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1.1 Introduction

Defining terms is important to avoid ambiguity, particularly in the era of global communication. Words, such as sepsis, nosocomial, colonization, and infection, are often used in an imprecise fashion. Although standardization in terminology is useful, revisions will be needed in the light of progress in biomedical knowledge. Definitions can be based on a variety of concepts, varying from abnormalities in patients' physiology and clinical features to sophisticated laboratory methods. A thoughtful introduction to clinical terminology can be found in the extensive writings of Feinstein [1, 2], who made use of set theory and Venn diagrams to categorize clinical conditions. The choice of boundaries between sets or values on measurement scales can be difficult. In practice, such boundaries are often somewhat fuzzy, for example in the diagnosis of ventilator-associated pneumonia [3].

The situation is further complicated by considering problems in measurement. An apparently simple temperature measurement is subject to variation in time, site, and technique, as well as to errors from device malfunction, displacement, or misuse. Most definitions of infection at various sites include fever as a necessary criterion, typically a temperature of $\geq 38.3^{\circ}\text{C}$. Do we have good evidence that this measurement is a reliable discriminator, in conjunction with other "necessary" criteria, in distinguishing the presence or absence of a particular type of infection [4]?

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Bone raised some important issues [5–8] for the terms sepsis and inflammation, a debate that continues. Other interesting approaches in the fields of sepsis, systemic inflammatory response, and multiple organ dysfunction are the use of “physiological state space” concepts by Rixen et al. [9] and ideas from “complex adaptive system” and network theory [10–13]. A number of consensus conferences have been held in recent years to seek agreement on definitions of infections as they apply to patients in the intensive care unit (ICU) [14].

The glossary outlined here forms a basis for our clinical practice in various aspects of intensive care infection and microbiology. We advocate definitions that are usable in routine clinical practice and that emphasize the role of surveillance samples in classifying the origins of infection.

1.2 Terms and Definitions

1.2.1 Acquisition

A patient is considered to have acquired a microorganism when a single surveillance sample is positive for a strain that differs from previous and subsequent isolates. This is a transient phenomenon, in contrast to the more persistent state of carriage.

1.2.2 Bloodstream Infection

Bloodstream infections (BSI) were classified into primary, secondary, and catheter related by the International Consensus Forum on ICU infections in 2005 [14]. Debate continues over the number and type of cultures required to detect pathogens in the blood [15]. The clinical impact of BSI depends on the pathogenicity of the invading microorganism, together with the nature and severity of the host response (see “Microorganisms,” and “Systemic inflammatory response syndrome (SIRS), sepsis, and septic shock” definitions).

1.2.2.1 Primary Bloodstream Infection

A recognized pathogen, which is not regarded as a common skin contaminant, is cultured from one or more blood cultures and the cultured organism is not related to an infection at another site, including intravenous-access devices. A primary BSI may also be present when a common skin organism, such as coagulase-negative staphylococci, is cultured repeatedly from peripheral cultures.

1.2.2.2 Secondary Bloodstream Infection

A recognized pathogen is cultured from one or more blood cultures and is identical to an organism responsible for an infection at another site.

1.2.2.3 Catheter-Related Bloodstream Infection

A pathogen is isolated from one or more blood cultures and is shown to be simultaneously present in an intravascular device, together with clinical signs of infection. No other source of the pathogen is identified in the patient. In practice, it may be difficult to distinguish between an endogenous and exogenous source unless surveillance cultures are available. If the patient has overgrowth of the relevant pathogen in the gastrointestinal tract, translocation is another possible mechanism for bacteremia.

1.2.3 Carriage/Carrier State

The same strain of microorganism is isolated from two or more surveillance samples in a particular patient. In practice, consecutive throat and/or rectal surveillance samples, taken twice a week (Monday and Thursday), yield identical strains.

1.2.3.1 Normal Carrier State

Surveillance samples yield only the indigenous aerobic and anaerobic flora, including *Escherichia coli* in the rectum. Varying percentages of people carry “normal” potential pathogens in the throat and/or gut. *Streptococcus pneumoniae* and *Haemophilus influenzae* are carried in the oropharynx by more than half of the healthy population. *Staphylococcus aureus* and yeasts are carried in the throat and gut by up to a third of healthy people.

1.2.3.2 Abnormal Carrier State

Opportunistic “abnormal” aerobic Gram-negative bacilli (AGNB) or methicillin-resistant *S. aureus* (MRSA) are persistently present in the oropharynx and/or rectum. MRSA and AGNB are listed under abnormal microorganisms. *E. coli*, isolated from the oropharynx in overgrowth concentrations [$>2+$ or $>10^5$ colony-forming units (CFU)/ml], also represents an abnormal carrier state.

1.2.3.3 Primary Carriage

Primary carriage is the persistent presence of both normal and abnormal potential pathogens in the admission flora surveillance (throat and rectum) samples.

1.2.3.4 Secondary Carriage

Secondary carriage is the persistent presence of abnormal bacteria in throat and/or rectum acquired during treatment in the ICU and which were not present in the admission flora. Commonly used antibiotics eliminate normal bacteria, such as *S. pneumoniae* or *H. influenzae*, but promote the acquisition and subsequent carriage of abnormal AGNB and MRSA. This phenomenon is sometimes referred to as “super” or “secondary” carriage. Overgrowth with microorganisms of low pathogenicity, such as coagulase-negative staphylococci and enterococci, can also occur during selective decontamination of the digestive tract (SDD).

1.2.4 Central Nervous System Infections

This important group of infections includes meningitis, meningoencephalitis, encephalitis, ventriculitis, and shunt infection. These conditions have some overlap and may also coexist with sinus or mastoid infections and septicemia. Microbiological diagnosis usually rests on culture of cerebrospinal fluid (CSF). Frequently, lumbar puncture is contraindicated in suspected meningitis [16]. For example, in meningococcal infection, contraindications include coagulopathy or when computed tomography (CT) scan features suggest a risk of tentorial pressure coning if lumbar puncture were to be done. Also, empirical antibiotics have frequently been started prior to hospital admission. These issues are particularly important in pediatric practice, where meningococcal DNA detection in blood and/or CSF by polymerase chain reaction (PCR) assays, together with bacterial antigen tests, improves diagnostic yield [17]. The use of molecular techniques, including PCR, in detecting septicemia in critically ill patients is still in the developmental stage but shows great promise [18]. In CNS infections, the usual nonspecific criteria of fever or hypothermia, leukocytosis or leukopenia, and tachycardia are present, with specific symptoms that may include headache, lethargy, neck stiffness, irritability, fits, and coma. Cutoff values depend on age and should be defined at age-specific percentile thresholds for physiological variables, e.g., >90th percentile for heart rate. Detailed definitions are not given here, as they would require a separate chapter.

1.2.5 Colonization

Microorganisms are present in body sites that are normally sterile, such as the lower airways or bladder. Clinical features of infection are absent. Diagnostic samples yield $\leq 1+$ leukocytes per high power field (HPF) [19], and microbial growth is $<2+$ or $<10^5$ CFU/ml.

1.2.6 Defense

1.2.6.1 Against Carriage

The defense mechanisms of the oropharynx and gastrointestinal tract, e.g., fibronectin, saliva, and gastric secretions, help prevent abnormal carrier states.

1.2.6.2 Against Colonization

Defense mechanisms of internal organs against microbial invasion, e.g., the mucociliary elevator in the airways and secreted immunoglobulins.

1.2.6.3 Against Infection

Defense mechanisms of the internal organs, beyond skin and mucosa, which include antibodies, lymphocytes, and neutrophils.

1.2.7 Endemicity

Endemicity is defined as at least one new case per month having a diagnostic sample positive for the outbreak strain. Endemicity can be interpreted as an uncontrolled, ongoing outbreak.

1.2.8 Infection

Infection can be remarkably difficult to define in clinical circumstances. Patients have often received empirical antibiotics. In principle, infection is a microbiologically proven clinical diagnosis of local and/or generalized inflammation. The microbiological criteria conventionally include $\geq 10^5$ CFU/ml of diagnostic sample from the infected organ and $\geq 2+$ leukocytes present per HPF in the sample. The thresholds chosen for clinical features and laboratory measurements depend on patient age and assessment timing. Assessment may include temperature changes, heart rate, changes in heart rate variability [10], white blood cell (WBC) counts, C-reactive protein [20], and procalcitonin [21, 22]. Infections can be classified according to the concept of the carrier state [23]:

- primary endogenous infection is caused by microorganisms carried by the patient at the time of admission to the ICU and include both normal and abnormal microorganisms;
- secondary endogenous infection is caused by microorganisms acquired on the ICU and not present in the admission flora. These microorganisms usually belong to the abnormal group. Potentially pathogenic microorganisms are acquired in the oropharynx and followed by carriage and overgrowth in the digestive tract. Subsequently, colonization and then infection of internal organs may occur following migration from the oropharynx into the lower airways or translocation across the gut mucosa into the lymphatics or bloodstream;
- exogenous infection is caused by microorganisms introduced into the patient from the ICU environment. Organisms are transferred directly, omitting the carriage stage, to a site where colonization and then infection occur.

1.2.9 Inflammatory Markers

Inflammatory markers are cells and proteins associated with the proinflammatory process. These include C-reactive protein [20], procalcitonin [21, 22], tumor necrosis factor alpha (TNF)- α , interleukin (IL)-1 and IL-6 [24], lymphocytes, and neutrophils. The onset, magnitude, and duration of changes in these factors vary with infection site and severity.

1.2.10 ICU infection

ICU infection refers to secondary endogenous and exogenous infections, which are infections due to organisms not carried by the patient at the time of ICU admission and transmitted via hands of carers [25]. The term nosocomial (literally, related to the hospital) is widely used but lacks a precise definition.

1.2.11 Intra-Abdominal Infection

Intra-abdominal infection occurs in an abdominal organ and the peritoneal cavity (peritonitis). Peritonitis can be a local or general inflammation of the peritoneal cavity. Local signs such as tenderness and guarding may be difficult to elicit in sedated ICU patients. Generalized, nonspecific features are fever (temperature $\geq 38.3^{\circ}\text{C}$), leukocytosis (WBC $> 12,000/\text{mm}^3$), or leukopenia (WBC $< 4,000/\text{mm}^3$). Ultrasonography and/or CT evaluation may contribute to the diagnosis. Isolation of microorganisms from diagnostic samples at a concentration of $\geq 2+$ or $\geq 10^5$ CFU/ml, with $\geq 2+$ leukocytes, confirms the diagnosis. Specific examples include fecal peritonitis due to colon perforation and peritonitis associated with peritoneal dialysis.

1.2.12 Isolation

Patients are nursed in separate cubicles or rooms, with strict hygiene measures, including protective clothing and hand washing by the staff, to control transmission of microorganisms. These measures particularly apply to patients infected with high-level pathogens or resistant microorganisms and those with impaired immunity.

1.2.13 Microorganisms

1.2.13.1 Normal Microorganisms

Normal microorganisms are carried by varying percentages of healthy people and include *S. aureus*, *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, *E. coli*, and *Candida albicans* [26].

1.2.13.2 Abnormal Microorganisms

Abnormal microorganisms are carried by people with chronic disease or those admitted to the ICU from inpatient wards or other hospitals. These are typically AGNB or MRSA. AGNB include *Pseudomonas*, *Acinetobacter*, *Klebsiella*, *Citrobacter*, *Enterobacter*, *Serratia*, *Proteus*, and *Morganella* spp. These organisms are rarely carried by healthy people [27, 28]. Microorganisms can be ranked by pathogenicity into three types:

- highly pathogenic microorganisms, e.g., *Salmonella* spp, may cause infection in an individual with a normal defense capacity;
- potentially pathogenic microorganisms, e.g., *S. pneumoniae* in community practice and *P. aeruginosa* in hospital practice, can cause infection in a patient with impaired defense mechanisms. These two types of microbes cause both morbidity and mortality;
- microbes of low pathogenicity cause infection under special circumstances only, e.g., anaerobes can cause abscesses when tissue necrosis is present. Low-level pathogens in general cause morbidity and little mortality.

Intrinsic pathogenicity refers to the capacity to cause infection. The intrinsic pathogenicity index (IPI) is defined as the ratio of the number of patients who develop an infection due to a particular microorganism and the number of patients who carry the organism in the throat and/or rectum. Indigenous flora, including anaerobes and *S. viridans*, rarely cause infections despite being carried in high concentrations. The IPI is typically in the range of 0.01–0.03. Coagulase-negative staphylococci and enterococci are also carried in the oropharynx in high concentrations but are unable to cause lower airway infections. High-level pathogens, such as *Salmonella* spp, have an IPI approaching 1 in the gut. Potentially pathogenic microorganisms have an IPI in the range of 0.1–0.3, and include the normal and abnormal potential pathogens, which are the targets of SDD.

1.2.14 Migration

Migration is the process whereby microorganisms carried in the throat and gut move to colonize and possibly infect internal organs. Migration is promoted by underlying chronic disease, some drugs, and invasive devices.

1.2.15 Outbreak

An outbreak is defined as an event in which two or more patients in a defined location are infected by identical, often multidrug-resistant, microorganisms transmitted via the hands of health care workers, usually within an arbitrary time period of 2 weeks. There are two different types of infection involved in outbreaks: secondary endogenous and exogenous. Outbreaks of secondary endogenous infection are preceded by outbreaks of carriage of abnormal flora, whereas outbreaks of exogenous infection are not. Outbreaks of carriage of microbes may therefore have considerable significance for infection control. These two types of outbreaks require different management approaches: SDD is designed to prevent secondary endogenous types of outbreaks, whereas emphasis on hygiene procedures, such as handwashing and cohort nursing, is needed to prevent exogenous outbreaks. SDD paste, applied to tracheostomy wounds, can reduce the risk

of exogenous transmission during an outbreak. Such outbreak episodes often occur with multidrug-resistant microorganisms, such as *Pseudomonas*, MRSA, or vancomycin-resistant enterococci (VRE). In the pediatric ICU, viruses such as respiratory syncytial virus or rotavirus can also be a major problem.

1.2.16 Overgrowth

Overgrowth is defined as the presence of a high concentration of potentially pathogenic microorganisms, $\geq 2+$ or $\geq 10^5$ CFU/ml, in surveillance samples from the digestive tract [29]. Gut overgrowth can harm the critically ill patient, as it can cause immunosuppression [30], inflammation [31], infection [32], and antimicrobial resistance [33]. Overgrowth control is the main mechanism of action of SDD. SDD restores immune function [34] and reduces inflammation [35], infection rates [36], and antimicrobial resistance [37].

1.2.17 Pneumonia

1.2.17.1 Microbiologically Confirmed Pneumonia

- presence of new or progressive infiltrates on a chest X-ray for ≥ 48 h, and
- fever $\geq 38.3^\circ\text{C}$, and
- leukocytosis (WBC $> 12,000/\text{ml}$) or leukopenia (WBC $< 4,000/\text{ml}$), and
- purulent tracheal aspirate containing $\geq 2+$ WBC/HPF, and
- tracheal aspirate specimen yielding $\geq 10^5$ CFU/ml, or
- protected brush specimen (PBS) yielding $> 10^3$ CFU/ml, or
- bronchoalveolar lavage (BAL) specimen yielding $> 10^4$ CFU/ml.

1.2.17.2 Clinical Diagnosis Only

The first four microbiological criteria are fulfilled, but tracheal aspirates, PBS, or BAL are sterile. Criteria for the diagnosis of pneumonias remain controversial [3]. The situation is sometimes complicated by viral etiologies and/or prior antibiotic treatment, particularly in infants and children. There is also overlap with other pathophysiological terms, such as pneumonitis and bronchiolitis.

1.2.18 Resistance

A microorganism is considered to be resistant to a particular antimicrobial agent if:

- the minimal inhibitory concentration of the antimicrobial agent against a colonizing or infecting microbial species is higher than the nontoxic blood concentration after systemic administration;
- the minimum bactericidal concentration of the antimicrobial agent against microbes carried in throat and gut is higher than the nontoxic concentration achieved by enteral administration.

1.2.19 Samples

1.2.19.1 Diagnostic

Diagnostic or clinical samples are taken from sites that are normally sterile in order to diagnose infection or evaluate response to therapy. Samples are taken on clinical indication only from blood, lower airways, CSF, urinary tract, wounds, peritoneum, joints, sinuses, or conjunctiva.

1.2.19.2 Surveillance

Surveillance samples are taken from the oropharynx and rectum on admission and subsequently at regular intervals (usually twice weekly). These specimens are needed to:

- evaluate the abnormal carriage level of potentially pathogenic microorganisms, in particular, overgrowth;
- assess the eradication of potential pathogens by enteral nonabsorbable antimicrobial regimens used in SDD protocols;
- detect the carriage of resistant strains.

1.2.20 Selective Decontamination of the Digestive Tract

SDD is an antimicrobial prophylaxis method consisting of parenteral cefotaxime and enteral and topical polymyxin E/tobramycin/amphotericin B (PTA) to prevent severe endogenous and exogenous infections of lower airways and blood in the critically ill patient requiring treatment in the ICU. The full SDD protocol has four components [25, 38, 39]:

- parenteral antibiotic (e.g., cefotaxime), is administered for the first few days to prevent or control primary endogenous infection;
- nonabsorbable antimicrobials are administered into the oropharynx and gastrointestinal tract when surveillance cultures show abnormal carriage; the usual combination is PTA;
- a high standard of hygiene is required to prevent exogenous infection episodes;
- regular surveillance samples of throat and rectum are obtained to diagnose carrier states and monitor SDD efficacy.

The policy at Alder Hey, Liverpool, UK is to use SDD “a la carte”, guided by the abnormal carrier state detected by surveillance samples. However, most ICUs that use SDD start the regimen on admission, irrespective of surveillance swab results.

1.2.21 Systemic Inflammatory Response Syndrome, Sepsis, and Septic Shock

Definitions for SIRS, sepsis, severe sepsis, and septic shock have been extensively reviewed in recent years, particularly in relation to the inclusion criteria for clinical trials [8, 40, 41]. Consensus definitions form categories based on cutoff

points in the value distributions of a number of variables. Cutoff points based perfusion indices can be difficult to evaluate in practice. Furthermore, a patient's clinical state can change rapidly [42]. Microbiological confirmation of infection may occur a considerable time after the clinical diagnosis of septic states. Cutoffs and thresholds must be adjusted in the pediatric population [43].

1.2.21.1 Systemic Inflammatory Response Syndrome

SIRS can be caused by a wide variety of clinical insults [8, 44, 45] and is manifested by two or more of the following:

- temperature >38 or $<36^{\circ}\text{C}$;
- heart rate >90 bpm;
- respiratory rate >20 breaths/min;
- WBC count $>12,000/\text{mm}^3$ or $<4,000/\text{mm}^3$, or $>10\%$ immature forms.

These variables must be adjusted in infants and children [46].

1.2.21.2 Sepsis

Sepsis is defined as SIRS with a clear infectious etiology.

1.2.21.3 Septicemia

Septicemia is sepsis with a positive blood culture. In contrast, bacteremia is defined as a positive blood culture in a patient exhibiting no clinical symptoms.

1.2.21.4 Severe Sepsis

Severe sepsis is defined as sepsis with organ dysfunction, hypoperfusion, or hypotension. Manifestations of hypoperfusion may include, but are not limited to, lactic acidosis, oliguria, and acute alterations in mental state.

1.2.21.5 Septic Shock

Septic shock is sepsis-induced hypotension, persisting despite adequate fluid resuscitation, together with manifestations of hypoperfusion. Hypotension is defined as a systolic blood pressure <90 mmHg or a reduction of >40 mmHg from baseline in the absence of other causes of hypotension.

1.2.22 Sinusitis

Sinusitis is infection of the paranasal sinuses—maxillary, ethmoidal, frontal, or sphenoidal. Symptoms and signs such as localized tenderness and purulent discharge may be absent in the sedated ICU patient. Fever (temperature $\geq 38.3^{\circ}\text{C}$)

and leukocytosis ($\text{WBC} > 12,000/\text{mm}^3$) or leukopenia ($\text{WBC} < 4,000/\text{mm}^3$) are the main clinical features. Plain radiographs or CT imaging may show fluid levels of obliteration in the sinus air spaces. Surgical drainage is performed to obtain microbiological confirmation ($\geq 2+$ or $\geq 10^5$ CFU/ml of pus, together with $\geq 2+$ leukocytes).

1.2.23 Tracheitis/Bronchitis

In the absence of pulmonary infiltrates on chest X-ray, tracheitis/bronchitis is defined as:

- purulent tracheal aspirate, and
- fever $>38.3^\circ\text{C}$, and
- leukocytosis ($\text{WBC} > 12,000/\text{mm}^3$) or leukopenia ($\text{WBC} < 4,000/\text{mm}^3$);
- $\geq 2+$ or $\geq 10^5$ CFU/ml of tracheal aspirate.

1.2.24 Translocation (Transmural Migration)

Translocation is defined as the passage of viable microorganisms from the throat and gut through mucosal barriers to regional lymph nodes and internal organs, including the blood.

1.2.25 Transmission

Transmission is defined as the spread of microorganisms between patients by means of “vectors” such as a carer’s hands. Transmission of potential pathogens is the crucial stage in the pathogenesis of secondary endogenous and exogenous infections. Measures to control transmission include isolation, hand washing, protective clothing, and care of equipment.

1.2.26 Urinary Tract Infection

Urinary tract infection is defined as infection of the urinary tract, most frequently the bladder. The common clinical features of dysuria, suprapubic pain, frequency, and urgency are often absent in the sedated ICU patient. The diagnosis rests on a freshly voided catheter urine specimen or suprapubic sample containing $\geq 10^5$ bacteria or yeasts per milliliter of urine and ≥ 5 WBC/HPF.

1.2.27 Wound Infection

Wound infection is defined as purulent discharge from wounds, signs of local inflammation, and a culture yielding $\geq 2+$ or $\geq 10^5$ CFU/ml. The isolation of skin flora in the absence of these features is considered contamination.

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Infection Control in the Intensive Care Unit

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(Eds.)

2012, XVIII, 513 p., Hardcover

ISBN: 978-88-470-1600-2