

# Chapter 2

## Sepsis Definitions

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### Introduction

Sepsis is the tenth leading cause of death in the United States [1]. Mortality in the United States from sepsis is more than the total number of deaths caused by prostate cancer, breast cancer, and AIDS combined [2]. It causes more hospitalizations than acute myocardial infarction and has become a leading cause of hospital expenditure [3, 4]. Ninety percent of physicians feel that sepsis is a “significant financial burden on the health care system in their country” [5]. The Center for Disease Control and Prevention cite an aging population, chronic illness, invasive procedures, immuno-suppressive drugs, chemotherapy, organ transplantation, antibiotic resistance, and increased awareness as causes for the increase in number of reported cases of sepsis each year in the United States. Despite the significance held by this disease in medicine it has been subject to many varying definitions over the years. The ongoing changes in the “definition” of sepsis reflect both a new emphasis on precision, needed for research, and an ever-expanding knowledge of its pathophysiology.

### History of the Definition of Sepsis

#### *Origins of the Definition of Sepsis*

The word “sepsis” was first used over 2000 years ago [σηψις] in ancient Greek literature, referenced by Homer, Hippocrates, Aristotle, Plutarch, and Galen to describe decay of organic material [6]. In its earliest derivation in 1989, Roger Bone

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and his colleagues introduced the concept of the “sepsis syndrome” which is the foundation of our systemic inflammatory response syndrome (SIRS) criteria [7]. The sepsis syndrome was first described by Bone in his post hoc analysis of the Methylprednisolone Severe Sepsis Study Group in 1989 where he defined it as “a systemic response to a suspected or documented infection and at least one organ dysfunction” [7]. It consisted of hypothermia or hyperthermia, tachycardia, tachypnea, infection, and end organ dysfunction from hypoperfusion.

### ***1991 International Consensus Conference***

Current use of the terminology “sepsis” was born out of the 1991 International Consensus Conference: Distinctions in the Definition of Severe Sepsis (hosted by the Society of Critical Care Medicine, European Society of Intensive Care Medicine, the American College of Chest Physicians, the American Thoracic Society and Surgical Infection Society) [8]. Bone’s work formed the basis of the first official definition for sepsis as stipulated by the International Sepsis Definition Conference. Lynn ascribes the philosophy of parsimony of the twentieth century as being one of the more influential factors in the creation of the definition [9]. This definition adopted both threshold decision making and consensus theories. The former enables clinicians at the bedside to ascertain a reasonable pretest probability for the pathology based on clinical and supporting diagnostics such as easy-to-obtain vital signs, while the latter utilizes expert opinion [10]. The goals of this conference were twofold: to allow early bedside detection of disease and subsequent therapeutic intervention and also to standardize research protocols [11]. More modern definitions of sepsis had been based on the central concept of SIRS, a term that describes both a complex immune cascade in response to infection or injury and is also used to delineate the clinical characteristics associated with that response. The clinical use of the term SIRS describes derangements in respiratory rate, heart rate, temperature, and white blood cell count. Meeting two of the four following criteria satisfies the requirement for SIRS: respiratory rate  $>20$  breaths per min or a  $\text{PaCO}_2 <32$  mmHg, heart rate  $>90$  beats per minute, temperature  $>38$  °C or  $<36$  °C, and white blood cell count  $>12,000/\text{mm}^3$  or  $<4000/\text{mm}^3$  or  $>10\%$  bandemia [8]. Guidelines stated that sepsis is SIRS with suspected or proven infection, while severe sepsis describes patients who fulfill the criteria for sepsis and in addition have organ dysfunction [12]. In its most severe manifestation, septic shock is defined as “acute circulatory failure characterized by persistent arterial hypotension [including systolic  $<90$  mmHg, mean arterial pressure  $<65$  mmHg, or a drop in systolic blood pressure of  $>40$  mmHg from baseline after adequate fluid resuscitation] unexplained by other causes” [11].

## 2001 International Consensus Conference

In the interim between 1991 and 2001 when the professional societies decided to revisit the definition, the SIRS criteria were widely used in research protocols [11, 13]. SIRS was acknowledged as a “systemic activation of the innate immune response, regardless of the cause” and therefore not specific to sepsis [11]. This prompted the professional societies consensus statement of 2001 to reject the use of the term SIRS in favor of the “signs and symptoms of sepsis” [11]. This would allow for early intervention as “findings indicative of early organ dysfunction may be the first symptoms noted by clinicians when making [the] assessment [for sepsis]” [11].

It was the goal of this committee to “provide a conceptual and practical framework to define the systemic inflammatory response to infection, which is a progressive injurious process that falls under the generalized term ‘sepsis’ and includes sepsis-associated organ dysfunction” [11]. The use of multiple organ dysfunction syndrome defined by deranged organ function such that the body cannot heal without intervention has become commonplace in critical care literature and is the basis for the use of the SOFA [12, 14].

The revision in 2001 sought to improve the definition by including clinical symptoms and physical exam findings such as altered mental status, oliguria, decreased capillary refill, and hyperglycemia without known diabetes [11] (Fig. 2.1). The use

	<p>Infection<sup>a</sup>  Documented or suspected <i>and</i> some of the following<sup>b</sup>:</p> <p>General parameters  Fever (core temperature <math>&gt;38.3^{\circ}\text{C}</math>)  Hypothermia (core temperature <math>&lt;36^{\circ}\text{C}</math>)  Heart rate <math>&gt;90</math> bpm or <math>&gt;2</math> SD above the normal value for age  Tachypnea: <math>&gt;30</math> bpm  Altered mental status  Significant edema or positive fluid balance (<math>&gt;20</math> mL/kg over 24 h)  Hyperglycemia (plasma glucose <math>&gt;110</math> mg/dl or <math>7.7</math> mM/l) in the absence of diabetes</p> <p>Inflammatory parameters  Leukocytosis (white blood cell count <math>&gt;12,000/\mu\text{l}</math>)  Leukopenia (white blood cell count <math>&lt;4,000/\mu\text{l}</math>)  Normal white blood cell count with <math>&gt;10\%</math> immature forms  Plasma C reactive protein <math>&gt;2</math> SD above the normal value  Plasma procalcitonin <math>&gt;2</math> SD above the normal value</p> <p>Hemodynamic parameters  Arterial hypotension<sup>b</sup> (systolic blood pressure <math>&lt;90</math> mmHg, mean arterial pressure <math>&lt;70</math>, or a systolic blood pressure decrease <math>&gt;40</math> mmHg in adults or <math>&lt;2</math> SD below normal for age)  Mixed venous oxygen saturation <math>&gt;70\%</math><sup>b</sup>  Cardiac index <math>&gt;3.5</math> l <math>\text{min}^{-1}</math> <math>\text{m}^{-2}</math><sup>c,d</sup>  Organ dysfunction parameters  Arterial hypoxemia (<math>\text{PaO}_2/\text{FIO}_2 &lt;300</math>)  Acute oliguria (urine output <math>&lt;0.5</math> ml <math>\text{kg}^{-1}</math> <math>\text{h}^{-1}</math> or 45 mM/l for at least 2 h)  Creatinine increase <math>\geq 0.5</math> mg/dl  Coagulation abnormalities (international normalized ratio <math>&gt;1.5</math> or activated partial thromboplastin time <math>&gt;60</math> s)  Ileus (absent bowel sounds)  Thrombocytopenia (platelet count <math>&lt;100,000/\mu\text{l}</math>)  Hyperbilirubinemia (plasma total bilirubin <math>&gt;4</math> mg/dl or 70 mmol/l)</p> <p>Tissue perfusion parameters  Hyperlactatemia (<math>&gt;3</math> mmol/l)  Decreased capillary refill or mottling</p>
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<sup>a</sup> Defined as a pathological process induced by a micro-organism

<sup>b</sup> Values above 70% are normal in children (normally 75–80%) and should therefore not be used as a sign of sepsis in newborns or children

<sup>c</sup> Values of 3.5–5.5 are normal in children and should therefore not be used as a sign of sepsis in newborns or children

<sup>d</sup> Diagnostic criteria for sepsis in the pediatric population is signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature  $>38.5^{\circ}\text{C}$  or  $<35^{\circ}\text{C}$ ), tachycardia (may be absent in hypothermic patients) and at least one of the following indications of altered organ function: altered mental status, hypoxemia, elevated serum lactate level, and bounding pulses

**Fig. 2.1** Diagnostic criteria for sepsis; adapted from Levy, ICM, 2003;29:530–538

of clinician judgment may seem nebulous but at least one study demonstrated good inter-operator agreement between clinicians for identifying an infectious source in septic patients in the intensive care unit (ICU), though the clinical decision-making process becomes more complex and concordance diminishes as subsets of infections are studied [15, 16]. The authors explain that the thresholds chosen for their criteria were selected to reflect the “‘reality’ for bedside physicians” [11]. The word “some” is used purposefully to credit physician experience and detection of protean and subtle clinical changes in a patient. This aim was specifically prioritized over using a more clear-cut checklist for purposes of research enrollment [11]. This flexibility while reflecting a more accurate real-life scenario does not allow for easy standardization of the definition.

### ***2010 Merinoff Symposium***

Despite the further clarifications crafted at these conferences, it was felt that the definitions did not adequately capture the underlying complex molecular processes that drove the sepsis syndrome. The 2001 meeting had been notable for giving more weight to the host response of severe sepsis rather than the virulence of the specific microbe. This was a well-known concept dating back to William Osler who said “except on few occasions, the patient appears to die from the body’s response to infection rather than from [the infection itself]” [17]. However, these earlier definitions still did not address how infection differs from sterile inflammation as seen in severe burns and pancreatitis [18]. It is thought that on a molecular level, the inflammatory cascade triggered by trauma for example is similar to that caused by pathogens in regards to leading to cell death [19]. In 2010, the first meeting of the Global Sepsis Alliance with representatives from various national governments and media was held at the Merinoff symposium to create a “public definition” and a “molecular definition” of sepsis that focuses on the deranged host response to the microbial insult [20]. The results were the following:

1. *Definition of sepsis:* Sepsis is a life-threatening condition that arises when the body’s response to an infection injures its own tissues and organs. Sepsis leads to shock, multiple organ failure, and death, especially if not recognized early and treated promptly [20].
2. *Molecular definition of sepsis:* Host-derived molecules and foreign products of infection converge on molecular mechanisms that cause unbalanced activation of innate immunity. Foreign and endogenous molecules interact with pathogen recognition receptors expressed on or in cells of the immune system. Activation of pathogen recognition receptors culminates in the release of immune mediators that produce the clinical signs and symptoms of sepsis [20].

## ***2016 The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)***

The most recent definition of sepsis stems from a 2016 task force which resulted in a change in terminology [21]. Simple infection with signs and symptoms of the inflammatory response but without organ dysfunction, formerly defined as sepsis, is now defined as *infection*. *Sepsis* is now defined as infection with evidence of organ dysfunction (as evidenced by Sequential Organ Failure Assessment [SOFA] score > 2). Previously, this was the definition of *Severe Sepsis*, a term that will no longer be used. This change was instituted primarily because the field was already using sepsis to imply a patient deteriorating with infection and organ dysfunction, leading to considerable confusion between the terms sepsis and severe sepsis. The definition of *Septic Shock* refers to patients with infection who also have hypotension (MAP < 65 mmHg or systolic < 90 mmHg) and are receiving vasopressors and with a lactate > 2 mmol/L.

## **Difficulties in Defining Sepsis**

### ***Shortcomings of the SIRS Criteria***

The SIRS criteria are useful because they can facilitate enrollment for research purposes and have been adopted for identification of potentially septic patients but their utility is limited by the lack of specificity. Up to 90% of patients admitted to the ICU fit the criteria for SIRS [22]. In an editorial by Vincent et al., the authors point out fundamental limitations in the current definition of sepsis (SIRS criteria with infection), including, that while all patients with sepsis have a known or presumed infection, not all infected patients have a clinically appreciable physiologic response that can be characterized as a syndrome thus making it challenging to create a practical clinical definition of sepsis [23, 24].

Another concern regarding SIRS criteria is their utility in patients who were already thought to have an acute injury or infection [25]. Gaieski and Goyal thus contend that this method does not properly ascertain the ability of this tool to discriminate undifferentiated patients for early intervention [25]. SIRS does however, have the ability to capture a very high percentage of people with sepsis as studied by Rangel-Frausto, who looked at the spectrum of SIRS/septic shock in the general hospital admissions of an academic center and found 68% fit SIRS criteria, 26% developing sepsis, 18% severe sepsis, and 4% septic shock with an inversely proportionate rate of mortality [26]. Reflecting these beliefs, the 2001 consensus meeting concluded that SIRS captured too broad a population and as such, additional signs and symptoms were proposed to the description and definition of sepsis. Only recently has the field begun to move away from the use of SIRS, propelled by the 2016 consensus definition.

## Staging of Sepsis

Another problem with trying to define sepsis comes from the observation that sepsis appears to have stages that can differ significantly in terms of clinical features and immune system characteristics. In general, these stages can be thought of as initiation, amplification, and resolution of the response but as time goes on, it appears even these subcategories may be too general. The 2001 consensus statement acknowledged potential limitations to the definition including the inability to stage or prognosticate the host response to infection [11]. The authors acknowledged the overly sensitive nature of SIRS and proposed PIRO—a hypothetical model for staging sepsis using premorbid conditions (P), the causative infection (I), host response (R), and the severity of organ dysfunction (O) [11]. The PIRO model is a system that allows staging of sepsis to risk stratify patients for illness and also for potential response to therapy [11] (Fig. 2.2). Follow-up studies seem to validate the use of PIRO to risk stratify patients with suspected infection [27].

Similar to oncologic staging, PIRO staging factors criteria such as variable genetic susceptibility to illnesses. It was proposed that this model could also describe the host response to infection [11], for example, a genetic polymorphism that causes a more aggressive inflammatory response to an invading organism [11]. Additionally, early detection of a pathogen through sensitive assays of microbial genomics or transcriptomics would allow further characterization of the host response to infection. Although several studies validate PIRO, it remains to be seen whether this system is robust enough for consistent application in the future. The PIRO system is further limited by the lack of specific genotypic targets that can

Domain	Present	Future	Rationale
Predisposition	Premorbid illness with reduced probability of short term survival. Cultural or religious beliefs, age, gender	Genetic polymorphisms in components of inflammatory response (e.g., Toll-like receptor, tumor necrosis factor, interleukin 1, CD14); enhanced understanding of specific interactions between pathogens and host diseases	At the present, premorbid factors impact on the potential attributable morbidity and mortality of an acute insult; deleterious consequences of insult depend heavily on genetic predisposition (future)
Insult (infection)	Culture and sensitivity of infecting pathogens; detection of disease amenable to source control	Assay of microbial products (lipopolysaccharide, mannan, bacterial DNA); gene transcript profiles	Specific therapies directed against inciting insult require demonstration and characterization of that insult
Response	SIRS, other signs of sepsis, shock, C-reactive protein	Nonspecific markers of activated inflammation (e.g., prolactin or interleukin 6) or impaired host responsiveness (e.g., HLA-DR); specific detection of target of therapy (e.g., protein C, tumor necrosis factor, platelet-activating factor)	Both mortality risk and potential to respond to therapy vary with nonspecific measures of disease severity (e.g., shock); specific mediator-targeted therapy is predicated on presence and activity of mediator
Organ dysfunction	Organ dysfunction as number of failing organs or composite score (e.g., multiple-organ dysfunction syndrome, logistic organ dysfunction system, Sequential Organ Failure Assessment, Pediatric Multiple Organ Dysfunction, Pediatric Logistic Organ Dysfunction)	Dynamic measures of cellular response to insult – apoptosis, cytopathic hypoxia, cell stress	Response to preemptive therapy (e.g., targeting micro-organism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present

**Fig. 2.2** PIRO system for staging sepsis; adapted from Levy, ICM, 2003;29:530–538, CCM, 31(4):1250–1256, April 2003

be analyzed quickly and are of phenotypic significance. Once this technology is accessible to the majority of physicians, it could allow for tailored therapy and prognosticating ability.

### ***Problems with in Early Stage Sepsis***

Ideally, the criteria by which to recognize a patient suffering from a complex process such as sepsis should be one that is easily memorized, tabulated, and reproducible. The invariable difficulties with recognizing patients early in the disease course for quickly evolving and devastating disease processes such as pulmonary embolism, acute coronary syndrome, and cerebrovascular accidents, for example, have led to evidence-based protocols to allow early intervention when possible. Unfortunately, the dynamic host-pathogen interaction that produces sepsis has not lent itself to methodology with enough sensitivity and specificity to identify high-risk patients without a high false-negative rate or alarm fatigue.

Currently, the focus on the early identification of septic patients includes the use of electronic warning scores that can tabulate patient risk based on data available in the patient chart [28]. Various systems for using the electronic patient record have been studied to identify patients at risk for deterioration. The 2009 Joint Commission stipulated a goal to improve the identification and response to sick ward patients [29]. To implement these medical emergency teams, critical care outreach teams, and rapid response systems to manage sick patients with infectious complications, there needs to be a sensitive method for defining sepsis. This would allow crisis detection of new physiologic deterioration in patients at risk of harm who requires urgent response of a predetermined fashion, whether it is personnel, equipment, or knowledge to then correct the imbalance in needs and care [30, 31].

These warning alert systems have evolved from single parameter tracking and triggering that showed low sensitivity and specificity to multiple parameter system such as the Patient at Risk score, to aggregate weighted systems that take into account the degree of derangement as exemplified by the Modified Early Warning Score (MEWS), which has improved sensitivity and specificity [32]. The MEWS is based on vital signs and documentation of effect of end organ damage in the form of altered consciousness and urine output. There is significant overlap between these chosen variables and those outlined by the professional societies as part of the accepted sepsis criteria.

### ***Adoption of the Term “Septic” in Medical Culture***

Another barrier to effective use of sepsis definitions is the common use of the word sepsis or septic by physicians to describe patients who appear very ill and are usually suffering from infection with end organ damage or shock. Patients who simply have at least two of four SIRS criteria in addition to a suspected or proven infection usually are admitted to the general wards and not often described as “septic” despite



having fit the clinical definition prior to 2016. The colloquial use of the descriptor “septic” in medical culture is acknowledged in the 2001 guidelines [11]. Other challenges in identifying an effective term include the diverse physiologic responses to infection among individuals and lack of specific biomarkers.

## **Defining Sepsis Through Clinical or Administrative Data**

Reporting of sepsis worldwide and nationally relies on proper documentation. These data help determine epidemiology and trends for incidence, prevalence, mortality, and specific infectious processes that have clinical and research-based public health implications. Governing bodies such as the New York State Department of Health has passed legislation, requiring hospitals to implement guideline-based treatment of sepsis. In addition, this protocol requires that institutions use administrative data to report back to the state department of health regarding their adherence and risk-stratified mortality rates. The Centers for Medicare and Medicaid Services (CMS) has adopted the use of claims based data to ascertain hospital case mix index and other indicators for reimbursement. CMS has required public reporting of hospital outcomes as they relate to medical infections since 2003, when they implemented the Hospital Inpatient Quality Reporting (Hospital IQR) program, as part of Section 501(b) of the Medicare Prescription Drug, Improvement, and Modernization Act. Since that time, more outcome measures on admission diagnoses coding such as pneumonia have been evaluated as part of hospital compensation. The gradual conversion of documentation to electronic medical records has made administrative data use possible by searching diagnosis codes.

## ***Coding***

The accurate applicability of data gathered through the use of electronic medical records relies heavily on physician documentation and understanding of coding. Little formal training is done on proper coding and emphasis is placed for billing purposes. Several studies including a recent systematic review have shown that ICD codes are less accurate at capturing sepsis than are reference standards such as documentation in notes [33, 34]. In this era of access to vast stores of data, much important information can be gathered from administrative data, but this is ultimately limited by the accuracy of coding. Coding also has implications for reimbursement and coders, trained to comb charts and ascribe proper codes for billing may lack the perspective that accurate coding provides for research and epidemiologic purposes [35]. The particular instrument used to abstract data should be matched to the outcome being evaluated as different tools have lesser or greater sensitivity to capture the population of interest and will capture a sample of mixed purity. Accurate estimation of sepsis incidence will be important for resource allocation and public reporting [36].



Criteria

Given the previously mentioned limitations of using billing data to identify sepsis patients, there have been efforts to use other forms of data from the medical record. The methods have sought to use existing medical data or specific data input from the physician or nurse providers [33]. There have been few validated methods of medical record data extraction for estimating the incidence of sepsis. Even among these protocols there is great variation in estimates, as wide as threefold [36]. Over the last two decades, several groups have attempted to identify accurate instruments for utilizing administrative data, specifically the *International Classification of Disease 9* (ICD9). We anticipate that future studies will incorporate ICD10.

Angus Criteria

One of the first protocols using administrative data, the Angus criteria, was validated by comparing a nurse-driven identification of a population of patients with the clinical syndrome of sepsis [3]. The algorithm for the Angus criteria first looks to identify patients coded for severe sepsis or septic shock. If patients do not have this code, all discharge diagnoses are reviewed for an infection code, if present then procedure codes/diagnoses codes are checked for organ dysfunction codes. Upon clinical review, the false-positive charts were most commonly found to have a different etiology of the organ dysfunction than sepsis.

Iwashyna et al. conducted a single center validation of the Angus implementation [37] (Fig. 2.3). This group looked at all patients admitted to the general medical wards from 2009 to 2010, reviewed by three internal medicine hospitalists by a

	True Positives (n = 60)	False Positives (n = 32)
Cardiovascular	27.6%	20.0%
95% CI	8.6%, 46.4%	0.8%, 39.3%
Neurological	26.4%	37.9%
95% CI	0.2%, 52.7%	0.0%, 87.4%
Hematologic	11.9%	18.0%
95% CI	0.0%, 27.2%	0.2%, 35.8%
Hepatic	0.8%	2.0%
95% CI	0.0%, 2.5%	0.0%, 6.4%
Renal	82.6%	32.1%
95% CI	71.4%, 93.8%	4.0%, 60.1%
Respiratory	9.9%	0.0%
95% CI	2.5%, 17.3%	0.0%, 10.9%

These values incorporate sampling weights.  
CI indicates confidence interval.

**Fig. 2.3** Prevalence of organ dysfunction by ICD9 among true positive and false-positive hospitalizations meeting the Angus criteria; adapted from Iwashyna et al., Med Care. 2014 Jun;52(6):e39–43

structured instrument (gold standard was clinical judgment from chart review of randomly selected positive and negatively screened cases) [37]. This revealed over 3000 patients who met the criteria (13.5% of cases sampled) [37]. After review, the Angus was found to have a positive predictive value of approximately 70%, negative predictive value of 91.5%, with a sensitivity of 50% and specificity of 96% [37]. This captured mostly patients with severe sepsis but not exclusively and thus the authors point out that its limitations should be noted, especially for the purposes of use in research [37].

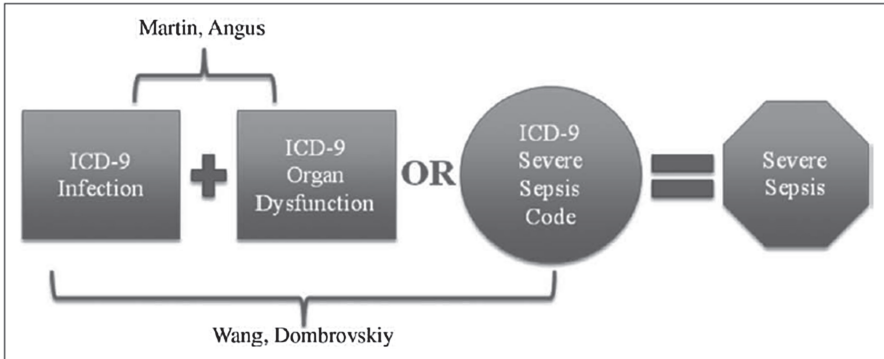
### **Martin Criteria**

A model created by Martin et al. sorts patients either by codes for septicemia, septicemic, bacteremia, disseminated fungal infection, disseminated candida infection or disseminated fungal endocarditis in addition to an organ dysfunction code or an explicit diagnosis: severe sepsis or septic shock [37]. The Martin implementation had a positive predictive value of 97.6% with a sensitivity of 16% [37]. The drawbacks to this instrument include the less formal use by physicians of the term “septicemic” (not requiring microbiologic data which is in discordance with the American Medical Association definition 2009 coding guidelines) [37]. Also, when it is used properly, it will miss immunologic and coagulopathic organ dysfunction caused by culture negative infection [37].

In this study, three trained hospitalists reviewed the charts sampled. This approach allowed for a more thorough study but highlights the lack of inter-operator agreement in chart review even for clinical judgment of sepsis, which was used as the gold standard for determination. Using the explicit criteria for diagnosis, there is a positive predictive value of 100% though sensitivity drops to less than 10% [37]. The authors point out that this is also limited to a single center and may vary across institutions [37].

### **Comparison of Different Methods**

The variability in cohorts identified by different methodologies for data abstraction has been seen not only in the United States but globally, as reported by Wilhelms et al. [38]. A retrospective study looking at data from 1987 to 2005 using both the Angus and Martin implementation yielded widely different patient groups (with a small percentage only [16.3%] being captured by both tools) [38]. It should be noted that Sweden did not have a specific code for severe sepsis at the time of this study. In addition, this study included data prior to the consensus statement from 1991 defining sepsis. Despite these limitations, there was a rising trend for capture of sepsis coding irrespective of methodology used [38]. Practices surrounding sepsis vary geographically as assessed by a survey-based study that demonstrated



**Fig. 2.4** Comparison of ICD classification systems; adapted from Gaieski et al. CCM 2013; 41:1167–74

different mortality based on place of admission to the ICU and different compliance with the sepsis bundle which may affect coding [39].

Comparing four methods head to head, Gaieski found that annual incidence of sepsis calculations varied up to 350%, with absolute values ranging from 300 per 100,000 to 1031 per 100,000 [36, 40, 41] (Fig. 2.4). This study was conducted over a 6 year period from 2004 to 2009 and there was an annual increase in incidence in sepsis independent of the method used [36]. ICD9 codes for sepsis, severe sepsis, and septic shock were not implemented until 2002, and data extractions using these terms were not examined until more recently. The divergence in estimates for the incidence of sepsis may be attributed to the increase in ICD9 codes for sepsis, which doubled during that period [36].

This group performed a retrospective cohort study using the nationwide inpatient sample (NIS) which is a public database sponsored by the Agency for Healthcare Research and Quality. In 2009, 44 states participated, capturing over 1000 hospitals and eight million admissions and is thought to represent one-fifth of the national sample [36]. The four techniques used were Angus, Martin, Wang, and Dombrovskiy, the former two using ICD9 codes for infection and organ dysfunction to identify severe sepsis and the latter pair using either infection plus organ dysfunction or a specific severe sepsis code. Gaieski mentions that there is more variability in the ability to capture infection with the ICD9 which includes over 1000 codes infection versus organ dysfunction that only encompasses 13 by comparison [36].

Annual growth was estimated by comparing 2009 data to 2004 data and assuming proportional increase. The average age of septic patients was similar among the four tools, while Angus and Wang captured more females, Wang and Dombrovskiy captured patients with longer average length of stay and number of organ dysfunctions. In this study period, approximately 40 million patients were found, thought to represent 20% of the national average [36]. Mortality estimates were described by total number of deaths and also case fatality rate and it was found that overall mortality increased, however case fatality rate decreased over 6 years [36]. This is in part due

Code Abstraction Method	Sensitivity to Identify Severe Sepsis Cases ( <i>n</i> = 1735)*	95% Confidence Interval
1. Severe sepsis (ICD-9-specific coding method, 995.92)	20.5%	18.6% to 22.4%
2. Combining end-organ dysfunction and infection codes (the Angus coding method)	47.2%	44.8% to 49.5%

Code Abstraction Method	Sensitivity to Identify Septic Shock Cases ( <i>n</i> = 321)*	95% Confidence Interval
1. Severe sepsis (ICD-9-specific coding method, 995.92)	49.5%	44.0% to 55.0%
2. Septic shock (ICD-9-specific coding method, 785.52)	42.4%	37.0% to 47.8%
3. Combining end-organ dysfunction and infection codes (the Angus coding method)	75.1%	70.4% to 79.8%

ICD-9 = International Classification of Diseases, 9th Revision.

\*Cases of septic shock (*n* = 321) were encompassed within the severe sepsis (*n* = 1735) population.

Categorical data are presented as proportions.

**Fig. 2.5** Sensitivities of two difference code abstraction methods for identifying cases of severe sepsis and septic shock determined by patient-level data; adapted from Whittaker SA et al., *Crit Care Med.* 2013;41(4):945–53

to improved interventions for sepsis such as early identification, fluid resuscitation, and timely administration of antibiotics despite a rise in the number of patients suffering from sepsis.

Overall, although Angus and Wang may be more sensitive and therefore identify patients with lower severity of illness, Dombrovskiy and Martin are less sensitive but capture more severely ill patients [36]. Only a small percentage of patients identified with the four instruments were assigned a specific sepsis code [36]. It was also found that of those patients with septic shock only half also were coded for severe sepsis [36]. This implies that the singular use of either the severe sepsis or septic shock code could greatly underestimate the incidence of both. Of those with specific sepsis coding, more were likely to have had higher severity of illness and identified with Dombrovskiy and Martin than with Angus and Wang [36]. A similar study in Sweden by Wilhelms found a large variation in capture based on which methodology was used for data abstraction [38]. It is important to note, however, in Gaeiski's study, organ dysfunction and mortality could not be attributed specifically to sepsis as individual charts were not made available to the authors [36].

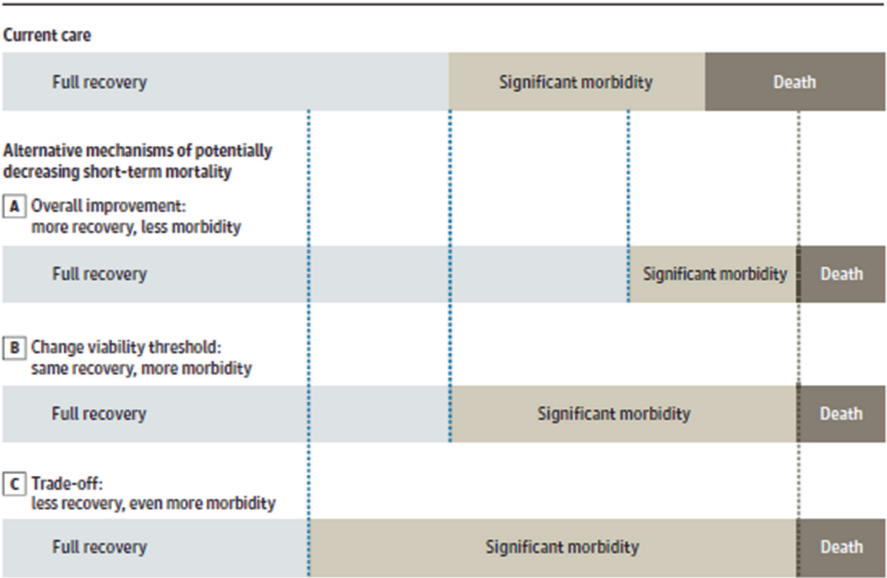
Whittaker et al. looked to study the sensitivity of various methods and assess whether patient outcome differed among variable coding [35] (Fig. 2.5). This retrospective cohort focused on ED admissions and validated coding through chart review. It was found that age, gender, and race did not affect specific coding for sepsis [35]. Of 1735 patients admitted with severe sepsis or septic shock, only 21.5% received a corresponding ICD9 code from 2005 to 2009 [35]. Similar to prior studies, the Angus classification was more sensitive than specific diagnostic coding for severe sepsis and septic shock and that there was no added benefit to using a combined approach [35]. Of those admitted directly to the ICU, 36% received the specific ICD9 code versus 6% of ward patients who fulfilled the criteria [35]. In addition, lower presenting systolic blood pressure, higher serum lactate measurements, higher Acute Physiology and Chronic Health Evaluation (APACHE-II) scores all correlated with proper coding [35].

*Trends in Mortality and Disability in Sepsis*

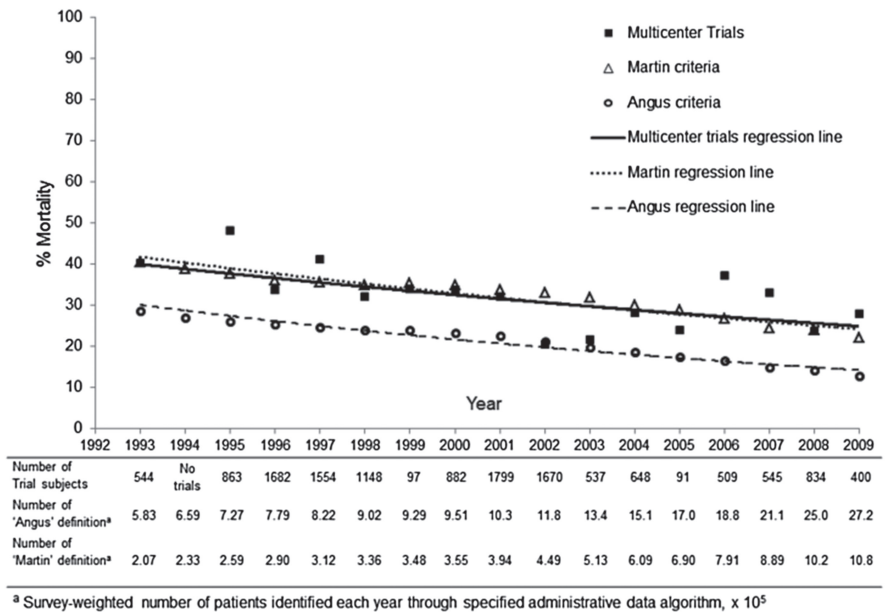
Given what appears to be a decline in mortality in sepsis, the impetus for accurately identifying hospitalized patients and therefore tracking trends in sepsis include redistribution of funds to disease states that are emerging public health issues or with increasing mortality and morbidity [42]. In addition, this further informs the accurate measurement of quality improvement and therapeutic intervention outcomes (accurately identifying secular trends in sepsis mortality) [42] (Fig. 2.6).

In an editorial by Iwashyna and Angus, the authors discuss the role of the Will Rogers effect as initially published by Feinstein et al. that describes the role of increased awareness and testing as well as the inclusion of less sick patients into the category of severe sepsis, which might then give the appearance of increased incidence and improved mortality [43]. Feinstein and colleagues described this phenomenon as it relates to lead time bias for cancer diagnosis and prognosis but is applicable to sepsis as pointed out by Iwashyna and Angus, who also suggest that increased awareness may influence changes in practice, not only in terms of coding, but for increasing admission to ICUs [44]. This may account for the observation that the initial estimate of 750,000 of sepsis present in 1996 has increased through the years to upward of three million [3, 36].

A meta-analysis to estimate the mortality trends in severe sepsis by Stevenson et al. compared clinical trial data from usual care group in multicenter sepsis trials searched on MEDLINE from 1991 to 2009 and data extraction from NIS samples



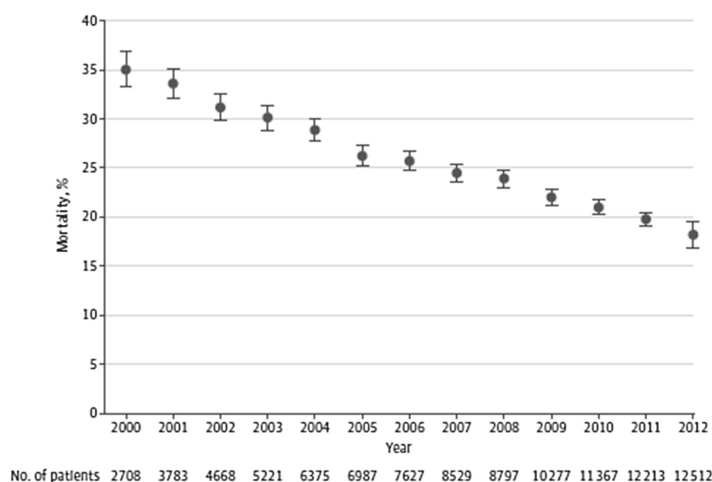
**Fig. 2.6** Potential mechanisms of decreasing short-term mortality among patients across a distribution of illness severity; adapted from Iwashyna TJ, Angus DC. JAMA. 2014;311(13):1295–7



**Fig. 2.7** Mortality trends in severe sepsis using martin and Angus criteria; adapted from Stevenson et al., Crit Care Med. 2014 Mar;42(3):625–31

from 1993 to 2009, using both Angus and Martin definitions showed a similar trend in decrease in case-specific mortality from sepsis in both arms (with a sample size of 14,418, adjusted for case mix index among institutions, stratified by severity of illness by several scoring systems) [42] (Fig. 2.7). This study was conducted because of the suggestion that decreasing case-specific mortality was attributed to the way in which ICD9 coding was utilized. Coding of less severe cases of sepsis would result in spurious decline in case fatality rate [42, 45–47]. Increase in coding for sepsis might in part be financially driven [36]. Another phenomenon to explain this trend is discharge from hospital to acute care prior to hospital death (increased survival to discharge without significant improvement in functional status from prior). Kumar et al. show significant increase in discharge to skilled nursing facilities from 2000 to 2007, using the Martin classification of severe sepsis on the NIS cohort. Interestingly, they also note the increase in practice of appropriate transition to comfort care in certain critically ill patients which would then magnify the decline of in-hospital mortality [48]. One concern about using short-term mortality outcomes as primary end points to critical care literature is the effect of discharging increasingly debilitated patients to long-term care facilities. Iwashyna and Angus describe the “mortality/morbidity trade off” when choosing a “viability threshold,” which is defined as the “degree of severity of illness beyond which death is unavoidable” [44] (Fig. 2.8).

These estimates are subject to inaccuracies related to the way in which the data is abstracted. Kaukonen and coauthors worked to eliminate some inflation bias by using a bedside nurse to score and identify severe sepsis after the initial abstraction



**Fig. 2.8** Mean annual mortality in patients with severe sepsis; adapted from Kaukonen KM et al., JAMA. 2014;311(13):1308–16

through administrative claims to capture the patients admitted to the ICU with infection [49]. The authors account for secular change in trends of mortality by comparing death in sepsis to critically ill patients as a whole and also by adjusting for death by the APACHE III score [49].

## Future Directions

In daily practice, clinicians often use the word “septic” to describe a patient who appears toxic and by strict definition usually qualifies as having severe sepsis as evidenced by organ dysfunction usually among the neurologic, cardiovascular, pulmonary, renal, and hepatic or coagulation systems. The 2001 review cited the European Society of Intensive Care Medicine/Society of Critical Care Medicine survey that demonstrated that 67% of physicians were concerned about not having a common definition of sepsis and 17% of those interviewed provided a unified definition of sepsis despite the consensus statement produced in 1991 [5]. Gaieski and Goyal proposed biomarker use, genetic profiling, and/or severity scores with bacterial assays to bolster our diagnostic ability [25]. The hope is to put sepsis diagnosis more in line with diseases such as acute myocardial infarction for which there is a serum marker for testing [11]. Unfortunately, to date, no single or panel of biomarkers has been shown to have the balance of sensitivity and specificity to be clinically useful. The current sepsis definition may cause a high false-positive rate; however, we must decide as physicians whether a life-threatening illness is better served by a simplified over-sensitive diagnostic tool or the one that may have a higher positive predictive value for serious illness but may not capture a sizeable portion of patients with the potential to become more ill and who may benefit from early intervention.



## Conclusions

As outlined in this chapter, there are various methods for defining sepsis and estimating the incidence and trends in mortality from administrative data. With the advent of the electronic medical record, vast amounts of data can be sorted to provide statistics on large samples. Using administrative datasets for determination of sepsis incidence and prevalence has significant flaws, which leads to great variability and ultimately, inaccuracy in the estimate of sepsis. Earlier studies quoted a mortality rate between 28% and 50% [50]. The true estimate of sepsis-related mortality is now in flux as the traditionally accepted values may be imprecise from variations in coding, inclusion criteria for randomized, controlled trials, and other factors.

Even with the recent revision of sepsis definitions, the ability for clinicians to identify patients with sepsis early remains a significant challenge. Twenty five years after the first publication establishing sepsis definitions the field still lacks proven, objective tools for diagnosing sepsis. For now, clinicians caring for patients with sepsis must wait and hope that, similar to the fields of cardiology and oncology, further research will provide the objective means necessary for early, accurate diagnosis and treatment.

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