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Sepsis: A Brief Overview of the Key Concepts

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Summary

The issue of sepsis has been discussed extensively in the medical and scientific community for decades. However, a unified understanding of the biological nature of this condition has yet to be established.

Aim. To provide a structured review of the key concepts commonly used in clinical practice and in the scientific literature related to sepsis.

Materials and Methods. A review of the scientific literature combined with the authors' professional experience.

Results. From a methodological perspective, it is suggested to conceptualize sepsis as a pathological condition due to generalized suppurative process. In this case, typical sepsis and septic shock are proposed to be considered two pathogenically separate, independently developing anatomo-clinical forms of sepsis.

Conclusion. It is proposed to consider as sepsis only conditions associated with pathogens that are capable of causing purulent inflammation. Non–purulent conditions not associated with pathogens of purulent infections are considered as generalization of bacterial, viral, protozoal, fungal diseases that may acquire toxic and especially toxic clinical forms designated as bacterial-toxic, or infectious-toxic (but not septic) shock. Typical sepsis and septic shock are proposed to be considered as independently developing clinical and anatomical forms of sepsis rather than the sequentially developing stages of the pathological condition.

Keywords: sepsis; septic shock

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Introduction

Sepsis has long been one of the most debated topics in modern medicine [11]. The key terms used in the discussion of sepsis still lack clear and universally accepted definitions. The terminology and interpretations provided by official WHO bodies are highly ambiguous, hindering a deeper understanding of the biological nature of sepsis and the core principles for formulating a diagnosis.

According to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis is defined as «a life-threatening organ dysfunction caused by a dysregulated host response to infection» [1].

It is further noted that «Most types of microorganisms can cause sepsis, including bacteria, fungi, viruses and parasites, such as those that cause malaria. Bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Escherichia coli, Salmonella* spp. and *Neisseria meningitidis* are the most common etiological pathogens. Manifestations of sepsis and septic shock can be the fatal complication of infections with seasonal influenza viruses, dengue viruses and highly transmissible pathogens of public health concern such as avian and swine influenza viruses, severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus and most recently, Ebola and yellow fever viruses». [2].

This broad interpretation effectively blurs the distinction between generalized suppurative infections and generalized forms of other (non-purulent) infections, as well as syndromes classified in ICD-10 [3], such as

— septicemia, including septic shock (A41.9),
— toxic shock syndrome (A48.3),
— septic shock (R57.2),
— other (endotoxin-mediated) shock (R57.8),
— systemic inflammatory response syndrome (SIRS), including severe sepsis (R65.1).

At the same time, the Sepsis-3 consensus introduced several notable advancements. First, systemic inflammatory response syndrome (R65) was removed from the diagnostic criteria for sepsis, removing a significant degree of clinical ambiguity. However, the current definition — «a life-threatening organ dysfunction caused by a dysregulated host response to infection» [1] — itself remains somewhat vague.

Table 1. Fundamental Differences Between Sepsis and Typical (Classical) Infections

Characteristic	Sepsis	Typical (Classical) Infections
Causative agent	Not monocausal	Monocausal*
Isolation of pure culture	Not always possible	Possible*
Experimental reproducibility	Impossible	Possible*
Contagiousness	Not contagious	Contagious**
Course pattern	Non-cyclic	Cyclic**
Immunity development	Does not occur	Occurs**
Typical organ-specific lesions	Absent	Present**
Primary infectious complex	Absent	Present
Primary septic focus	Present	Absent

Note. * — criteria from Koch's postulates. ** — consequences derived from Koch's postulates.

Second, a new definition of septic shock was introduced, described as «a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality» [1, 4].

By introducing the term septic shock, the Sepsis-3 international consensus effectively recognizes the conceptual model of sepsis developed more than 70 years ago by Academician I. Davydovsky [5]. In fact, septic shock closely corresponds to the variant of sepsis without the formation of purulent metastatic foci — previously referred to as septicemia in the Soviet and Russian literature.

To the best of our knowledge, this condition does not correspond to the «purulent-resorptive fever» described by Davydovsky, which he defined as «a fairly routine intoxication originating from a wound and associated with the periodic entry of non-sterile degradation products from the wound into the circulation» [6].

Main Provisions of the Paper

The purpose of this publication is to present in a structured manner the key concepts traditionally used in clinical practice and the scientific literature when discussing sepsis. The issues of postmortem verification of organ dysfunction — as critical diagnostic features of typical sepsis and septic shock — have been comprehensively addressed in the article by Rybakova M. (2021) [7].

Although sepsis is caused by microorganisms (infectious agents), it is clear that it does not fulfill all the classical criteria of a typical infectious disease (Table 1):

- it lacks a single, typical causative agent (i.e., it is not monocausal);
- in most cases, the pathogen cannot be isolated in pure culture;
- it cannot be reliably reproduced in experimental models;
- it is not contagious;
- it does not follow a cyclical course;
- it does not induce specific immunity;
- it does not produce characteristic organ lesions;
- it does not present with a classic infectious complex (e. g., primary affect, lymphangitis, lymphadenitis), but typically involves a primary septic focus.

It is important to emphasize that the first three criteria represent the essential characteristics of infection according to the classical Koch's postulates, while the remaining ones are direct logical consequences. As a result, sepsis has characteristics that are in many ways the exact opposite of those of classical infections. Therefore, the direct attribution of sepsis to infection as its cause seems to be fundamentally incorrect.

According to I. V. Davydovsky, neither sepsis nor purulent-resorptive fever — although caused by infectious agents — should be considered «infectious diseases in the strict sense» [5, 6].

It is also noteworthy that sepsis is extremely difficult to reproduce in experimental settings [8, 9], despite numerous modeling attempts. The pathological processes induced in these experiments differ significantly from clinical human sepsis.

Sepsis is currently defined as «life-threatening organ dysfunction caused by a dysregulated host response to infection» [8]. However, such a definition allows for the conflation of two distinct concepts — «infection» and «infectious agent» — a logical fallacy known as ignoratio elenchi, which violates the fundamental law of identity in classical logic. The use of the term «infection» without appropriate clarification serves as a rhetorical device that allows sepsis to be indiscriminately associated with any infectious disease or infectious agent. This is logically flawed: first, because sepsis does not meet the classical criteria of Koch's postulates (see Table 1); and second, because not every infectious agent is capable of inducing sepsis.

Traditionally, in the Russian medical literature, sepsis was described as a generalized purulent process characterized by the presence of a localized septic focus and systemic dissemination either in the form of purulent metastases (septicopyemia) or as infectious-toxic shock (septicemia) [5].

Given that the spread of the infectious process occurs in a wide range of bacterial (e. g. typhoid fever, epidemic typhus, tuberculosis, syphilis), viral (e. g. viral hepatitis, smallpox, viral hemorrhagic fevers), protozoal (e. g., schistosomiasis, trypanosomiasis), fungal (e. g., systemic candidiasis), chlamy-

dial (e. g., ornithosis), mycoplasmal, and other diseases, it is obvious that a clear distinction must be made between these conditions and sepsis. This requires careful consideration of the following points:

1. The concept of sepsis is not the same as that of infection, even when qualified by phrases such as «life-threatening organ dysfunction».

2. The concept of sepsis is not synonymous with that of generalized infection, regardless of similarities in their clinical presentations.

3. The ability — or inability — of a given infectious agent to induce purulent inflammation is a defining criterion.

It is important to emphasize that sepsis is not an infection in the classical sense, but rather a generalized suppurative process, underscoring the need to distinguish sepsis from generalized forms of common infections.

This definition logically leads to the following conclusions

1. Generalized forms of typical infections caused by pathogens incapable of inducing purulent inflammation (such as certain bacteria, mycoplasmas, viruses, protozoa, fungi, etc.) should not be classified as sepsis.

2. Generalized forms of typical infections that retain the basic characteristics of classical infectious diseases (e. g., transmissibility) should not be classified as sepsis.

3. Shock or toxic states associated with highly virulent forms of classical infections should be considered complications of the primary disease, not septic shock.

The spread of the septic process occurs by hematogenous or lymphatic routes. However, as noted, «the blood and lymph of healthy individuals regularly transport various microorganisms. In conditions such as malnutrition, surgery, or other traumatic insults, bacteremia is a common occurrence» and therefore «bacteremia alone is not evidence of sepsis» [5].

Examples of proper documentation of the cause of death in the medical death certificate.

Ia) Infectious-toxic shock (A48.3)
b) Typhoid fever (A01.0)
c) —
d) —

or

Ia) Endotoxic shock (R57.8)
b) Coronavirus infection (U07.1)
c) —
d) —

According to the Sepsis-3 consensus, there are two distinct clinicopathologic subsets of sepsis: typical sepsis (sepsis, septicemia) and septic shock. These are not sequential stages of a single disease, but rather mutually exclusive, independent clinicopathologic entities. It follows that typical sepsis should not be viewed as a condition that inevitably progresses to septic shock, nor should septic shock be viewed as a direct consequence of typical sepsis.

The immediate cause of death (line Ia of the medical death certificate) should include either sepsis (A40-A41) or septic shock (R57.2), but not both.

Example of an incorrect entry for the cause of death on the medical death certificate:

Ia) Septic shock (R57.2)
b) Sepsis due to *Staphylococcus aureus* (A41.0)
c) Skin abscess, furuncle and carbuncle of buttocks (L02.3)
d) —

Example of correct entry:

Ia) Sepsis due to *Staphylococcus aureus* (A41.0)
b) Skin abscess, furuncle and carbuncle of buttocks (L02.3)
c) —
d) —

Although it is well established that sepsis lacks a single specific causative pathogen — reflecting its polyetiologic or non-monocausal nature — some empirical observations have been reported regarding the etiologic features of different clinicopathologic forms of sepsis [10] (Table 2). However, these findings remain anecdotal and lack robust statistical validation.

The identification of Gram-negative bacteria as the more common etiologic agents in septic shock and Gram-positive bacteria as the more common culprits in typical sepsis underscores the fundamental distinction between the two major clinicopathologic forms of sepsis defined by the Sepsis-3 consensus, namely typical sepsis and septic shock. This supports the conclusion that they are not sequential stages of the same disease process, but rather distinct and mutually exclusive clinicopathologic entities.

Table 2. Selected Etiological Features of Sepsis [10].

Staphylococcus aureus
• Widespread small-focus purulent metastases
• Tricuspid valve septic endocarditis
Streptococcus pyogenes
• Large-focus purulent metastases
• Mitral valve septic endocarditis
Streptococcus pneumoniae
• Tendency toward granulomatous reactions
Gram-negative bacteria
• Bacterial shock (currently defined as septic shock)

Professor I. V. Davydovsky noted that «in practice, the question of the causative agent of sepsis is reduced [almost exclusively] to three of the oldest symbionts of the human body: staphylococci, streptococci, and Escherichia coli. These microbes are completely uncharacteristic for entering into complex nosological relationships with the host» [5].

The view that extensive purulent foci — such as diffuse purulent peritonitis, pleural empyema, deep fascial phlegmons, and multiple large pulmonary abscesses – may actually inhibit the formation of metastatic purulent lesions seems justified [10]. Therefore, they cannot be considered as sources of generalized purulent dissemination and, consequently, should not be considered as causes of sepsis. Shock or toxic syndromes associated with such extensive purulent foci should be interpreted as complications of the underlying disease rather than as manifestations of sepsis or septic shock.

Example of an incorrect entry of the cause of death on the medical death certificate:

I a) Sepsis due to *Staphylococcus aureus* (A41.0)

b) Generalized purulent peritonitis (K65.0)

c) Diverticular disease of the colon with perforation and abscess (K57.2)

d) —

Example of a correct entry of the cause of death on the medical death certificate:

I a) Toxic shock syndrome (A48.3)

b) Generalized purulent peritonitis (K65.0)

c) Diverticular disease of the colon with perforation and abscess (K57.2)

d) —

The core terms and concepts traditionally used in discussions of sepsis require further clarification.

The term sepsis is equivalent to septicemia, and in the English-language literature the two are conventionally used interchangeably — they are considered complete synonyms.

Historically, in the Russian medical literature, septicemia referred specifically to sepsis without the formation of purulent metastases. However, this interpretation was not accepted by the international professional community. It was only with the Sepsis-3 consensus (2016) that the new term septic shock was introduced, which effectively describes the same condition — sepsis without suppurative metastasis.

Given the introduction of the term septic shock, the term septicemia should now be reserved for its original meaning: in English, septicemia is synonymous with sepsis.

The term septic shock, newly defined by the Sepsis-3 Consensus (2016), refers to a form of sepsis characterized by the absence of purulent metastases and accompanied by severe systemic intoxication and clinical signs of shock.

The term severe sepsis is used to describe typical sepsis with the formation of purulent metastases and prominent infectious and toxic manifestations, but without being classified as septic shock.

The term septicopyemia still used in the Russian literature has no equivalent in English; it was introduced as the opposite of septicemia, referring to typical sepsis with purulent metastasis development.

The term bacteremia refers to a transient condition characterized by the transport of bacteria (or bacterial colonies) through the bloodstream, often accompanied by bacterial embolism. Blood cultures are not consistently positive, which can only be explained by the fact that blood is not a habitat, but a transport medium in the hematogenous dissemination of the suppurative process. It is no coincidence that bacteremia (A49.9) is excluded from the diagnostic criteria for sepsis.

The terms toxic shock and infectious toxic shock are combined in ICD-10 into a single category, toxic shock syndrome, including bacterial toxic shock (A48.3).

The term endotoxin-associated shock is included into a separate ICD-10 category «Other shock» (R57.8), although all of these conditions are clinically identical and differ only in the primary damaging effect, which is of an «overwhelming force» nature.

The term systemic inflammatory response syndrome (SIRS) is classified under the three-character code R65 in ICD-10. The Sepsis-3 Consensus (2016) does not remove the term completely, but only excludes it from the diagnostic criteria for sepsis. In addition, one of the four-digit subcategories is recommended for use in coding severe sepsis (R65.1).

Conclusion

1. Sepsis is a generalized suppurative process that is fundamentally different from typical infections. It is polyetiologic (not caused by a single agent), the pathogen usually cannot be isolated in pure culture, it cannot be reliably reproduced experimentally, it is not contagious, it does not follow a cyclical course, it does not induce specific immunity, and it lacks characteristic organ involvement. It typically originates from a primary septic focus rather than a primary infectious complex.

1.1 Generalized forms of infection caused by pathogens that do not induce purulent inflammation and that have characteristic features of classical infections should not be classified as sepsis.

1.2 Generalization of the suppurative process occurs by hematogenous or lymphogenous routes. However, bacteremia (A49.9) is not a defining diagnostic feature of sepsis because the blood does not serve as a habitat but merely as a transport medium during the hematogenous spread of the suppurative process.

2. Typical sepsis (A40-A41), including severe sepsis (R65.1), is primarily caused by Gram-positive flora and is characterized by the presence of multiple purulent metastases. Septic shock (R57.2), typically caused by gram-negative flora, presents predominantly with features of bacterial toxin-mediated shock, while purulent metastases generally do not have time to form by the time of death. Special types of sepsis — such as bacterial (infective) endocarditis (I33) and chronic sepsis (sepsis lenta) — do not have distinct ICD-10 codes.

2.1 Typical sepsis (including severe sepsis) and septic shock should be considered distinct clinicopathologic entities. Sepsis should not be considered a condition that necessarily progresses to septic shock, nor should septic shock be considered a direct consequence of sepsis.

2.2 Extensive purulent foci such as diffuse purulent peritonitis, pleural empyema, compartmental pleural effusions, and multiple large pulmonary abscesses tend to inhibit the development of purulent metastases. Therefore, they should not be considered sources of generalized purulent spread and, consequently, should not be considered causes of sepsis. Shock states or intoxication syndromes associated with extensive purulent foci should be considered a complication of the underlying disease rather than manifestations of sepsis or septic shock.

2.3 Despite similarities in clinical presentation between septic shock and shock syndromes associated with typical infections, the latter should be distinguished from sepsis by the presence of features characteristic of classical infections. Shock associated with highly toxic forms of typical infections should be considered a complication of the primary disease rather than septic shock.

3. It is suggested not to use the terms septicopyemia and septicemia anymore. The contemporary equivalent of septicopyemia could be «typical sepsis», while septicemia corresponds to the term defined as «septic shock».

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