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Literature Review

Sepsis Antibacterial Therapy Perspective Possibilities of Sepsis Curing, Using Drugs that Activate the Cholinergic Anti-Inflammatory Pathway

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Abstract

Literature data, as well as the results of our experimental studies (after the cholinergic anti-inflammatory mechanism - «cholinergic anti-inflammatory pathway» - we established in 1987) allow us to suppose, that n-cholinomimetic (α7nAChRs agonists, nicotine), acetylcholinesterase reversible inhibitor, adrenomimetics (β2ARs agonists) and m-cholinomimetic (m1-cholinomimetics), along with a range of therapeutic measures, in particular, with prescription of antibiotics, can be considered as promising agents for the treatment of sepsis and septic shock.

Keywords: Cholinergic Anti-Inflammatory Pathway; Sepsis; α7nachr Agonist; β2ars Agonist; Acetylcholinesterase Reversible Inhibitor; Proinflammatory Cytokines

Sepsis antibacterial therapy

Septicaemia and septic shock are a major public health problem. Every year, around the world, it causes the death of more than a million people. Mortality from sepsis, depending on various factors, ranges from 12 to 60% of all deaths associated with diseases and their complications [1], and there is an increase in the number of cases of sepsis and the mortality rate from it [2]. Sepsis is a clinical syndrome with the development of life-threatening organ dysfunction caused by impaired regulation of response to infection. In septic shock, there is a critical reduction in tissue perfusion; many organs, including lungs, kidneys and liver, can also be severely affected. The most common causes in immunocompetent patients are various types of gram-positive and gram-negative bacteria. Atypical bacterial or fungal infections may be contributing factors in immunodeficient patients. Symptoms include fever, hypotension, oliguria and blurred consciousness. Diagnosis is based on clinical studies combined with bacteriological sowing results indicating the presence of infection; early detection and treatment are crucial. Aggressive infusion resuscitation, antibiotics, surgical removal of an infected area or necrotic tissue, drainage of purulent secretions and maintenance therapy are used as treatment [3-5].

The role of optimized antimicrobial therapy in pathogen clearance and mortality reduction is not currently in doubt. Parenteral administration of antibiotics is administered as soon as possible after taking blood samples, biological fluids and damaged tissues for gram staining and sowing. Early empirical therapy initiated immediately after suspicion of sepsis is important and can be crucial. The choice of antibiotic requires a reasonable assumption based on: the anticipated source of infection (e.g. pneumonia, urinary tract infection); clinical conditions; the proven or suspected presence of pathogens and their sensitivity characteristics characteristic of the hospital department or facility; and previous results of bacteriological sowing.

Typically, a wide range of gram-positive and gram-negative antibacterial are used first; patients with compromised immunity should also receive an empirical antifungal agent. There are many possible starting points for treatment; if available, knowledge

about the specifics of the pathogens in the institutional environment and their susceptibility to antibiotics (antibiotics) should be used to select an empirical treatment. In general, typical antibiotics for empirical effects on Gram-positive bacteria are vancomycin and linezolid. Empirical therapy against gram-negative bacteria is more feasible and includes broad-spectrum penicillin's (e.g. piperacillin/tazobactam), 3rd or 4th generation cephalosporins, imipenem and aminoglycosides. The initial broad spectrum of action is reduced depending on the pathogen and its sensitivity to antibiotics [6].

The following principles of antibiotic therapy for sepsis are currently recommended (International Guidelines for Management of Sepsis and Septic Shock: 2016) [7,8]:

- Intravenous administration of antimicrobial agents should be initiated immediately after the identification of the pathogen and/or within 1 hour of the onset of the first symptoms of sepsis/septic shock (strong recommendation, moderate quality of evidence, evaluation applicable to both conditions).
- Empirical antimicrobial therapy is recommended in patients with sepsis/septic shock, including at least two classes of broad-spectrum antibiotics to treat a wider range of microorganisms or suspected pathogen, including bacteria, potential fungi and viruses (strong recommendation, moderate quality of evidence).
- Correction, in the form of a narrowing of empirical antibiotic therapy, should be made in the case of identification of the pathogen and its sensitivity and/or in the case of clinical improvement (best practice recommendation - British Pharmacological Society (BPS).
- Prophylactic prescribing of antibacterial in patients with severe inflammatory diseases of non-infectious genesis (severe pancreatitis, thermal burns of the skin, etc.) is not recommended (best practice recommendation - BPS).
- The dosing strategy for antimicrobial agents should be based on generally accepted pharmacokinetic/pharmacodynamic principles and should take into account the function of the organs and some specific features of antibacterial agents in patients with sepsis or septic shock (best practice recommendation - BPS).
- In the case of septic shock, initial empirical combined antibiotic therapy (using at least two antibiotics of different classes) should be directed towards a more likely range of pathogens (poor recommendation, poor quality of evidence).
- Routine clinical practice does not recommend combined antibiotic therapy for neutropenic fever/bacteriemia (strong recommendation, moderate quality of evidence).
- Combination antibacterial therapy is not recommended for the ongoing treatment of most other serious infections, including bacteriemia and sepsis without signs of shock (poor recommendation, poor quality of evidence).
- Combination antibacterial therapy is not recommended for routine treatment of neutropenic fever/bacteriemia (strong recommendation, average quality of evidence).
- In cases where combined antimicrobial therapy was originally used to treat septic shock, it is recommended that it be de-escalated or discontinued within the first few days in response to clinical improvement and/or proof of infection resolution. This applies to both etiotropic (positive culture of the pathogen) and empirical (in the case of negative bacteriological research) antibiotic therapy (best practice recommendation - BPS).
- Adequate duration of antibiotic therapy for the majority of infections associated with sepsis/septic shock is 7-10 days (poor recommendation, poor quality of evidence).
- Longer-term antibacterial use may be warranted in patients with slow clinical response to therapy; bacteriemia caused by Staphylococcus aureus; some fungal and viral infections; and patients with neutropenia (poor recommendation, poor quality of evidence).
- Shorter courses of antibiotic therapy may be available for certain patients, for example, in patients with rapid clinical response, and after adequate remediation of the source of infection in case of abdominal/ urinary sepsis or uncomplicated pyelonephritis (poor recommendation, poor quality of evidence).
- A daily assessment of the possibility of de-escalation of antimicrobial therapy in patients with sepsis/septic shock is recommended (best practice recommendation - BPS).
- Procalcitonin levels can be used to assess the duration of antimicrobial therapy in patients with sepsis (poor recommendation, poor quality of evidence) [7,8].

Perspective possibilities of sepsis curing, using drugs that activate the cholinergic anti-inflammatory pathway

Cholinergic stimulation, as we established in 1987 [9] and in subsequent studies, significantly reduces the mortality of albino mice from sepsis caused by intraperitoneal or intrapulmonary administration, respectively of *E. coli* and *P. vulgaris* [9-13]. Thus, the cholinergic anti-inflammatory mechanism has been discovered in 1987 [9], named «cholinergic anti-inflammatory pathway» in 2000 [14] after the research its implementation at the organismal, cellular and subcellular levels [10,13-15]. It should be noted that in 1995 it was proved the possibility of cholinomimetics for emergency activation of antimicrobial resistance of the organism in sepsis [10,11]. In the future, the study of the cholinergic anti-inflammatory pathway caused by the action of acetylcholine on α7n-acetylcholine receptors (α7nAChRs) cells of the monocyte-macrophage system (MMC), followed by inhibition of the production by the cells of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and reduced mortality from sepsis were devoted hundreds of articles various authors [12-22]. Reduced production of TNF-α, IL-1β, IL-6 (anti-inflammatory effect occurrence) for cholinergic anti-inflammatory pathway is provided kinase JAK2, transcription factor STAT3, NF-κB transcription factor) [14,19-23].

We have established on outbred mice that that acetylcholine chloride in a dose of 20 mg/kg 6 h after subcutaneous injection significantly reduces mortality of mice from sepsis induced by intraperitoneal injection of 2×10^9 CFUs diurnal culture of *E. coli* in 2.0 ml of saline and the blood levels of proinflammatory cytokines TNF-α, IL-1β, and IL-6 [18].

It was established in experiments on noninbred mice that activation of α7n-acetylcholine receptors (α7nAChR) by anabasine in single doses of 1.0 and 5.0 mg/kg for 2 h before modeling sepsis (intraperitoneal injection of 2×10^9 CFUs diurnal culture of *E. coli*) cause a significant dose-dependent reduction of mortality of mice due to a decrease in the amount of proinflammatory cytokines TNF-α, IL-1β and IL-6 in the blood. Anabasine in single doses of 0.1 mg/kg had no significant impact on the studied parameters [24].

The same action is taken by reversible inhibition of cholinesterase and nicotine on mouse mortality and blood levels of pro-inflammatory cytokines during the early phase of sepsis. So, the experiments on outbred albino mice have shown that Proserpine (reversible cholinesterase inhibitor) and nicotine (nicotinic receptor agonist) in a equivalent dose of 0.2 DL_{50} injected 2 h before sepsis induction significantly reduced animal mortality from experimental infection due to reduction of blood concentrations of proinflammatory cytokines TNF-α, IL-1β and IL-6 [25].

The stimulation of nicotinic and muscarinic cholinoreceptors (nAChR, mAChR) in outbred albino mice with nicotine and aceclidine, respectively, in single equilethal doses 0.5 DL_{50} 6 h before sepsis induction (intraperitoneal injection of $2,5\times10^9$ CFUs diurnal culture of *E. coli*) significantly reduced animal mortality due to a decrease in blood concentrations of proinflammatory cytokines IL-1β, IL-6, and MIP-2. Stimulation of mAChR (injection of aceclidine) stimulated the neutrophilic phagocytic and metabolic activity. Realization of the cholinergic anti-inflammatory pathway (stimulation of the peripheral nicotinic cholinoreceptors, in particular, α7nAChR and central muscarinic holoreceptors (in particular, m1AChR) was modulated by stimulation of the mAChR of the phagocytic monocytic system cells [26].

The activation of α7nAChR with anabasine (0.5 LD_{50}) and the use of antibodies to TNF-α (1 mg/kg) 2 h before sepsis modeling significantly reduces mortality of mice from experimental sepsis due to a decrease in the blood concentration of TNF-α, IL-1β, and IL-6. After combined administration of anti-TNF-α antibodies and anabases, an additive effect was observed [22]. The same influence caused the effect of m1AChR agonist (TBPB) and α7nAChRs agonist (GTS-21). Combined treatment with TBPB and GTS-21 determined their additive effect [23].

When the cholinergic anti-inflammatory pathway is realized, in addition to the excitation of α7nAChRs [12,15,27,28], which cause the effects already mentioned, nAChRs activation of the brain substance of the adrenal glands and sympathetic ganglia occurs, which leads to the production of epinephrine and norepinephrine (NE), which activation of MMS adrenergic receptors and reduce the production of pro-inflammatory cytokines [28]. At this *N. vagus*, releasing acetylcholine (ACh) in the celiac ganglion, causes excitation of the spleen nerve, the action of NE through its efferent fibers on T lymphocytes, the production of ACh by these lymphocytes, activation of ACh of α7nAChRs of MMS cells of the spleen [15,28]. Epinephrine and NE probably activating the adrenergic receptors of cells of the MMS (direct action) [28], β2-adrenergic receptors (β2ARs) of spleen T lymphocytes (indirect effect) [16], cause the same effect as activation of α7nAChRs, leading to reduction in

the synthesis of proinflammatory cytokines by cells of the MMS [15,17,21].

Experiments on random-bred albino mice showed that of β2-adrenoreceptor agonist hexaprenaline sulfate significantly reduced mortality of mice from experimental sepsis (intraperitoneal administration of E. coli) in 4 and 24 h after modeling by reducing blood levels of proinflammatory cytokines TNFα, IL-1β, and IL-6. The antagonist of β2AR ICI-118,551 eliminated this effect [21]. The combined administration of NF-κB inhibitor (BAY 11-7082) and β2-adrenoreceptors agonist have an additive effect [23].

The influence study of various drags on mortality of mice and the concentration of proinflammatory cytokines in blood at sepsis caused by *E. coli* showed that administration m-cholinomimetic (aceclydine), n-cholinomimetic (nicotine), reversible inhibitor of acetylcholinesterase (neostigmine methyl sulfate), n-cholinomimetic α7nAChRs agonist (GTS-21), epinephrine hydrochloride, andromimetic β2ARs agonist (hexaprenaline sulfate) causes decrease in mice mortality in sepsis caused by the administration (i.p.) of *E. coli* O157:H7 and the concentration of TNF-α, IL-1β and IL-6 in the blood in comparison with parameters at sepsis without use of drugs [29].

Thus, n-cholinomimetic (α7nAChRs agonists, nicotine), reversible inhibitor of acetylcholinesterase, andromimetic (β2ARs agonists) and m-cholinomimetic (m1-cholinomimetics), along with a range of therapeutic measures, in particular, with prescription of antibiotics, can be considered as promising agents for the treatment of sepsis and septic shock.

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