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Review

Mechanisms and pathways for the clearance of bacteria from blood circulation in health and disease

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ABSTRACT

Available data do not support the concept that leukocytes engulf and kill bacteria in the bloodstream. Leukocytes cannot recognize or engulf bacteria in flowing blood; therefore, phagocytosis is impossible in the bloodstream and occurs instead outside of the bloodstream in the body tissues. Erythrocytes capture bacteria in the circulation using an electric charge and kill them using oxidation. The dead bacteria are then disintegrated and digested by the reticuloendothelial system (RES), particularly in the liver and the spleen.

Contents

1. Introduction

Until recently, there has been no concise explanation of how bacteria are cleared from the bloodstream. Available data do not support the idea that leukocytes are able to engulf bacteria in the bloodstream. In the last century, substantial efforts were made to understand how bacteria is cleared from the circulation. Research revealed that most microorganisms were less capable of provoking disease when injected intravenously than when administered by any other route. Living bacteria disappeared swiftly from the circulation [1,2]. Humoral immunity had no effect on the clearing of bacteria if the host had no prior experience with the invading microorganism [3]. When living bacteria were injected into veins, 90–99.9% disappeared within the first 10 min to five hours [4]. Suppressing leukocyte phagocytosis did not slow down bacteria clearance. Starvation [5], irradiation [6,7], agranulocytosis [8–10], injections of corticotropin [11], nor the use of adrenal steroids [10] had any affect on bloodstream bacteria clearance. Factors such

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as shock [12], splenectomy [3], renal failure [13], the presence of overwhelming infection [14,15], intoxication by endotoxins [12], changes in blood clotting [13], or removal of platelets [16,17] also had little to no effect on the clearing of bacteria. Among these factors, the last was the most effective, with only rare complications from bacteremia. This phenomenon is well-known in heroin and morphine addicts. When taking the drug intravenously, they regularly inject a large number of bacteria (especially in case of self-made drugs) into the bloodstream, but sepsis is a rare complication. Bacterial endocarditis is the main complication, but it does not happen often. The incidence of infective endocarditis in intravenous drug users has been estimated to be 5.3 cases/100,000 person-years [18]. Another estimate is approximately two to four cases of endocarditis per 1000 years of injection by drug users [19–21]. Hussey and Katz found an incidence of 8% bacterial endocarditis in 102 addicts with a variety of infections [22]. Endocarditis usually is caused by *Staphylococcus aureus* (60.8% of cases), *streptococci* (16.2%), *Pseudomonas aeruginosa* (13.5%), mixed bacteria (8.1%), and *Corynebacterium JK* (1.4%) [23]. Rare cases of bacteremia with *Clostridium butyricum* [24] and *Paenibacillus larvae* [25] have been described in intravenous drug users. Clinical studies have also demonstrated lower mortality in patients with bacteremia due to central venous catheter infections as compared to other sources of infection [26,27].

In a healthy man, bacteremia is likely to be an everyday event. Transient bacteremia originating in the oral cavity occurs commonly during eating, chewing gum, brushing the teeth, or using toothpicks [28,29]. For example, rates for bacteremia in adults range from 23% to 57% as the result of tooth brushing [29]. The oral cavity contains an immense amount of bacteria: 1 mL of saliva may contain 750 million bacteria and 1 g of subgingival plaque may contain 200 billion bacteria [30–32]. More than 700 bacterial species have been found in the oral cavity [33]. After tooth extractions or brushing, 126 individual species of bacteria have been isolated in blood cultures [34]. The frequency of bacteremia after tooth extraction is 39–100% [35–38]. The microorganisms are cleared from the bloodstream within a few minutes to one hour after tooth extraction [39–42]. Rapid clearing of bacteria from the circulation means that mechanisms other than phagocytosis are used to achieve bacterial clearing [43].

2. Phagocytosis of bacteria in the blood stream is impossible

Phagocytosis was studied both *in vivo* and *in vitro*, and found to occur in the tissues, rather than in the bloodstream, so it is not the process by which bacteria are cleared from the circulation. Phagocytosis is impossible in the bloodstream because leukocytes cannot recognize or engulf bacteria in high-velocity blood flow. The mean velocity of blood in the aorta is 40 cm/s, in capillaries 0.03 cm/s, and in the venae cava superior and inferior, 15 cm/s [44–46]. In the aorta, a bacterium1 μm in size travels a distance in 1 s that exceeds its body size by a factor of 400,000 (in capillaries and venae cavae, the distances travelled in 1 s exceed the bacterium's body size by a factor of 300 and 150,000, respectively). In the bloodstream, all cells are moving very quickly, so recognition and "catching" of bacteria must be immediate and rapid. For phagocytic leukocytes, the average time required for bacterial engulfment has been observed to be at least 15 min [47]. In conditions auspicious for phagocytosis, efficient uptake of 3-μm Fc targets by neutrophils occur over slightly more than a minute (~66 s) and the engulfment of similarly sized zymosan occurs even more slowly, over ~167 s [48]. Other research has shown that the duration of phagocytosis (depending upon engulfed particle size) ranges from 70 ± 10 s to 210 ± 60 s [49]. Thus, phagocytosis requires a relatively long time span and is only possible outside of the blood circulatory system, particularly in tissues, connective tissue, subepithelial space, the lymphatic system, and in other locations where the velocity of liquids is minimal [43]. In the bloodstream, the only phenomenon that provides rapid attraction and fixation of bacteria is their interaction with electric charges [43]. Leukocytes cannot attract and fix bacteria onto their surfaces using the charge because the zeta potential of leukocyte membranes is weak. Leukocytes cannot be charged by plasma flow and rubbing against other cells because their membranes are thin, soft, elastic, and wrinkled [50,51]. The changeable shape of leukocytes prevents triboelectric charging as well. There are also other factors that contribute to the failure of leukocytes to clear bacteria from the bloodstream, but the main reason is that leukocytes in the bloodstream are not able to recognize, attract, or engulf bacteria.

3. Leukocytes cannot clear bacteria from the bloodstream because of their scant availability, short life span, and vulnerability

The number of available bactericidal cells is important for bloodstream clearing. Leukocytes represent less than 0.1% of blood cells (99.9% are erythrocytes, which outnumber leukocytes by a ratio of 1000:1)[52]. Only 68% (60% neutrophils and 8% monocytes) of peripheral blood leukocytes are "professional" phagocytic cells [53]. They have approximately 1500 fewer chances to come in contact with bacteria than erythrocytes [43]. Neutrophils cannot renew their lysosomes (used in digesting microbes) and die after engulfing a few pathogens [53]. Moreover, the life span of a circulating human neutrophil is short, about 5.4 days [54], whereas erythrocytes circulate for about 100–120 days, living 18–22 times longer than neutrophils [55].

It is quite common for billions of bacteria to enter the bloodstream. The number of leukocytes (20–30 million in peripheral blood) is not enough to clear bacteria. Moreover, leukocytes are vulnerable with respect to many bacteria, and the latter are able to kill phagocytes [60–63]. Incomplete (imperfect) phagocytosis occurs often, and for many microorganisms, phagocytosis is indispensable for proliferation and dissemination [56–59].

4. Triboelectric charging prevents bacterial proliferation in the bloodstream

In clinical practice, bacteremia is detected by culturing the blood from the median cubital vein. This approach only detects bacteremia in venous blood. Bacteremia may be in the arterial blood as well and is detected by culturing blood from indwelling arterial lines [64]. An arterial catheter is not a reliable sampling site for blood cultures and does not replace venipuncture [65,66]. *Escherichia coli* have been demonstrated as the most common bacteria to cause bloodstream infections in almost all population-based studies in 5 continents [67–71]. *Escherichia coli, S. aureus*, coagulase-negative *staphylococci*, *streptococci*, other *Enterobacteriaceae* and *P. aeruginosa* are common bacteria in bloodstream infections [72].

Bacteria enter the bloodstream from the following sources:

(a) a tissue reservoir (local infection): the infection enters via the venous blood
(b) the lungs: the primary infection moves through pulmonary veins to enter the systemic arterial blood
(c) the lymphatic system: bacteria enter the venous blood through terminal lymphatic vessels, the right atrium and ventricle of the heart, then, through the lungs, the bacteria enter the left atrium and ventricle of the heart and the systemic circulation