The International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit

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Objective: **To develop definitions of infection that can be used in clinical trials in patients with sepsis.**

Context: **Infection is a key component of the definition of sepsis, yet there is currently no agreement on the definitions that should be used to identify specific infections in patients with sepsis. Agreeing on a set of valid definitions that can be easily implemented as part of a clinical trial protocol would facilitate patient selection, help classify patients into prospectively defined infection categories, and therefore greatly reduce variability between treatment groups.**

Design and Methods: **Experts in infectious diseases, clinical microbiology, and critical care medicine were recruited and allocated specific infection sites. They carried out a systematic literature review and used this, and their own experience, to prepare a draft definition. At a subsequent consensus conference, rapporteurs presented the draft definitions, and these were then refined and improved during discussion. Modifications were circulated electronically and subsequently agreed upon as part of an iterative process until consensus was reached.**

Result: **Consensus definitions of infection were developed for the six most frequent causes of infections in septic patients: pneumonia, bloodstream infections (including infective endocarditis), intravascular catheter-related sepsis, intra-abdominal infections, urosepsis, and surgical wound infections.**

Conclusions: **We have described standardized definitions of the common sites of infection associated with sepsis in critically ill patients. Use of these definitions in clinical trials should help improve the quality of clinical research in this field. (Crit Care Med 2005; 33:1538–1548)**

KEY WORDS: definition; infection; sepsis; severe sepsis; septic shock; sepsis syndrome; intensive care unit; critical care; clinical trials

Infection is a major problem in the intensive care unit (ICU), and infection is an integral part of sepsis. Almost any epidemiologic or intervention study that deals with infection or its consequences will need to include definitions of infection at various sites as part of its protocol. Although there are a number of published systems that suggest working definitions of infection that can be used, for instance for infection control purposes (1), there are no universally agreed upon definitions of infection as they apply to patients with severe sepsis or septic shock in the ICU. Some of the infections that occur in the ICU can easily be included within existing definitions. For instance, the use of the standard microbiological definition of a urinary tract infection as $>10^5$ colony-forming units (cfu)/mL of pure growth of an organism is not unreasonable for a noncatheterized ICU patient. However, in many more common and more serious infections that are encountered in the ICU, these "standard" definitions are neither appropriate nor particularly helpful. The most obvious example is pneumonia, which presents particular problems.

It would greatly improve the quality and comparability of clinical trials of sepsis if there were a set of definitions for infection, customized for patients in the ICU, that could find widespread acceptance. Therefore, the International Sepsis Forum (ISF) convened an international consensus conference to formulate a set of definitions of infections that occur commonly in the ICU. The purpose of these proposed definitions is to determine whether the infection is likely to be present in patients who have the clinical syndrome of severe sepsis or septic shock. The definitions have been developed specifically for use in clinical studies of sepsis and thus are intended to maximize specificity and minimize false positives. It is recognized that in clinical practice, a different definition might be used to define who should receive antibiotic therapy, but this type of more sensitive definition will have more false positives.

METHODS

A panel of international experts in the fields of intensive care medicine, infectious diseases, and clinical microbiology, all of whom had a particular interest in sepsis, were invited to participate in a 2-day consensus conference held in Coral Gables, FL (November 8 and 9, 2003). The ISF provided logistic support for the meeting, but not all of the panelists were members of the ISF.

Before the panel convened, the joint chairs (JC and TC) used published epidemiologic databases to identify the six most common sites

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of infection that occurred in the ICU (2). (Although other sites, such as central nervous system infections, do sometimes give rise to shock, they are rare and it was agreed not to include them.) Each of the chosen sites was then allocated to two members of the panel who would act as rapporteurs for the group. For each infection site, the rapporteurs were asked to carry out a literature review and to seek expert advice and opinion to provide a draft definition. The remit from the co-chairs was to develop a definition that was based on published evidence, insofar as that was possible, and that was suitable for use as part of a clinical trial in septic patients. It was important that the definition was practicable and did not require specialist or unusual equipment (e.g., a definition based on a polymerase chain reaction method would be unsuitable). General clinical features of infection (e.g., fever, tachycardia, etc., as used in the current consensus definitions of sepsis and septic shock) (3) were regarded as a given and did not need to be reiterated for each site. The draft definitions drawn up by the rapporteurs were circulated to the entire group before the consensus conference.

Rapporteurs presented the draft definitions to the conference, and these were refined and improved during discussion. Modifications were circulated electronically and subsequently agreed upon as part of an iterative process over a period of approximately 7 months until consensus was reached.

RESULTS

The six most common infection sites were identified as pneumonia, bloodstream infections (including infective endocarditis), intravascular catheter-related sepsis, intra-abdominal infections, urosepsis, and surgical wound infections (2). In the following sections we provide a brief rationale and background and the suggested formulation of each definition.

Pneumonia

For the purposes of defining whether pneumonia is present or absent, it is not necessary to make the distinction between community-acquired pneumonia (CAP), health care-related pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia (VAP), although their associated risk factors and presentations differ (4–7).

Controversy continues about how to best diagnose VAP, but specificity is improved only after microbiological culture data are obtained, information that is seldom available when patients are first evaluated for the etiology of sepsis symptoms (6, 8, 9). Therefore, the definition is designed to maximize the likelihood of the patient having respiratory infection, using clinical criteria, but the initial diagnosis of pneumonia can be modified once microbiological data become available. With such data, pneumonia can be classified, *post hoc*, as falling into one of three categories (Table 1):

Microbiologically confirmed or definite: Clinically present with abnormal chest radiograph and the isolation of a likely pulmonary pathogen, or the isolation of a likely/possible pulmonary pathogen in high concentration from a quantitative lower respiratory tract sample, or positive serology (4, 5, 7, 10).

Probable: Clinically present with abnormal chest radiograph but without microbiological or serological confirmation

Possible: Abnormal chest radiograph of uncertain cause, with low or moderate clinical suspicion of pneumonia, but with microbiological or serologic criteria of definite or probable pneumonia

For enrollment in sepsis trials, it may not be possible to include only patients with microbiologically confirmed clinical infection since the use of antibiotics (either urgently for sepsis, or before the onset of sepsis) can interfere with the yield of microbiological testing. For sepsis trials, we propose that patients with clinical pneumonia be included initially and that the trial design specify whether microbiological confirmation has been obtained *post hoc*, so that the reader can determine the degree of generalizability to any other patient population. Most clinical trials in sepsis are designed as "intent to treat," and hence all patients are included in the primary data analysis. However, *post hoc* information, although not useful to draw efficacy conclusions, may be useful to examine subsets of pneumonia patients for hypothesis generation.

The clinical diagnosis of pneumonia requires the presence of a radiographic infiltrate, with suspicion that the infiltrate is caused by infection. This can be determined by measurements of fever, white blood cell count, degree of sputum purulence, degree of oxygenation impairment, and the presence of potential pathogens in lower respiratory tract secretions (9, 11, 12). In CAP, the diagnos-

Table 1. Pneumonia

Microbiologically confirmed: The patient must have a new or progressive radiographic infiltrate, along with a high clinical suspicion of pneumonia (or a CPIS of ≥6, using a Gram stain of a lower respiratory tract sample) plus a definite cause established by the recovery of a probable etiologic agent from a) an uncontaminated specimen (blood, pleural fluid, transtracheal aspirate, or transthoracic aspirate); b) the recovery from respiratory secretions of a likely pathogen that does not colonize the upper airways (e.g., *Mycobacterium tuberculosis*, *Legionella* species, influenza virus, or *Pneumocystis jiroveci (carinii)*; c) recovery of a likely/possible respiratory pathogen in high concentrations using quantitative cultures of a lower respiratory tract sample (endotracheal aspirate, BAL, or protected specimen brush); or d) positive serology (4, 5, 7, 10).

Probable: The patient must have a new or progressive radiographic infiltrate along with a high clinical suspicion of pneumonia (or a CPIS of ≥6, using a Gram stain of a lower respiratory tract sample) plus detection (by staining or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, endotracheal or bronchoscopic aspirate, or quantitatively cultured bronchoscopic BAL fluid or brush catheter specimen), but in concentrations below the diagnostic threshold, or the presence of a negative lower respiratory tract culture if collected within 72 hrs after starting a new antibiotic regimen (61).

Possible: Abnormal chest radiograph of uncertain cause, in a patient with a low or moderate clinical suspicion of pneumonia, but with microbiological or serological evidence of definite or probable pneumonia (as defined above).

CPIS, clinical pulmonary infection score; BAL, bronchoalveolar lavage.

The CPIS scoring system grades each of the six features on a scale from 0 to 2, as follows: tracheal secretions: 0 = rare, 1 = abundant, 2 = purulent; radiographic infiltrates: 0 = absent, 1 = patchy or diffuse, 2 = localized; fever (°C): 0 = ≥36.5 and ≤38.4, 1 = >38.4 and ≤38.9, 2 = >38.9 or <36; leukocytosis (/mm^3): 0 = ≥4000 and ≤11,000, 1 = <4000 or >11,000, 2 = <4000 or >11,000 and ≥500 band forms; Pa_{O_2}/F_{IO_2}: 0 = >240 or acute respiratory distress syndrome (ARDS), 2 = ≤240 and no ARDS; microbiology: 0 = negative; 2 = positive.

tic sensitivity and specificity of each of these components have not been formally investigated; a new infiltrate plus the presence of fever, and at least two of purulent sputum, cough, change in leukocyte count, and impaired oxygenation, would be enough for the diagnosis of probable pneumonia. Rapid diagnostic tests such as *Legionella* or pneumococcal urinary antigen and newer tests such as soluble triggering receptor expressed on myeloid cells (13) may provide early data about etiology, although such tests are not always widely available and require full validation. Serologic testing for *Legionella*, *Mycoplasma*, and *Chlamydophila pneumoniae* is available but generally requires collection of acute and convalescent samples to look for a fourfold rise in titer. Blood and pleural cultures, if positive, can be diagnostic of a bacterial etiology. In the diagnosis of VAP and severe CAP, these six components have been combined into the clinical pulmonary infection score (CPIS), and although this tool has not been used in other types of pneumonia, it includes all of the clinical features used to diagnose pneumonia (9, 11). For the purpose of a more specific (rather than sensitive) definition of any form of pneumonia, the patient should have a CPIS of $\geq$6 (Table 1).

In its original description, the microbiological criteria used for the CPIS were culture results from a lower respiratory tract sample, but one recent study calculated the score using a Gram stain of a bronchoalveolar lavage or blind protected telescoping catheter sample and scored the results as either positive or negative. Using this approach, the CPIS for patients with confirmed VAP was significantly higher than the value for nonconfirmed VAP (12).

The probability of pneumonia should be assessed *post hoc*, once culture data are available, and the presence of a positive quantitative culture of a lower respiratory tract sample (at a threshold of 10^3 for protected specimen brush, 10^4 for bronchoalveolar lavage, and 10^5–10^6 for endotracheal aspirate) increases the probability that pneumonia is present (14–16).

Bloodstream Infections

Bloodstream infections (BSIs) account for 30–40% of all cases of severe sepsis and septic shock (2). However, the incidence of BSI as a cause of severe sepsis is probably underestimated in the hospital setting, since blood cultures are frequently drawn from patients treated with broad-spectrum antibiotics. Conventionally, BSIs have been divided into two categories: a) primary BSI comprising BSI of unknown origin in patients without an identifiable focus of infection, and intravascular catheter-related BSI; and b) secondary BSI defined as a BSI caused by a microorganism related to an infection at another site. The proportion of primary BSI reported in the literature varies broadly between studies, ranging from <5% to >30% (2, 17–21). This wide variation reflects differences of study aim and design (i.e., epidemiologic studies vs. sepsis treatment trials, prospective vs. retrospective studies) and of definitions (i.e., limited to BSI of unknown origin in some studies, while also including intravascular access device-related BSI in other studies).

Landmark studies performed in the 1980s and 1990s have provided very helpful definitions of BSI that have been used by numerous investigators (17, 20). In recent years, the definitions of nosocomial infections of the Centers for Diseases Control and Prevention (CDC) have been the gold standard used in most epidemiologic studies. The latest update of these definitions was published in 1996 (1), in which BSIs were divided into laboratory-confirmed BSI and clinical sepsis. Albeit widely used, there are several problems with the CDC definitions. Designed for nosocomial infections, these definitions are not suited for community-acquired infections. The definitions have not been updated since 1996 and make reference to obsolete microbiological diagnostic tools, such as detection of bacterial antigens in blood. The CDC document does not provide a definition for secondary BSI, nor does it address the concept of repeated episodes of BSI. Indeed, in critically ill ICU patients, multiple episodes of BSI frequently occur that may be caused by the same (i.e., persistent or relapsing BSI) or by different microorganisms (i.e., reinfection). Finally, one of the criteria used by the CDC to define BSI requires that appropriate antimicrobial therapy be instituted by a physician. Clearly, BSI should be defined independently of the physician's decision to initiate or withhold antimicrobial therapy. In summary, the existing CDC definitions have a number of limitations when applied to clinical sepsis studies.

Several studies in patients with sepsis syndrome have examined which aspects of the history, clinical symptoms and signs, and laboratory variables might help predict the presence of a BSI (22–25). In general, prediction models using these factors are characterized by a relatively high specificity but a very low sensitivity. Misclassifications are frequent, and the clinical utility of these predictive models remains to be demonstrated.

Definitions for the principal clinical entities—a) BSI of unknown origin or primary BSI and b) secondary BSI—are given in Tables 2 and 3.

Infective Endocarditis

Infective endocarditis accounts for about 1% of all cases of severe sepsis and is associated with a mortality rate of 33% (26). Despite their wide acceptance, the classic von Reyn criteria (23) for diagnosis of infective endocarditis were not well suited for clinical use. In 1994, Durack et al. (27) proposed new diagnostic criteria for infective endocarditis, referred to as the Duke criteria, based on microbiological data and echocardiographic imaging findings. According to these criteria, patients are classified into three diagnostic categories (definite, possible, and rejected infective endocarditis). The usefulness of these criteria in assessing patients suspected of infective endocarditis has been validated by numerous studies. Recently, modifications of the Duke criteria have been proposed to take into account several identified shortcomings of the original criteria, including the increasing diagnostic role of transesophageal echocardiography, the relative risk of infective endocarditis in BSI due to *Staphylococcus aureus*, the high number of patients categorized as having possible infective endocarditis, and a poor diagnostic sensitivity in suspected cases of Q fever endocarditis (28). Additional modifications have been proposed but have not been prospectively evaluated. Therefore, the proposed definitions of infective endocarditis are those based on the modified Duke criteria proposed by Li et al. (28).

Catheter-Related Sepsis

The diagnosis of catheter-related infection (CRI) is often a diagnosis of exclusion, at least at the time of enrollment, since the definitive diagnosis will only be possible in most instances once

Table 2. Bloodstream infection (BSI) of unknown origin (i.e., primary BSI)

Patient must meet the following two criteria:
Patient has a recognized pathogen (defined as a microorganism not usually regarded as a common skin contaminant, i.e., diphtheroids, *Bacillus* species, *Propionibacterium* species, coagulase-negative staphylococci, or micrococci) cultured from one or more blood cultures
or
A common skin contaminant (e.g., diphtheroids, *Bacillus* species, *Propionibacterium* species, coagulase-negative staphylococci, or micrococci) cultured from two or more blood cultures drawn on separate occasions (including one drawn by venipuncture)
and
The organism cultured from blood is not related to an infection at another site, including intravascular-access devices

Table 3. Secondary bloodstream infection (BSI) (other than catheter-related BSI)

Patient must meet the following two criteria:
Patient has a recognized pathogen defined as a microorganism different from a common skin contaminant (i.e., diphtheroids, *Bacillus* species, *Propionibacterium* species, coagulase-negative staphylococci, or micrococci) cultured from one or more blood cultures
The organism cultured from blood is related to an infection with the same organism at another site

culture results are available (i.e., 24–48 hrs after clinical suspicion of CRI and enrollment in a clinical trial), together with the confirmed absence of other sources. Clinical findings are too nonspecific to establish a diagnosis of catheter-related sepsis, and many more patients are suspected of having a CRI than have a confirmed CRI (29, 30). Therefore, to decrease the probability that patients without CRI are enrolled in a clinical trial, we have focused on identifying those patients at the highest risk of CRI.

Ideally, when bacteremia occurs in a patient having an indwelling catheter and no other obvious source is identified, confirmation of whether bacteremia originates from the catheter (i.e., is "catheter-related") or is secondary to another source must be sought. This is done by taking appropriate cultures which may or may not require catheter removal (31). A clinical suspicion of catheter infection in the presence of otherwise unexplained severe sepsis or septic shock, however, should prompt catheter removal (29) and appropriate cultures of the catheter tip (i.e., quantitative or semiquantitative catheter segment culture) (32, 33), blood cultures (at least one peripheral and one central blood culture), and exit site or hub cultures depending on the presentation (Fig. 1).

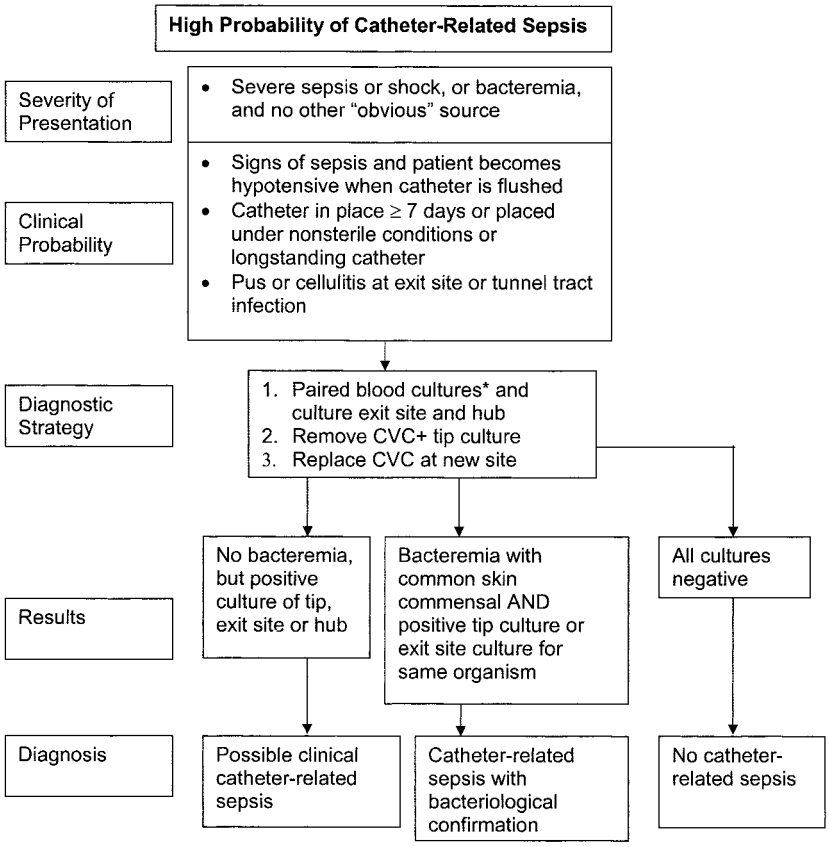

Figure 1. Diagnostic strategy for suspected catheter-related sepsis. *CVC*, central venous catheter. *A minimum of two blood culture sets are required, including at least one set of central and peripheral blood cultures taken simultaneously.

As shown in Figure 1, the clinical probability of CRI increases when a catheter has been in place ≥7 days, and in particular when a catheter has been longstanding (e.g., in place ≥21 days) or has been placed using nonsterile technique. In addition, although a rare occurrence, hypotension upon flushing the catheter is a strong sign that the catheter is infected. Local signs at the catheter exit site also increase the clinical probability of CRI. Local signs suggestive of CRI include, in increasing order of specificity, erythema or induration extending ≥2 cm of the catheter exit site, cellulitis along the subcutaneous tract of the catheter, and pus at the catheter entry site. Whereas the presence of pus is virtually diagnostic of infection, the other signs are nonspecific. The majority of CRI occurs in the absence of local symptoms.

In definitions used for CRI surveillance purposes, all bacteremias originating from patients who have a central venous catheter in place and no other identifiable source of infection are classified as catheter-associated bacteremia (34). This definition is sensitive but nonspecific. For the purposes of enrolling patients with sepsis in clinical trials, only patients whose bacteremia is actually sec-

ondary to catheter infection and intravascular seeding from a colonized catheter should be included. The most challenging problem that arises when evaluating a patient with possible catheter-related bacteremia is ascribing a sepsis syndrome to catheter infection when bacteremia is due to a common skin commensal and only one positive blood culture (central or peripheral) is available or has been obtained. In this situation, repeat cultures, with culture of the catheter tip, must be performed to confirm catheter-related bacteremia. The likelihood of catheter-related bacteremia will depend on the microorganism, the number of bottles taken in a set, and the clinical picture. True confirmation that the catheter is the source of infection requires that the same organism is grown from peripheral blood and the catheter segment or that a central blood sample is read as positive ≥2 hrs earlier than a peripheral blood sample inoculated at the same time, or there is a differential count of >5:1 in favor of the central sample (35). When such information is not available for technical reasons (lack of cultures, defective processing), the positive blood culture either is a contaminant or, if viewed as clinically significant and no other source has been identified, is termed "catheter-associated bacteremia."

Catheter infection rarely causes severe sepsis in the absence of bacteremia; however, blood cultures may not grow organisms in some patients receiving antibiotics. The catheter tip, exit site, or hub will often grow organisms. As shown in Figure 1, we define cases falling into this category as "possible clinical catheter-related sepsis." This diagnosis is usually made in retrospect, since it requires a positive (semi-) quantitative catheter tip or segment culture in a patient with clinical sepsis and no other apparent source than the catheter and the sepsis resolves within 48 hrs of catheter removal in the absence of new antibiotic therapy.

Definite catheter-related sepsis with bacteriologic confirmation is defined in Table 4 along with different methods for microbiological confirmation of the etiology of the infection.

Intra-Abdominal Infections

Intra-abdominal infections comprise a very heterogeneous group of infectious processes that share an anatomical site of origin between the diaphragm and the pelvis. Their clinical course is dictated by a number of infection-related factors including the microbiology, the anatomical location, the degree of localization, and the presence of correctable anatomical

Table 4. Catheter-related sepsis with bacteriologic confirmation

Definite catheter-related sepsis with bacteriologic confirmation is defined as at least one peripheral positive blood culture and one of the following:
- A positive semiquantitative (>15 colony-forming units [cfu]/catheter segment) or quantitative (≥10^3 cfu/catheter segment) catheter tip culture (i.e., catheter colonization), whereby the same microorganism (species and antibiogram) is isolated from the catheter segment and peripheral blood
- A positive hub or exit site culture growing the same microorganism as peripheral blood

or
- Positive paired central and peripheral blood cultures growing the same organism, where the central blood culture is positive ≥2 hrs earlier than the peripheral blood culture or has five times the growth of the peripheral blood culture

Table 5. Primary peritonitis

Primary peritonitis (also referred to as spontaneous bacterial peritonitis) is defined as a microbial infection of the peritoneal fluid in the absence of a gastrointestinal perforation, abscess, or other localized infection within the gastrointestinal tract

Microbiologically confirmed: the presence of a clinically compatible presentation of primary peritonitis with the isolation of microbial pathogens (in peritoneal fluid or blood) along with evidence of acute inflammatory reaction within the peritoneal fluid (i.e., >500 leukocytes/mL) with a neutrophilic predominance, an ascitic fluid pH of <7.35 (arterial to ascitic pH difference of >0.1), or a lactate concentration of >2.5 mg/L

Probable: Clinically appropriate setting with evidence of an inflammatory ascitic fluid (>500 leukocytes/mL with a neutrophil predominance) in the presence of a positive Gram stain but negative peritoneal fluid cultures or in the presence of a positive blood culture for a pathologic organism with inflammatory cells in ascitic fluid

Possible: A compatible clinical illness with an inflammatory peritoneal fluid (>500 leukocytes/mL) in the absence of a positive culture (in peritoneal fluid or blood) or Gram stain

Table 6. Secondary peritonitis

Secondary peritonitis is a microbial infection of the peritoneal space following perforation, abscess formation, ischemic necrosis, or penetrating injury of the intra-abdominal contents

Microbiologically confirmed: Isolation of one or more microbial pathogens found in the peritoneum or the blood >24 hrs after a gastrointestinal perforation of the stomach, esophagus or duodenum, or any perforation of the small bowel distal to the ligament of Treitz. Spillage of luminal contents during an operative procedure is not sufficient evidence of perforation that allows for definitive diagnosis of peritonitis. Furthermore, a penetrating abdominal wound or documented perforation that is surgically repaired within 12 hrs of its occurrence is not sufficient evidence to support diagnosis of secondary bacterial peritonitis.

Probable: Compatible clinical illness associated with documented evidence of perforation (free air in the abdomen on radiographic studies or surgical confirmation of peritoneal inflammation following luminal perforation in the absence of microbiologically confirmed peritonitis). A Gram stain in the absence of a positive culture from the peritoneum would be considered probable secondary bacterial peritonitis.

Possible: Upper gastrointestinal perforation or penetrating abdominal trauma that is surgically repaired without further evidence of microbiologic confirmation or clinical signs or symptoms supportive of a diagnosis of bacterial or fungal peritonitis.

A finding of an inflammatory peritoneal fluid in the presence of a documented but localized intra-abdominal abscess in the absence of culture confirmation would also be considered possible secondary bacterial peritonitis.

derangements involving abdominal viscera. Importantly, infections arising within the abdomen can be considered to be two-compartment infections—the first, the overt focus on infection, and the second resulting from the presence of a dense microbial flora in the adjacent gastrointestinal tract (36, 37).

Intraperitoneal infections tend to be associated with a greater degree of physiologic derangement. In addition, the unique defense mechanisms of the peritoneal cavity promote their localization through the formation of abscesses. Although retroperitoneal inflammation in conditions such as pancreatitis can be devastating in its consequences, retroperitoneal infections typically take a more indolent course. Solid organ infections involving the liver and spleen typically do not arise secondary to anatomical derangements and may be amenable to nonoperative or minimally invasive management (38–41).

Primary peritoneal infections (primary peritonitis) are those that arise in the absence of an identifiable anatomical derangement in the intra-abdominal viscera (Table 5).

Secondary peritoneal infections (secondary peritonitis) are those occurring secondary to an anatomical derangement such as perforation or obstruction of a hollow viscus (Table 6). The infecting flora is the indigenous flora of the gastrointestinal tract, with the important proviso that if the anatomical defect is in the stomach or duodenum, anaerobic organisms are rare, but *Candida* may be a pathogen.

Tertiary peritonitis can be defined as peritonitis that persists or recurs ≥48 hrs following apparently successful management of primary or secondary bacterial peritonitis (Table 7). It is characterized by a nosocomial flora including coagulase-negative staphylococci, *Candida*, *Enterococci*, *Pseudomonas*, and *Enterobacter* and is associated with overgrowth of the gastrointestinal tract with the same organisms.

Within this classification, device-related infections such as chronic ambulatory peritoneal dialysis peritonitis or ventricular peritoneal shunt infections (Table 8) would be considered secondary infections (secondary to a colonized device) or tertiary infections when they recur or persist (42).

Classification of Intra-Abdominal Infections. Intra-abdominal infections can be classified into three categories: microbiologically confirmed, probable, and possible (as defined in Tables 5–13). Cultures from drain sites are not considered diagnostic of intra-abdominal infection. Isolation of intrinsically less virulent organisms (i.e., coagulase-negative staphylococci, *Bacillus* species, micrococci, etc.) will be considered only if these organisms are isolated in pure culture and in significant quantities ($>10^5$ cfu/mL, 2+ or greater on direct culture plating or moderate to many on primary culture plating) from intra-abdominal sources. Blood cultures with microbial pathogens compatible with intra-abdominal infection will also be considered microbiologically confirmed infection in the presence of clinical signs and symptoms indicative of an intra-abdominal infection.

Definitions for other specific types of intra-abdominal infections (i.e., intra-abdominal abscess, biliary tract infections, pancreatic infections, typhlitis and toxic megacolon) are given in Tables 9–13 (40, 43, 44).

Table 7. Tertiary peritonitis

Tertiary peritonitis is defined as persistent intra-abdominal inflammation and clinical signs of peritoneal irritation following secondary peritonitis from nosocomial pathogens.
Microbiologically confirmed: Isolation of one or more nosocomial pathogens from peritoneal fluid or blood in an appropriate clinical situation (>48 hrs after treatment for primary or secondary peritonitis).
Probable: Compatible clinical illness with documented secondary peritonitis with persistent peritoneal inflammation (>500 leukocytes/mL peritoneal fluid) in the absence of microbiologically confirmed microbial persistence in the peritoneal space.
Possible: Compatible clinical illness with persistent signs of systemic inflammation but without clear documented evidence of persistent inflammation within the peritoneal space following secondary bacterial peritonitis.

Table 8. Peritoneal dialysis-related peritonitis

Microbiologically confirmed: In a patient receiving peritoneal dialysis, an acute inflammatory process within the peritoneum (>100 leukocytes/mL) with a predominance of neutrophils in the presence of culture documentation in peritoneal fluid or blood of a pathogenic microorganism.
Probable: An inflammatory process (>100 leukocytes/mL with a neutrophil predominance) of the peritoneum during the course of peritoneal dialysis, with Gram stain evidence of an infection but without culture documentation from blood or the peritoneal space.
Possible: Abnormal accumulation of inflammatory cells in the peritoneum (>100 leukocytes/mL) with a predominance of neutrophils in the absence of Gram strain and culture evidence of infection.

Table 9. Intra-abdominal abscess

Microbiologically confirmed: Clinical, radiographic, and direct surgical confirmation of an inflammatory collection within the peritoneal space or surrounding structures with isolation of one or multiple microbial pathogens from the fluid collection. Microbiologic confirmation will require specimen collection from percutaneous aspirations under sterile technique or direct surgical observation with acquisition of culture material directly from the abscess cavity or the blood.
Probable: The presence of an abnormal collection of fluid in the intra-abdominal contents or surrounding structures with evidence of inflammatory cells and/or positive Gram stain but with negative cultures from that fluid accumulation or blood.
Possible: Clinical or radiographic evidence of an abnormal fluid accumulation within the abdominal contents or surrounding structures but without microbiologic or surgical confirmation.

Urosepsis

There are only a few specific studies of urinary tract infection (UTI) in populations of ICU patients with severe sepsis/septic shock, and although both bacterial UTI and candiduria are very common, their importance as the primary source for severe sepsis and septic shock remains unclear. In particular, lower UTI among noncatheterized patients is considered to be a very rare cause of severe sepsis/septic shock and is not considered further here.

Catheter-associated UTI (CAUTI) is the most common nosocomial infection, accounting for up to 40% of all infections and >1 million infections in U.S. hospitals each year (45, 46). Up to a half of patients requiring an indwelling urethral catheter for ≥5 days will develop bacteriuria or candiduria. The daily incidence of CAUTI is relatively constant during closed drainage, at least for the first 10 days, with 2–16% of patients acquiring infection each day. Infection is nearly universal at 30 days. According to a recent National Nosocomial Infections Surveillance report, nosocomial UTI (mostly CAUTI) rates range from 5.3 to 10.5 per 1000 urinary catheter-days in ICUs. Importantly, silent catheter-associated bacteriuria comprises a huge reservoir of resistant organisms in the hospital, particularly on critical care units (47–49).

In a noncatheterized patient, the definition of a bacteriologically significant urinary tract infection ($>10^5$ cfu/mL, Table 14) is widely accepted, but definitions for CAUTI are less clear. However, Stark and Maki (50) showed that in a catheterized patient, the isolation of $>10^3$ cfu/mL organisms is highly predictive of infection, and if antibiotics are not given, the level will rise quickly to $>10^5$cfu/mL. However, these "significant" CAUTIs are rarely symptomatic (51). The CDC has attempted to discriminate between symptomatic and asymptomatic UTI and CAUTI (52), but these definitions are not wholly suitable for ICU patients who frequently are unable to report symptoms

Table 10. Biliary tract infection

Microbiologically confirmed: An acute inflammatory process of the biliary tract or surrounding structures with the isolation of pathogenic microorganisms obtained via percutaneous or direct surgical collection of samples in the lumen of the gall bladder or the biliary tract or the blood.
Probable: An appropriate clinical syndrome with evidence of microbial infection verified by Gram stain from the biliary system but with negative cultures from the biliary system or blood for enteric microbial pathogens.
Possible: This includes patients with clinical evidence of biliary tract infection with surgical or radiographic evidence of suppurative complications but in the absence of microbiologic verification, positive blood cultures, or a Gram stain evidence of active infection. In the presence of ascending cholangitis, a positive blood culture is sufficient to make the diagnosis of microbiologically confirmed, ascending cholangitis (>50% of patients will be bacteremic with this biliary tract infection). A positive culture from the biliary tract in the absence of clinical symptoms (bactobilia) is not sufficient to make a diagnosis. Positive culture from a T-tube drainage from the common bile duct is not sufficient evidence to make a diagnosis of biliary tract infection if the tube has been in place for >24 hrs.

Table 11. Pancreatic infection

Microbiologically confirmed: This requires direct confirmation of positive microbial cultures from the pancreas or surrounding structures by percutaneous aspiration or direct visualization and culture at the time of surgery or from the bloodstream.
Probable: The presence of surgical or radiographic evidence of an abnormal collection of an inflammatory focus within the substance of the pancreas or surrounding structures with a positive Gram stain from the pancreatic collection in the absence of culture documentation.
Possible: Radiographic or direct surgical inspection with evidence suggestive of pancreatic abscess or other type of infection.

Table 12. Typhlitis

Typhlitis is defined as transmural inflammation and variable degrees of necrosis and infection of the cecum and colon found in immunocompromised hosts (primarily in neutropenic patients and HIV-infected patients).
Microbiologically confirmed: Detection of microbial pathogens within the submucosa of the bowel wall of the cecum following surgical excision.
Probable: The presence of a pathogenic microorganism in the systemic circulation or peritoneum in the appropriate clinical situation with radiographic evidence of air in the bowel wall, thickening, or hemorrhagic necrosis on abdominal computed tomography scan or direct surgical inspection of the cecum.
Possible: A compatible clinical presentation with radiographic evidence of bowel wall edema and/or gas and/or hemorrhagic necrosis within the bowel wall of the cecum without microbiologic or surgical confirmation.

Table 13. Toxic megacolon

Toxic megacolon is defined as an acute dilation of the colon due to diffuse inflammation or necrosis of the bowel wall in the absence of mechanical obstruction.
Microbiologically confirmed: The isolation of pathogenic microorganisms within the peritoneum, blood, or bowel wall from surgically resected tissues in patients presenting with the clinical picture of toxic megacolon with radiographic evidence of dilatation of the lumen of the large bowel >6 cm.
Probable: Radiographic evidence of acute dilation of the lumen of the large bowel >6 cm in the appropriate clinical situation with evidence of peritoneal inflammation and/or positive Gram stain but without pathologic evidence of microbial invasion of the bowel wall and/or submucosal necrosis.
Possible: A clinical presentation compatible with toxic megacolon and radiographic evidence of acute dilatation of the lumen of the large bowel >6 cm without microbiologic or pathologic confirmation.

yet may well have a clinically significant (as opposed to simply a microbiologically significant) infection. Other criteria such as the presence of pyuria provide only limited additional information (53). Table 15 provides an approach that attempts to reconcile some of these difficulties.

Most clinicians recognize that isolated candiduria (i.e., in the absence of evidence of *Candida* species colonization or infection at other sites) rarely requires treatment; nevertheless, candiduria can occasionally be the only accessible evidence of deep candidiasis. Candiduria is rare in normal healthy adults, and even in an unselected hospital population only about 2% of urine samples received in the laboratory will show candiduria, although this number rises to 10–12% in "high-risk" patients such as those on hematology-oncology units (54). However, *Candida* species are clearly associated with urinary infection much more frequently in catheterized patients, and especially in catheterized patients in the ICU. Some studies have reported that up to a quarter of catheter-related UTIs are caused by *Candida* species, and in some series, *Candida* is identified as one of the most frequent microbial pathogens isolated from urine samples on a surgical ICU (55). Note this does not necessarily imply there is *Candida* urinary tract infection.

It is clear that there is very considerable uncertainty about the criteria to be used in interpreting the finding of candiduria. There are some reasonably reliable data on the interpretation of candiduria in noncatheterized patients. The early work of Goldberg et al. (56) suggesting that *Candida* species counts $>10^4$/mL represent clinically significant infection (56) has largely been supported by others, although there are certainly reports suggesting that lower counts can be associated with symptoms and indeed that lower counts often quickly increase to higher counts if untreated. Conversely, prospective observational studies of patients with candiduria (75% of whom were catheterized) have suggested that most patients with counts $\leq 10^3$/mL remain asymptomatic and require no treatment (57).

Hence, in the clinical setting, and in particular on the ICU, clinicians will very rarely rely on microbiology alone to decide on the significance of candiduria. They will integrate other clinical information, just as they would in any other clinical site. Definitions for sepsis studies

Table 14. Urosepsis in noncatheterized patients

1. Lower urinary tract infection
   Is usually not considered as a possible source of severe sepsis/septic shock, but if required the conventional microbiological definition of $>10^5$ cfu/mL can be used
2. Upper urinary tract infection (kidney, ureter, or tissue surrounding the retroperitoneal or perinephric space)
   Must meet one of the following criteria:
   Organism isolated from culture of fluid (other than urine) or tissue from the affected site
   An abscess or other evidence of infection seen on direct examination, during surgery, or by histopathologic examination
   Or two of the following:
   Fever (>38°C); urgency; localized pain or tenderness at involved site; and any one of the following: microscopic examination (urinalysis or Gram stain) showing pyuria or $\geq 10^5$ cfu/mL; purulent drainage from the affected site; pyuria; hematuria; organism isolated from urine culture; positive Gram stain; radiographic evidence of infection (e.g., ultrasound, computed tomography, magnetic resonance imaging, radiolabeled scan).

cfu, colony-forming units.

Table 15. Urosepsis in catheterized patients (urinary catheter is present or has been removed within the past 6 days)

1. Lower urinary tract infection
   The presence of suggestive signs and symptoms including fever (>38°C), urgency, frequency, dysuria, pyuria, hematuria, positive Gram stain, pus, suggestive imaging
   and
   Positive dipstick for leukocyte esterase and/or nitrate **or** pyuria ($\geq$10 white blood cells/μL or $\geq$3 white blood cells/high-power field of unspun urine) **or** organisms seen on Gram stain of unspun urine **or** frank pus expressed around the urinary catheter **or** $>10^3$ cfu/mL **or** if the patient can report symptoms, modified CDC criteria have to be met
2. Upper urinary tract infection (kidney, ureter, bladder, urethra, or tissue surrounding the retroperitoneal or perinephric space)
   Must meet **one** of the following criteria:
   Organism isolated from culture of fluid (other than urine) or tissue from the affected site; an abscess or other evidence of infection seen on direct examination, during surgery, or by histopathologic examination
   or two of the following:
   Fever (>38°C), urgency, localized pain or tenderness at involved site, and any of the following: purulent drainage from the affected site, pyuria, hematuria, organism isolated from culture, positive Gram stain, radiographic evidence of infection (e.g., ultrasound, computed tomography, magnetic resonance imaging, radiolabeled scan)

Modified CDC criteria (1)
   1) One of the following: fever (>38°C), urgency, frequency, dysuria or suprapubic tenderness, **and** a urine culture $\geq 10^5$ cfu/mL with no more than two species of organisms
   or
   2) Two of the following: fever (>38°C), urgency, frequency, dysuria or suprapubic tenderness, **and** any of the following:
      a) positive dipstick for leukocyte esterase and/or nitrate
      b) pyuria ($\geq$10 white blood cells/μL or $\geq$3 white blood cells/high-power field of unspun urine)
      c) organisms seen on Gram stain of unspun urine
      d) two urine cultures with repeated isolation of the same uropathogen with $\geq 10^2$ cfu/mL in nonvoided specimen
      e) two urine cultures with $\leq 10^5$ cfu/mL of single uropathogens in a patient being treated with appropriate antimicrobial therapy

cfu, colony-forming units; CDC, Centers for Disease Control and Prevention.

with UTI as the source are provided in Tables 14, 15 and 16.

Skin and Soft-Tissue Infections

Infections of the skin and soft tissue are common and encompass a spectrum of illness severity, from focal cellulitis producing only mild symptoms to life-threatening necrotizing infections resulting in extensive tissue loss and substantial acute morbidity and mortality (58–60). They may arise spontaneously, or following trivial and unapparent trauma, or as a consequence of local trauma such as a burn or surgical procedure. Infections arising at the site of a surgical procedure are relatively common and are termed surgical site infections.

Local signs of inflammation are the hallmark of a soft tissue infection. Features of severe sepsis rarely accompany a superficial surgical site infection and suggest concomitant tissue necrosis, a deep surgical site infection, or a particularly virulent infecting organism. Fluctuance suggests a subcutaneous abscess. Necrotizing infection is suggested by the presence of pain (usually severe and constant in the case of necrotizing fasciitis), discoloration of the overlying skin, bullous lesions, or soft tissue crepitus; these findings, however, are neither sensitive nor specific for the recognition of tissue necrosis, and extensive necrotizing infection of the subcutaneous tissues may be present with only minimal findings in the overlying skin.

The diagnosis of infection of the skin and soft tissues is most commonly accomplished by direct examination, obtaining cultures to identify the infecting organisms and to aid in the selection of an optimal antimicrobial agent. Superficial surgical site infection is diagnosed by opening a portion of the surgical wound and draining pus. A microbiological diagnosis of cellulitis can sometimes be made by aspiration of the involved area. Biopsy can be used to determine whether tissue necrosis is present and to facilitate quantitative culture, a technique that is useful in the diagnosis of burn wound infection. Radiologic examination—particularly computed tomography—is of value to define the extent of the process and to identify deep sites of infection.

The terminology used to classify skin and soft-tissue infections is complicated and confusing as it is based on frequently overlapping classification criteria, such as degree of extension (focal or localized vs. diffuse), depth of infection (superficial vs. deep), histologic characteristics (necrotizing vs. nonnecrotizing), and clinical presentation (uncomplicated vs. complicated). For the sake of simplicity, skin and soft-tissue infections can be subdivided into surgical and nonsurgical infections (Table 17). Surgical site infection is an infection that arises within 30 days of an operative procedure and at the site of surgical intervention. Definitions have been adapted from those of the CDC (1). Excluded from these definitions are stitch abscesses or infected episiotomies. Nonsurgical skin and soft-tissue infections comprise erysipelas, impetigo, folliculitis, cellulitis, pyodermas, abscess, necrotizing cellulitis or fasciitis or myositis (these terms encompass several distinct clinical and bacteriologic entities: progressive bacterial synergistic gangrene, idiopathic scrotal or Fournier's gangrene, streptococcal gangrene, clostridial cellulitis/myonecrosis ["gas gangrene"], nonclos-

Table 16. Candiduria

A. In catheterized patients
Candiduria $\geq 10^3$ cfu/mL represents asymptomatic candiduria
B. In noncatheterized patients[a]
Candiduria $\geq 10^4$ cfu/mL represents asymptomatic candiduria
Patients who satisfy either of the above criteria **and** have clinical signs and/or symptoms of urinary tract infection based on CDC criteria[b] can be designated as having clinically significant *Candida* urinary tract infection[c]
C. Upper urinary tract infection
Same criteria as upper urinary tract bacterial infection (see Table 15)

cfu, colony-forming units; CDC, Centers for Disease Control and Prevention.

[a]Catheter not present for ≥7 days; [b] relevant signs/symptoms based on CDC criteria are fever >38°C, urgency, frequency, dysuria, and suprapubic tenderness; [c] this excludes *Candida* pyelonephritis or other deep infections of the bladder, urethra, or associated retroperitoneal structures.

Table 17. Skin and soft tissue infections

1. Surgical site infections
Surgical site infection is defined as an infection that arises within 30 days of an operative procedure and at the site of surgical intervention. Symptoms and signs suggestive of a surgical site infection include wound erythema and blanching, tenderness, pain, purulent discharge, fever (temperature >38.0°C), and leukocytosis. A superficial surgical site infection involves the skin or subcutaneous tissues alone, whereas a deep surgical site infection involves the fascia or muscle layers, and an organ space surgical site infection involves the deeper anatomic areas opened during the surgical procedure.
2. Nonsurgical site infections
Cellulitis is defined as an acute spreading infection of the skin and underlying soft tissue suggested by the presence of a rapidly expanding erythema, local tenderness, pain, swelling, lymphangitis, and lymphadenopathy, which is frequently accompanied by systemic signs and symptoms including malaise, fever (temperature >38.0°C), and chills.
Necrotizing cellulitis and fasciitis are defined as acute, rapidly progressing, and life-threatening destructive (i.e., necrotizing) infections of the subcutaneous tissues dissecting along tissue planes. Although these two clinical entities exhibit some distinctive clinical and microbial characteristics, they share common features. The symptoms and signs suggestive of necrotizing cellulitis or fasciitis are intense local pain (a cardinal feature), exquisite tenderness, erythema (initially discrete but evolving to red-purple and then blue-gray cutaneous lesions often with hemorrhagic bullae), swelling, edema, crepitations (in the case of necrotizing cellulitis), and extensive tissue necrosis, which are associated with prominent systemic toxicity (toxic shock syndrome, severe sepsis, or septic shock).

Use of these definitions in clinical trials should help improve the quality of clinical research in this field.

tridial myonecrosis, polymicrobial necrotizing fasciitis), and myositis/pyomyositis/myonecrosis (58–61).

Definitions for the principal clinical entities—cellulitis and necrotizing cellulitis or fasciitis—are given in Table 17.

Infection Classification for Skin and Soft Tissue Infections.

Microbiologically confirmed skin and soft tissue infection is defined by the isolation by culture or Gram stain of a microorganism from a wound or skin lesion that has drained pus, or from a skin aspirate or biopsy of the subcutaneous tissues of an erythematous skin lesion or wound.

Probable skin and soft tissue infection is defined as compelling clinical and laboratory evidence (such as spreading cutaneous erythema and blanching, or drainage of purulent material on opening a surgical wound, with or without lymphangitis, in association with fever >38.0°C, or leukocytosis) of the presence of a skin and soft tissue infection based on radiographic, clinical, and surgical findings but without microbiological confirmation.

Possible skin and soft tissue infection is defined as clinical (such as mild cutaneous erythema associated with fever >38.0°C), laboratory (such as leukocytosis), or radiographic findings suggestive of the presence of a skin and soft tissue infection but with insufficient evidence to confirm diagnosis.

Infections are further classified as superficial or deep, based on whether the deep fascia or muscle layers are involved.

CONCLUSIONS

The increasing sophistication of clinical trial design for the investigation of new therapeutic entities in sepsis means that we need to pay more attention to issues such as accurate definition of infection. In the past, deciding whether a patient did or did not have an infection was largely left to the discretion of the investigator, and there is little doubt that this contributed to significant heterogeneity in the patient population enrolled in clinical trials. As new drugs and treatments for sepsis become more specific in respect of particular subpopulations in whom they are indicated, we will need tools to attain greater precision in defining those populations. We believe these definitions may help in developing those tools. A further benefit would be the potential to provide a framework for guiding diagnostic or even therapeutic decision making in the ICU. The merit of these definitions, be they used for enrollment in clinical trials or indeed for other purposes, will require formal testing and validation, but in the meantime we believe that they are an important step forward in the process of improving the quality of clinical trials in patients with sepsis.

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