if not corrected. The incidence of sepsis in 1991 was approximately 200/100,000 population [2].

The mortality attributed to sepsis dropped from 27.8% for the period of 1979 to 1984 down to 17.9% from 1995 through 2000. During this study, the number of patients admitted with sepsis went from 164,072 in 1979 to 659,935 in 2000. The number of hospital deaths because of sepsis also increased from 43,579 (21.9 per 100,000 population) to 120,491 (43.9 per 100,000 population) over the same period. The number of patients with organ failure also increased from 19.1% up to 33.6% likely because of increased awareness of the relationship of sepsis and organ failure.

SIRS with the presence of infection has gone on to be the hallmark for defining sepsis in the United States. These criteria for adults include the following:

- Temperature less than 36 °C or greater than 38 °C.
- Heart rate greater than 90 bpm.
- Respiratory rate greater than 20 breaths/min.
- White blood cell count less than 4000 cells per millimeter cubed or greater than 12,000 cells per millimeter cubed or the presence of greater than 10% immature neutrophils.

When 2 or more of these criteria are found with the presence of infection, the patient is then described as having sepsis. If the patient also has evidence of acute organ dysfunction, they are then described as having severe sepsis.

The Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine introduced the Sequential Organ Failure Assessment score in 1996 to describe the degree of organ dysfunction for patients with sepsis in the intensive care unit (ICU) [3]. These data points are frequently measured in the intensive care units and are thus excellent sources for later analysis.

A meta-analysis of mortality data from 1991 to 2009 in patients with severe sepsis showed a reduction in mortality rates from 46.9% down to 29% over the years 2006-2009 [4]. It is also mentioned that sepsis continues to be a top 10 cause of death in the United States. These reductions in mortality were postulated to be a result of improved processes in care as well as earlier administration of antibiotics. The Surviving Sepsis Campaign care bundles were also introduced in 2002. The leadership of the Surviving Sepsis Campaign has representatives from the Society of Critical Care Medicine and European Society of Intensive Care Medicine. It has no representation from hospital medicine or infectious disease societies.

The Surviving Sepsis Campaign began with the goal of reducing sepsis mortality by 25% using seven interventions [5]. These included:

- Increased awareness of sepsis
- Improving diagnosis of sepsis
- Increasing the use of appropriate treatment
- Educating all healthcare providers
- Improving post-ICU care

- Developing Guidelines for the care of patients with sepsis
- Implementing a process improvement program

In 2003, infectious disease and critical care physicians from 11 organizations developed management guidelines for the use by the bedside clinician to be used by the Surviving Sepsis Campaign [6]. At this time the use of C-reactive protein and procalcitonin were introduced as other possible markers for sepsis. It was mentioned that a procalcitonin level over 1.5 had a sensitivity of 100% and a specificity of 72%. It was also recommended that all patients with suspected severe sepsis should have blood cultures drawn.

It was further mentioned in 2001 that the European Society of Intensive Care Medicine reported 71% of members had no common definition of sepsis despite over 800 articles citing the use of SIRS plus infection to define sepsis [7]. The Society of Critical Care Medicine concluded that "unfortunately, a clinically useful set of criteria for diagnosing sepsis and related conditions will necessarily be somewhat arbitrary. There is no "gold standard" (such as troponin levels for the diagnosis of myocardial infarction) against which the diagnostic criteria can be calibrated. Diagnostic criteria will be judged successful if clinicians regard them as an aid for decision making at the bedside. The diagnostic scheme requires sufficient sensitivity and specificity to be a clinical aid." They also mention the "criteria should not be so cumbersome that clinicians will resist a commitment to memory or application."

This group also concluded that few if any patients in the early stages of the inflammatory response were diagnosed with sepsis. The bedside clinician would use the clinical presentation to determine if the patient "looks septic" to make the diagnosis. The Sequential Organ Failure Assessment (SOFA) score was also introduced to define organ dysfunction for the diagnosis of severe sepsis. They later concluded that the use of biomarkers such as are procalcitonin, lactic acid, and C-reactive protein in defining sepsis was premature. The concepts of sepsis, severe sepsis, and septic shock remained useful to clinicians and researchers. They ended with stating that the "facilitation of bedside diagnosis should have priority over standardized sepsis entry criteria for clinical trials.

Table 1: Comparison of SOFA Score and APACHE II Score data points collected and scored.

	SOFA Score	APACHE II Score
Pre-existing immunocompromised status or severe organ failure		X
Age		X
Temperature		X
Mean Arterial Pressure	X	X
pH		X
Heart Rate		X

Respiratory Rate		X
Sodium		X
Potassium		X
Creatinine	X	X
Renal Failure		X
Hematocrit		X
White Blood Cell Count		X
Glasgow Coma Scale	X	X
FiO2	X	X
Bilirubin	X	
Platelets	X	

The SOFA score compares with the APACHE II score in that they have both been developed in the ICU to measure the severity of disease and then develop a predicted mortality for that patient. The APACHE II score is measured within 24 hours of admission to the ICU with any one of 212 conditions and measures the 20 physiologic variables listed above in **Table 1** [8]. The APACHE II score is not specific to any of these disease processes, but is more useful in determining disease severity. Similarly, SOFA score is used to identify patients with the highest risk of mortality because of sepsis but does not itself identify the disease process of sepsis.

The Surviving Sepsis Campaign published updated guidelines in 2008 for the management of severe sepsis and septic shock [9]. This resource described goal-directed therapy for patients with severe sepsis of which a mortality rate was one in four. Severe sepsis was defined as sepsis plus organ dysfunction or tissue hypo perfusion. Hypotension was also defined as a systolic blood pressure less than 90 mmHg or a mean arterial pressure of less than 70 mmHg. Septic shock was defined as hypotension, which persisted despite adequate fluid resuscitation. This was to be accomplished in the initial 6 hours after presentation.

In 2012, the Surviving Sepsis Campaign again described sepsis utilizing SIRS criteria and included some additional variables. These variables were: altered mental status, significant edema, elevated C-reactive protein, plasma procalcitonin level more than 2 SD above normal, hypotension, oliguria, urine output <0.5 ml/kg, INR >1.5, platelet count <100,000, and lactic acid level >1.0. The goals of rapid fluid resuscitation remained the same for severe sepsis. The guidelines were translated into care bundles to be completed at 3 hours and within 6 hours.

To be completed at 3 hours

- Measure lactic acid level
- Obtain blood culture before administering antibiotics

- Administer broad-spectrum antibiotics
- Administer 30 ml/kg crystalloid for hypotension or lactic acid level >4 mmol/L

To be completed within 6 hours

- Provide vasopressors for hypotension not responsive to fluid resuscitation and achieve a mean arterial pressure of >65 mmHg
- If persistent hypotension or lactic acid level >4, measure CVP and central venous oxygen saturation
- Remeasure lactic acid level if lactic acid was elevated

In 2016, the Society of Critical Care Medicine published the Surviving Sepsis Campaign Guideline for Sepsis. This consensus panel described sepsis as a continuum from simple sepsis through septic shock [10].They concluded the term severe sepsis was redundant and deleted it. Sepsis was defined as a condition of life-threatening organ dysfunction due to a dysregulated host response to infection. The Sequential Organ Failure Assessment (SOFA) score was brought back, and a score of > 2 was associated with an in-hospital mortality of > 10% and was the recommended definition of sepsis. Septic shock remained to be defined the same as before.

The panel reported that organ failure scoring systems currently exist, and none are in common use. This would include the APACHE and APACHE II systems for critically ill patients. The "SOFA score is not intended to be used for patient management but as a means to characterize a septic patient" [10]. This would make sense since this is a mortality prediction tool used in the ICU, and is rarely ever used in other settings. The use of qSOFA and SOFA scores were never designed as a stand-alone definition of sepsis. The task force also mentions there was no process to operationalize these definitions for sepsis and septic shock.

Quick SOFA (qSOFA) was also described to include a respiratory rate >22, altered mental status, and systolic blood pressure <100 mmHg. When a patient has two of the three criteria, this should also prompt the evaluation for sepsis. This was primarily recommended for screening patients outside of the ICU.

It has also been recommended that the ICD-10 code for simple sepsis be eliminated. Sepsis as defined by the Third International Consensus Definitions for Sepsis and Septic Shock recommended the use of code R65.20 for sepsis and septic shock be coded as R65.21. (**Table 2** of reference 9) The ICD-10-CM guidelines on sepsis also states that when organ dysfunction is present, the patient should be coded in accordance with the instructions for severe sepsis unless the organ dysfunction is not due to sepsis. [11] Using these criteria, the ICD-10-CM code for sepsis, unspecified organism- A41.9, would no longer be considered sepsis and should not be

used.

Table 2: Comparison of sepsis codes by ICD-10-CM.

Clinical Description	Sepsis-3 coding recommendation	CMS coding required
2 or more SIRS plus infection	None	A41.9 (sepsis)
2 or more SIRS plus infection and any attributable organ dysfunction	None	R65.2 (severe sepsis)
SOFA Score of 2 or more	R65.2 (severe sepsis)	None
Sepsis with persistent hypotension despite volume expansion +/- vasopressor support	R65.21 (severe sepsis with septic shock)	R65.21 (severe sepsis with septic shock)

Providing diagnostic codes in accordance with the ICD-10-CM is required to generate an accurate description of the patient's disease, illness, injury, or procedure performed. We are required under the Health Insurance Portability and Accountability Act (HIPAA) to assign codes based on the ICD-10 manual. In this manual, sepsis and severe sepsis are distinguished from each other by the presence or absence of organ dysfunction. In the Final Rule published January 16, 2009, the office of the Secretary of Health and Human Services adopted the provisions of the ICD-10-CM for the purposes of coding and reporting. This was enacted as part of HIPAA and applies to all organizations covered by them. Hospitals are also paid based upon the codes submitted, as well as compared to other hospitals in terms of cost per patient, mortality, and hospital value-based purchasing revenue determinations.

Sepsis-3 criteria have not been endorsed by many U.S. medical societies including the Infectious Disease Society of America for a multitude of reasons [12]. The Centers for Medicare and Medicaid Services (CMS) has also published a response to the Sepsis-3 criteria stating, "the existing sepsis definitions, including the use of SIRS criteria, have been instrumental in training clinicians and nurses on how to best identify the earliest stages of sepsis" [13]. They went on to say the task force's definition structure "does not clearly identify patients in the early stages of sepsis where rapid resuscitation provides the greatest patient benefit and improves survival. A change to the existing definition could disrupt the 15-year trend toward further reduction in sepsis mortality."

2. Discussion

Sepsis is now the most expensive condition treated in the United States hospitals. It affected 1.5 million Americans in 2007 and cost over $20 billion in 2011 [14]. Severe sepsis has a morality rate of 30%-40%, and it is commonly accepted that early suspicion and initiation of appropriate treatment is critical to improving outcomes. The Sepsis Alliance has estimated the mortality from sepsis increases 8% for each hour care is delayed. This has led to the development of early warning systems, which look for signs of early sepsis such as fever, tachycardia, hypotension, and tachypnea. We routinely measure lactic acid levels as an

indicator of organ dysfunction. The problem being that lactic acid levels also are not specific for infection.

Between the years of 1999 and 2014, there were 2,470,666 Americans who died with sepsis listed as being related to their death [15]. This was 6% of all deaths for that period. The number of people affected has also increased from 139,086 in 1999 to 182,242 in 2014. The rate of hospital admissions for sepsis and risk of mortality has also been studied [16]. One cohort included patients admitted to 21 hospitals between 2010 and 2012 in Northern California. The other included data from the Healthcare Cost and Utilization Project Nationwide Inpatient Samples (NIS). The NIS sample included 6.5 million hospitalizations in 2010. They also mentioned that sepsis was underdiagnosed in both groups when looking at the presence of organ dysfunction as defined by the 2002 Surviving Sepsis Campaign members.

The presence of sepsis has a rate of between 4.3% and 16.7% of all hospital admissions, and most cases of sepsis are present on admission. The hospital mortality rate for these patients was between 9.8 and 17.7% and in some instances accounted for over half of all hospital deaths.

CMS continues to require the use of SIRS criteria and infection in the validation of sepsis diagnoses. The SEP-1 core measure is also built upon the suspicion of sepsis followed by lactic acid level measurement to determine if the patient has severe sepsis and to guide resuscitation efforts.

Some of the commercial insurance companies have embraced the Sepsis-3 definition citing the low specificity of SIRS criteria [17]. The insurance industry often, and correctly, points out that not all patients with SIRS criteria are septic. The example of a patient with strep throat, a white blood cell count of 13,000, and a heart rate of 95 with normal blood pressure is clearly not septic.

It is common knowledge that as the baby-boomers are retiring; the population of patients between 65 and 85 years of age is also increasing. This is also the population with the greatest incidence of sepsis and sepsis related mortality. These patients frequently require higher intensity of services when they are admitted to the hospital. This has been reported by CMS as the reason for an increase in case mix index in December 2012 [18]. We also now have more patients than ever with pre-existing organ dysfunction. Sepsis induced organ dysfunction is often occult and not identified, resulting in a delayed diagnosis and treatment of sepsis.

It is not feasible to ask medical providers to evaluate patients and to arrive at a diagnosis based upon the patient's insurance. It is certainly agreed that sepsis is a life-threatening condition. There should be basic criteria which are easily applied and readily available coupled with sound clinical judgment to determine if a patient is septic.

At present time, it makes sense to continue to diagnose sepsis utilizing SIRS criteria with the presence of infection in a patient who appears to be ill and coded as A41.9. For those with a SOFA score of 2 or more, they should be diagnosed with severe sepsis, ICD-10-CM code R65.10, as was recommended by the consensus committee for Sepsis-3. The diagnosis of severe sepsis should not be changed. We need to educate our medical providers on the utilization of SOFA scores, as this will likely become more commonly utilized in the future. We also await a greater consensus among the various societies and CMS to determine the direction we take in the future.

We need to focus our efforts of providing the safest care possible to our patients. This would mean that we should ensure nothing delays the diagnosis of the process responsible for more in-hospital deaths than any other. A de-emphasis of sepsis will likely delay initiation of appropriate treatment, thus leading to increases in mortality and morbidity.

3. References

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