Journal of Critical Care 40 (2017) 229–242

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Sepsis and septic shock: Pathogenesis and treatment perspectives

Hayk Minasyan

Mamikonyanz 38-38, Yerevan 0014, Armenia

ARTICLE INFO

Keywords:
Bacteremia
Sepsis
Septic shock
Pathogenesis
Treatment

ABSTRACT

The majority of bacteremias do not develop to sepsis: bacteria are cleared from the bloodstream. Oxygen released from erythrocytes and humoral immunity kill bacteria in the bloodstream. Sepsis develops if bacteria are resistant to oxidation and proliferate in erythrocytes. Bacteria provoke oxygen release from erythrocytes to arterial blood. Abundant release of oxygen to the plasma triggers a cascade of events that cause: 1. oxygen delivery failure to cells; 2. oxidation of plasma components that impairs humoral regulation and inactivates immune complexes; 3. disseminated intravascular coagulation and multiple organs' failure. Bacterial reservoir inside erythrocytes provides the long-term survival of bacteria and is the cause of ineffectiveness of antibiotics and host immune reactions. Treatment perspectives that include different aspects of sepsis development are discussed.

Contents

E-mail address: haykminasyan@rambler.ru.

http://dx.doi.org/10.1016/j.jcrc.2017.04.015
0883-9441/

1. Introduction

Sepsis is both best known yet most poorly understood medical disorders [1]. Sepsis leads to shock, multiple organ failure and death if not recognized early and treated promptly [2]. It is a serious clinical condition that represents a patient's response to infection and has a high mortality rate [3]. Sepsis remains the dominant challenge in the care of critically ill patients [4]. More than 30 million cases of sepsis worldwide per annum are estimated. The incidence of sepsis increases 9-13% annually, a mortality rate is 33–35% [5-12] (Table 1). The most common sites of infection are the lungs (40%), abdomen (30%) and urinary tract (10%) [13]. Sepsis may be caused by gram-positive, gram-negative and poly microbial infection [14,15]. Gram-negative infection most often occurs in the lungs [16]. *Staphylococcus aureus* and Streptococcus pneumoniae are gram-positive isolates, whereas *Escherichia coli*, Klebsiella species, and Pseudomonas aeruginosa predominate among gram-negative isolates [17,18]. Gram-positive organisms cause sepsis by producing exotoxins and by their cell wall components [19]. Gram-negative bacteria cause sepsis by their membrane lipopolysaccharides (endotoxins) [20]. Bacterial toxins play a pivotal role in the pathophysiology of sepsis, however, the literature illustrates that no single mediator/system/pathway/pathogen drives the pathophysiology of sepsis [21]. Current knowledge of sepsis pathogenesis includes infection interaction with the host before bacteria enter the bloodstream [1,22-26]. Actually, the mechanisms of host defense in the tissues differ from the mechanisms of intravasal (bloodstream) defense because extravasal defense is provided mainly by leukocytes whereas intravasal defense is fulfilled by erythrocytes. The humoral immunity events take place in pre-septic stage and interfere with the study of sepsis "per se." As a result, the pathogenesis and pathophysiology of some pivotal aspects of sepsis remain unclear.

2. Pre-septic (local) and septic (bloodstream) stages of infection

Not all bacteremias lead to sepsis. People have everyday bacteremia, particularly, from oral cavity, but sepsis rarely develops [27-31]. It occurs when the infection is resistant to host antibacterial defense. The latter is different in the tissues and the bloodstream. If the infection develops locally (tissue, cavity, etc.) and then enters the bloodstream, there are two stages of sepsis: pre-septic (local) and septic (generalized). If infection enters the bloodstream directly from an external source (contaminated intravenous injection, bite, etc.), the pre-septic stage is absent. Local antibacterial defense is provided by phagocytosis (leukocytes and their local versions: resident macrophages), complement, NETs, etc., whereas in the bloodstream bacteria are killed by bactericidal humoral factors and oxygen that is released from erythrocytes [32,33]. Bacteria proliferate in the tissues being resistant to complement. Blood natural resistance factors (complement, lysozym, etc.) are not effective if infection enters the blood from the tissues. Sepsis develops when bacteria in the bloodstream survive oxidation on the surface of erythrocytes [32-36].

3. The features of sepsis causing bacteria

Relatively few pathogens can cause sepsis. For causing sepsis bacteria should have certain features that provide their survival, proliferation and dissemination in human body. The characteristics of the pathogens, that most frequently cause sepsis, may or may not be common for all of them (see Table 2).

Sepsis causing bacteria are both gram positive and gram negative. Gram-positive organisms are better suited to invade host tissues than gram-negative organisms [37]. The lack of endotoxin in the outer cell wall is compensated for by the presence of exposed peptidoglycan and a range of other toxic secreted products. Cell wall components of gram-positive bacteria may signal via the same receptor as gram-negative endotoxin [37]. Gram-negative organisms are associated with poorer outcomes in first-hit infections; an inverse relationship between Gram status and mortality is observed in second-hit infections [38].

The majority of sepsis causing bacteria is facultative anaerobes [39]. This type of respiration is the most flexible and it facilitates pathogen survival, proliferation and dissemination in the variety of environmental conditions. The pathogens that are not facultative anaerobes, may express additional respiratory mechanisms that make their respiration close to facultative anaerobes [40,41].

All sepsis causing bacteria produce superoxide dismutase (SOD), catalase and glutathione peroxidases (Table 2), that protect them against oxidative stress caused by reactive oxygen species. The primary source of oxidative stress for sepsis causing bacteria is the attack by host phagocytic cells. All successful pathogens have evolved effective systems for defense against oxidative stress [42]. Phagocytes utilize the cytotoxic effects of the reactive oxygen species, such as superoxide, hydrogen peroxide, and the highly toxic hydroxyl radical. Sepsis causing bacteria have evolved effective enzymatic pathways of oxidant inactivation, including those catalyzed by superoxide dismutase (SOD),

Table 1
The dynamics of sepsis and septic shock incidence and mortality.

The dynamics of sepsis and septic shock incidence and mortality.

SEPSIS	Data	Study	Number of participants, trials	Country of study	Year of publication	Authors
Incidence	31.5 million[a]	2015	27 studies	Worldwide	2016	Fleischmann et al. [5]
	436/100,000	2012	USCB[b]	USA	2016	Stoller et al. [6]
Incidence increase	13.0% annually	2004–2009	36 trials	USA	2013	Gaieski et al. [7]
	9.0% annually	2008–2012	82,300	Italy	2017	Yébenes et al. [8]
Mortality	33.2%[c]	2006–2009	14,418	Worldwide	2014	Stevenson et al. [9]
	35·3%[c]	2012	2973	Worldwide	2014	Vincent et al. [10]
Mortality decline	From 40.4% to 31.4%	From 1998 to 2009	203,481	USA	2013	Walkeyet al. [11]
	From 35.0% to 18.4%	From 2000 to 2012	101,064	Australia, New Zealand	2014	Kaukonen et al. [12]

[a] – Global estimates of sepsis (cases a year)
[b] – US Census included 308,745,538 individuals
[c] – 28 day mortality