Neutrophil Activity Depending On Microorganism Resistance To Antibacterial Therapy In Sepsis Patients

Khayitov D. H.

Bukhara State Medical Institute

ABSTRACT

Sepsis has been and continues to be the most frequent cause of mortality in intensive care units. Despite modern methods of diagnosis and treatment, high mortality in sepsis patients remains a worldwide problem. One important aspect in the management of sepsis is antibiotic therapy, but the efficacy of this treatment can be severely compromised by resistance of microorganisms to the antibiotics used. Neutrophils, key cells of the immune system, play a crucial role in fighting infection. However, how neutrophil levels and activity are altered by microbial resistance to antibiotic therapy in patients with sepsis remains a subject of active research.

Keywords: antibiotic-resistant microorganisms, leukocyte sensitivity, immune properties of the organism, neutrophil traps, septic patients.

Introduction. The World Assembly and the World Health Organisation (WHO) consider sepsis a public health priority, having adopted a resolution to improve the prevention, diagnosis and clinical management of sepsis. The mortality rate remains high (30-50%) in surgical hospitals and intensive care units. The incidence of sepsis and septic shock continues to increase steadily.

Sepsis is defined as a dysregulation of the organism's response to an infectious agent with dysfunction of one or more organ systems. Organ dysfunction in sepsis is manifested by various signs such as tissue hypoperfusion, lactoacidosis, oliguria, acute changes in brain function including acute confusion [1,2].

Sepsis is a cascade of events resulting from innate and adaptive immune responses; it is characterised by activation of different cell types and release of both pro-inflammatory and anti-inflammatory molecules. In the initial phase of sepsis, a predominantly hyperinflammatory state develops due to the interaction of cells with the infectious agent, followed by a state of immune hyporesponsiveness [2,3].

Neutrophils are the first cells to migrate across the vascular epithelium and reach the site of infection [4]. The chemokines CXCL1, CXCL2, leukotriene B4 and interleukin-8 (CXCL8) released at this stage act on leukocyte coagulation, inducing stable binding between adhesion molecules and creating a concentration gradient that stimulates neutrophil transmigration from the bloodstream to the site of infection [5]. Changes in the neutrophil response profile in sepsis have been the focus of various studies. For example, identifying changes in cell signalling pathways may provide a basis for targeted drug development aimed at treating this condition [6].

Under normal conditions, circulating neutrophils have a short half-life (7-12 hours in vivo), but their lifespan is prolonged in sepsis. The level of the anti-apoptotic protein Mcl-1 (myeloid cell leukaemia), which plays a key role in neutrophil apoptosis, was found to be elevated in neutrophils isolated from patients

with severe sepsis [7]. Neutrophil migration in vivo involves four distinct phases, all of which are disrupted during sepsis: mobilisation and release from the bone marrow, marginalisation and rolling, adhesion and transmigration [8].

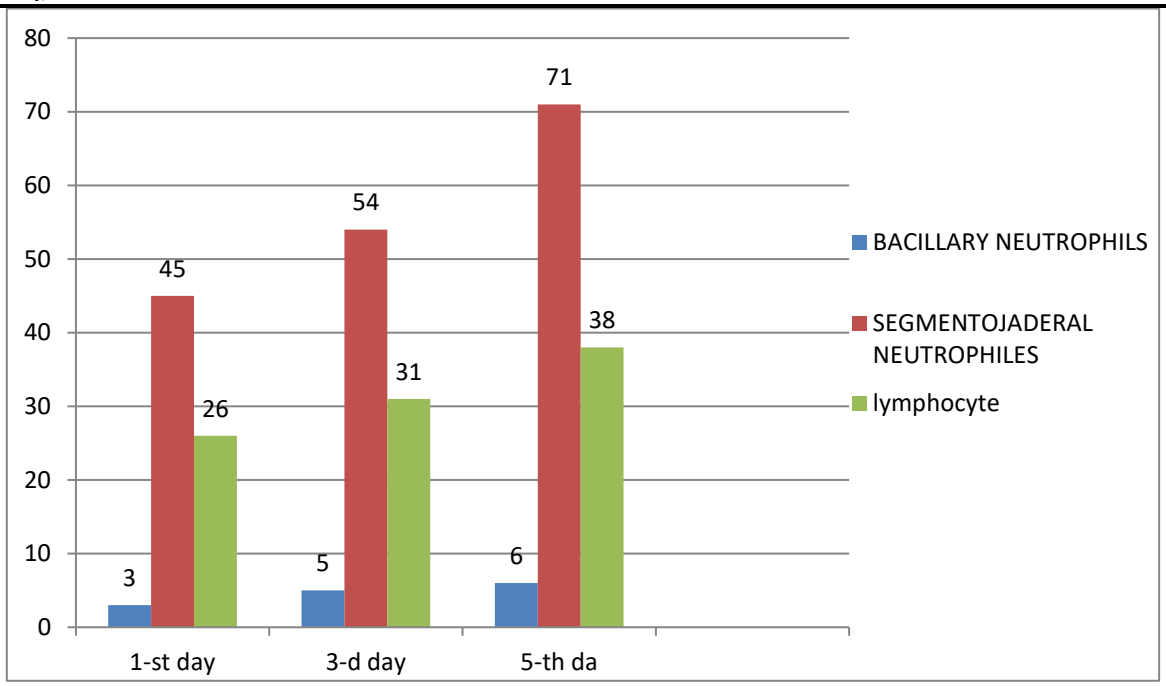
Antimicrobial activity of neutrophils includes recognition of invading pathogens and microbial components, downstream signalling pathway leading to the release of inflammatory cytokines and chemokines, generation of oxidants, phagocytosis and formation of neutrophil extracellular traps (NETs) [9,10,11]. All these effector functions of neutrophils are thought to be affected by sepsis. Neutrophil extracellular traps (NETs) play an important role in the antimicrobial activity of neutrophils and consist of a network of chromatin fibres associated with granules of antimicrobial peptides and enzymes such as myeloperoxidase, elastase and cathepsin G that capture and kill invading microbial pathogens [12]. The formation of NVL depends on the effects of bacterial [13] and neutrophil elastase released from azurophilic granules on neutrophils, which can decondense nuclear chromatin and further confer antimicrobial properties along with other serine proteases and NVL-associated myeloperoxidase [14,15]. The role of NVL in controlling the spread of pathogens in sepsis has not been fully elucidated.

Target of the study: To establish the relationship of neutrophil ratios in antibiotic-resistant microorganisms with improvement of treatment results and reduction of patients' mortality in sepsis development by optimisation of complex intensive therapy.

Material and methods. Blood samples of 34 patients (15 women, 19 men, aged 26-73 years) with sepsis were studied. The patients were divided into two groups: in group I the causative agents of sepsis were antibiotic-resistant microorganisms, in group II - microorganisms sensitive to antibiotics. Identification of isolated microorganisms and determination of sensitivity was carried out using routine microbiological methods. The functional activity of neutrophils was evaluated in blood: phagocytic activity of neutrophils, lysosomal activity, evaluation of intracellular oxygen-dependent metabolism of neutrophils, counting of neutrophil extracellular traps.

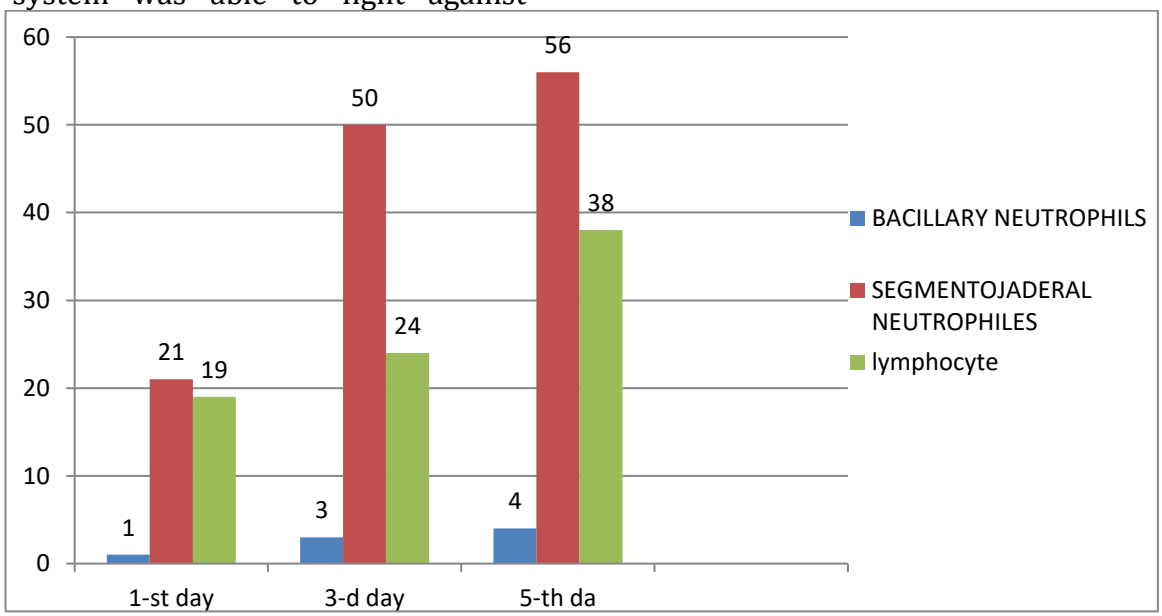
Results. The data of patients who were in the department of surgical intensive care of Bukhara branch of RSCEMP were included in the scientific study. Materials of 34 patients were studied, including 20 patients with different types of peritonitis with subsequent complication of sepsis and 14 patients after abdominal surgical interventions with subsequent development of sepsis. The age of patients varied from 26 to 73 years (mean age was 44,6±1,8 years). According to gender - men were 22 (64,7%), women - 12 (35,3%). All patients underwent standard diagnostic methods (BAC blood culture, abdominal ultrasound, as well as laboratory tests (leukoformula, neutrophil to lymphocyte ratio index - ISNL). BAC culture was assessed in all patients and it was found that in 8 (25.3%) of the patients studied, the causative agents of sepsis were antibiotic-resistant microorganisms, in the remaining 26 (74.7%) sensitivity to certain types of antibiotics (macrolides, cephalosporins, beta-lactams) was detected. On abdominal ultrasound, the condition of infected foci in 20 patients (pancreas (30%), gallbladder (30%), appendicular outgrowth (40%)) indicated increased density and architectonics of the organ, granulations and infiltration. Septic complication developed in 14 subjects after surgical interventions (cholecystectomy (27%), appendectomy (68%), enteroanastomosis (5%)).

Leukoforms taken from all the patients studied on the 1st, 3rd and 5th day revealed a significant difference in the neutrophil to lymphocyte ratio index in the two groups (Graph 1).



Graph 1. Dynamics of indicators of the control I group

A significant increase in the total number of leucocytes in group I by 45.4% was found compared to group II (Graph 2). The increased number of neutrophils indicated that the immune system was able to fight against bacteremia inside the organism. The indicators of neutrophil absorptive activity (phagocytosis activity) in group I were 44.3% higher than in group II.



Graph 2. Dynamics of indicators of group II

The results of induced and spontaneous NST-test and phagocytic number in patients in group I were also increased by 22.4%. And there was also a tendency to increase neutrophil extracellular traps in group I by 22.8%.

Conclusion. The indicators of functional activity of neutrophils in patients with sepsis, the causative agent of which is antibiotic-resistant microorganism, when compared with septic patients, in whom the causative agents are resistant to antibiotics, are different and characterised by an increase in neutrophils and

lymphocytes. The control group showed an increase in the phagocytic capacity of neutrophils by 22.4% compared to group II. Antibioticresistant organism though insensitive to antibiotic therapy indicated a hyperreactive response to endotoxins of pathogens than group II. Because of this, this topic requires further study and research to identify improved standard therapy for patients with antibiotic resistant organism.

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