Clinical features and immune status in patients with erysipelas

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Key words:
erysipelas, recurrent erysipelas, lactoferrin, ceruloplasmin.

Relevance. The average incidence of erysipelas in Ukraine is 10,8 per 10 thousand population, in other European countries – 4,3 per 10 thousand population[1] [2].

The causative agent of erysipelas is beta-hemolytic Streptococcus serogroup A (β-HSA). Despite the reliability of this etiological factor, only in 5 % of cases it is possible to isolate β-HSA. When establishing the diagnosis of erysipelas, testing for streptococcus is considered impractical, since it can be released from the skin surface of healthy people, and antibodies to the pathogen can be a consequence of other forms of streptococcal infection suffered previously[3].

The share of severe course and complications with a predominance of intoxication syndrome in the clinical picture of the disease has increased, and cases of hemorrhagic forms of erysipelas have become more frequent (more than 60 %). The disease is characterized by a tendency to relapse (30 – 40 %), slow repair in the focus of inflammation[4].

It should be noted that erysipelas has a negative impact on the course of concomitant diseases and causes the development of many complications. Thus, in the structure of lymphostasis of the lower extremities, the proportion of secondary ones caused by erysipelas is 35 – 40 %. Each subsequent case of recurrent erysipelas increases the degree of lymphatic edema by 3 to 5 % from the baseline. Chronic lymph venous insufficiency in turn leads to disability of able-bodied persons. The highest mortality rate is recorded in elderly patients[5] [6].

The main direction of therapy is the use of antibacterial drugs. Insufficient effectiveness of traditional erysipelas treatment regimens, both in relation to the reverse development of clinical symptoms in the acute period of the disease, and in relation to the prevention of relapses, has led scientists to search for new methods of therapy, including the appointment of antibiotics in combination with immune correctors, magnetic therapy, and laser therapy.

Thus, despite a large number of studies devoted to various aspects of pathogenesis, clinic, diagnosis, treatment and prevention, erysipelas remains one of the most common human infectious diseases. The high proportion of complications, frequent relapses, the development of resistance to antibiotic therapy and the lack of preventive methods attract attention and require further study.

The aim is to study the state of research on clinical, epidemiological and immunological features of erysipelas, to determine the directions for solving the problem of preventing relapses of the disease.

Materials and methods – meta-analysis of databases with scientific publications (Pubmed / Medline, Scopus, Ebsco, Index Copernicus) was carried out, and a bibliographic and semantic research method was used.

Review and discussion

Clinical and epidemiological features of erysipelas at the present stage are: an increase in the proportion of severe course and complications with a predominance of intoxication syndrome in the clinical picture of the disease, up to the development of infectious and toxic shock, an increase in the number of patients with hemorrhagic forms, slow repair in the focus of inflammation[7] [8] [9].

It was found that beta-HSA causes the disease more often in the presence of such risk factors: diabetes mellitus, disorders of lymph and blood circulation, and skin trophism, work with limited mobility, bad habits

1 Michael Y, 2021, 18–21

2 Chemych, 2019, 26–32

3 Galli L, 2019, 532-551

4 Seybold U, 2018, 37-40

5 Chemych, 2019, 26–32

6 Seybold U, 2018, 37-40

7 Michael Y, 2021, 18-21

8 Chemych, 2019, 26–32

9 Seybold U, 2018, 37-40

(alcoholism, smoking, drug abuse), violation of the integrity of the skin or mucous membranes, mycotic lesions of the feet, etc[10] [11].

Various provoking factors play an important role in the development of erysipelas: microtrauma and pustular skin diseases, acute and chronic sore throats, hypothermia, stressful situations, as well as chronic vascular diseases of the lower extremities and lymphostasis[12]. Severe lymphostasis, in turn, is a predictor of relapses. Recently, secondary purulent complications of a local nature, as well as general septic ones, ending in the development of infectious and toxic shock, have become much more common[13].

Features of the clinical course are formed based on the premorbid background, primary symptoms of the disease, as well as in accordance with the body's immune response to the infectious process. Clinical signs of the risk of developing purulent complications in primary erysipelas are the bullous nature of local changes. The risk of transition from the primary form to the recurrent one is associated with the duration of the disease, its complicated and severe course, and is associated with hyperglycemia[14].

The severity of the disease depends on the duration of hospitalization, the presence and nature of concomitant diseases[15]. Despite numerous studies on various aspects of this disease, many of them have not yet been resolved. In particular, the pathogenesis of erysipelas and mechanisms of its chronicity, features of the development of endogenous intoxication syndrome and, as a result, the lack of effective methods of treatment and prevention of relapses, complications and adverse consequences[16] [17].

The predominant localization of the pathological process in the lower extremities, a tendency to relapse (up to 60 %) and the formation of chronic lymph venous insufficiency with elephantiasis, lead to disability and a significant deterioration in the quality of life of patients, often even at working age[18]. The absence of a significant anti-relapse effect of various groups of antibiotics requires further research aimed at studying the epidemiological features, etiology, pathogenesis of erysipelas and identifying risk factors.

Erysipelas is an infectious and allergic disease with the presence of infectious-toxic and allergic components in its pathogenesis[19].

Intoxication syndrome accompanies many pathological conditions and is caused by the accumulation of toxic substances in body fluids, is one of the pathogenetic factors that determines the severity of erysipelas, the development of complications, and often the consequences. In severe cases, toxic shock caused by Streptococcus may develop[20].

Endotoxemia develops in all pathological conditions associated with increased catabolism or blockade of the detoxification systems of the body, that is, as a result of an imbalance of the components of the detoxification system or with the failure of one of the links, or simultaneously all the components[21] [22].

The development of endogenous intoxication syndrome not only forms the clinical picture, but also determines the consequences of the disease[23] [24] [25] [26]. The primary infectious focus and endotoxemia often recede into the background, and the consequences of deep metabolic disorders come first. Endogenous intoxication in erysipelas is polyetiological in nature. It is possible to distinguish the main primary mechanisms of its development: production or exchange, due to the excess production of various endogenous toxic substances; resorption, when there is resorption of toxic substances from the focus of infection during tissue breakdown; reperfusion, in which substances accumulated in ischemic tissues enter the systemic bloodstream, as well as released from cells when they are damaged by active oxygen and excess free radicals against the background of

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10 Sondo KA, 2018, 273-276

11 Willems P, 2017, 331-335

12 Hanses F., 2017, 745-751

13 Leung TN, 2018, 593-601

14 Willems P, 2017, 331-335

15 Klotz C, 2019, 703-709

16 Villefrance M, 2017, 179

17 Hon KL, 2020, 125-131

18 Clebak KT, 2018, 433-454

19 Rath E, 2018, 27-34

20 Karakonstantis S., 2020, 183-191

21 Brennecke, S., 2017, 263-270

22 Brishkoska-Boshkovski V., 2019, 937-942

23 Celenay, S. T., 2019, 307-317

24 Jendoubi, F., 2019

25 Jia, W., 2015, 129-133

26 Drerup, C., 2020, 1417-1425

failure of antioxidant protection; retention, in which the accumulation of endogenous toxins occurs as a result of violation of their elimination; infectious, as a result of ingestion microorganisms, products of their metabolism and decay from the focus of invasive infection[1] [2] [3].

There is a specific intoxication caused by bacteria and their toxins and non-specific (endogenous), due to substances formed in the body's tissues, regardless of the characteristics of the pathogen. The degree of specific intoxication in erysipelas can be assessed based on the severity of antigenemia, bacteremia, and toxemia. It was found that there is no direct correlation between the intensity of antigenemia and the severity of the main clinical signs, and intoxication reflects not so much the intensity of antigenemia as the body's response to the pathogen. The severity of non-specific intoxication depends on the level of concentration of toxic substances formed as a result of the breakdown of proteins and fats under the influence of microbial toxins [4] [5].

Studies to establish a direct link between the clinical signs of intoxication with specific toxic substances, efforts to find a "universal" marker of intoxication, did not give the desired results. It is most often impossible to isolate a toxin or a set of toxic substances specific to certain forms of the disease (tumor, burn, hypoxic, inflammatory, etc.). Currently, endogenous intoxication by the mechanisms of occurrence and implementation is a complex pathological polyetiological process with a universal general biological mechanism of pathogenesis[6].

Endogenous toxins are products of normal metabolism in high concentrations (lactate, pyruvate, uric acid, urea, creatinine, bilirubin glucuronide) and can be excessively formed with distorted metabolism (ketones, aldehydes, alcohols, carboxylic acids, ammonia); products of cell and tissue breakdown from foci of tissue destruction and/or from the gastrointestinal tract with violation of the barrier function of membranes (lipases, lysosomal enzymes, cationic proteins, myoglobin, indole, skatole, phenol); components and effectors of the body's regulatory systems in excessive quantities; activated enzymes (lysosomal, proteolytic, products of activation of the kallikrein-kinin cascade, blood coagulation systems and fibrinolysis); inflammatory mediators, biogenic amines, cytokines, prostaglandins, leukotrienes, acute phase proteins and biologically active substances; active compounds formed during lipid peroxidation (LPO); microbial toxins (exo- and endotoxins) and other factors of pathogenicity of microorganisms (pathogenic, conditionally pathogenic); foreign immune products of cellular decay, antigens and immune complexes-aggressors[7] [8] [9].

For a long time, the clinical concept of "intoxication" did not have a biochemical basis for research and could not be quantified. Medium-molecular peptides are considered a universal marker of endogenous intoxication, the level of which reflects the degree of protein catabolism and correlates with the main clinical and prognostic criteria for metabolic disorders[10].

One of the leading mechanisms of endotoxicosis development is the activation of free radical oxidation processes, which on the one hand is important for non – specific protection of the body, on the other – can lead to significant damage to cell membranes, organs and systems[11].

Any pathological process occurs against the background of the formation of reactive oxygen species and the intensification of free radical oxidation of biosubstrates[12]. The processes of free radical oxidation of lipids are carried out in the cells of most human organs and tissues. The resulting LPO products perform certain physiological functions in the body – they regulate the processes of restoration of biological membranes, change the metabolic activity of the cell[13] [14] [15].

The release of O^2 from white blood cells, especially neutrophils and phagocytes, and amplification (LPO) is one of the mechanisms of microbial damage. These processes also determine the sensitivity of receptors and cell reactivity, an increase in the rate of renewal of membrane phospholipids and the prostaglandin precursor –

1 Ezawa, M., 2019

2 Inghammar, M., 2014

3 Karakonstantis, S., 2020, 183-191

4 Karppelin, M., 2010, 729-734

5 Lazzarini, L., 2005, 383-389

6 McNamara, D. R., 2007, 709-715

7 Mokni, M., 2006, 108-112

8 Pavlotsky, F., 2004, 89-95

9 Rob, F., 2018, 39-43

10 Sundaresan, S., 2017, 383-390

11 Sunderkötter, C., 2020

12 Sunderkötter, C., 2019, 345-371

13 McNamara, D. R., 2007, 709-715

14 Mokni, M., 2006, 108-112

15 Wojas-Pelc, A., 2007, 457-464

arachidonic acid. This is of great importance, since prostaglandins act as specific regulators of the cells and tissues in which they were formed and are interstitial hormones[16] [17].

It is known that the degree of activity of membrane lipoperoxidation processes depends on the ratio of the activity of the pro-oxidant and antioxidant systems. Excessive LPO intensity of biological membranes may be the result of increased activity of the pro-oxidant system or antioxidant insufficiency, as well as a combination of these factors[18] [19].

Studies have shown that ceruloplasmin (CP) is the main blood antioxidant, binds superoxide radicals, and interferes with the LPO of cell membranes[20] [21].

CP is a protein that has the properties of the enzyme ferroxidase and is involved in the oxidation of divalent iron with air oxygen (reducing oxygen to water). Plasma CP synthesis is mainly carried out by liver cells and maintaining its level in the blood is controlled by a number of hormones and mediators of the immune system: glucagon, corticosteroid hormones, prostaglandins of Class E2, interleukin-1[22] [23].

CP is known to be involved in iron metabolism by oxidizing Fe2+ to Fe3+ and is a universal antioxidant[24]. For the past 30 years, CP has been used as an antioxidant, hematopoietic stimulator, and means of reducing intoxication and immunosuppression[25]. Interacting with myeloperoxidase, it inhibits its pro-oxidant properties[26].

However, the relationship of disorders of the balance of free radical oxidation, the antioxidant defense system and endotoxicosis with each other, as well as the severity of metabolic disorders in the pathogenesis of erysipelas, is still insufficiently studied.

An equally important role in the development of the inflammatory response to bacterial agents as a pro-inflammatory factor is played by the biologically active protein lactoferrin, which has attracted the attention of researchers around the world for more than 70 years. It belongs to the family of transferrin proteins, a cationic glycoprotein synthesized by exocrine glands and neutrophils, and carries iron into cells and controls the level of free iron in the blood and in external secretions[27] [28].

Lactoferrin is considered to be the most polyvalent protein involved in protecting the body from tissue damage and infections in general. Due to the tendency of the main N-terminal domain to interact with various microbial targets, lactoferrin not only has antimicrobial, anti-inflammatory properties (especially those associated with the suppression of pro-inflammatory cytokines such as IL-6), but also modulates innate and adaptive immune responses. Since high levels of IL-6 are involved in iron homeostasis disorders, lactoferrin becomes a powerful regulator of iron and inflammatory homeostasis[29] [30].

Despite the long-standing interest in lactoferrin, modern scientists have repeatedly drawn attention and forced us to reconsider our current understanding, although incomplete, of the many ways in which this enzyme affects complex immune responses. Signaling through these receptors is thought to be the main lever used by lactoferrin to influence immune cells and cellular activity that controls cytokine balance[31].

Lactoferrin, in addition to its anti-inflammatory activity, shows significant activity against bacterial adhesion, invasion and colonization. When analyzing literature data reporting conflicting results regarding its role in inflammatory processes ranging from pro – and anti-inflammatory activity in vitro, dependence on cell models, the metabolic state of cells, stimulating or infectious agents was established[32].

Conclusions. Erysipelas is an urgent problem of our time. Provoking factors and the patient's belonging to the risk group play a significant role in its development. There is an increase in the number of severe course and

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16 Pavlotsky, F., 2004, 89-95

17 Zhu, H., 2013, 450-452

18 Sundaresan, S., 2017, 383-390

19 Dos Reis, 2021, 1-14

20 Sunderkötter, C., 2019, 345-371

21 Vasquez, K. T., 2021, 33011-33016

22 Inghammar, M., 2014

23 Landi, C., 2021

24 Karppelin, M., 2010, 729-734

25 Zanardi, A., 2021, 1-13

26 Lazzarini, L., 2005, 383-389

27 Pavlotsky, F., 2004, 89-95

28 Sundaresan, S., 2017, 383-390

29 Legrand D., 2016, 10-5

30 Lepanto MS, 2019, 13-23

31 Zhu, H., 2013, 450-452

32 Sunderkötter, C., 2020

complications, which leads to disability of working-age patients and an increase in mortality among the elderly. Accordingly, excessive intensity of lipid peroxidation of biological membranes may be the result of increased activity of the pro-oxidant system or antioxidant insufficiency, as well as a combination of these factors.

The role of ceruloplasmin that binds superoxide radicals and prevents lipid peroxidation of cell membranes was studied. The relationship of disorders of the balance of free radical oxidation, the antioxidant defense system and endotoxicosis with each other in the pathogenesis of erysipelas requires further study.

The importance of lactoferrin in the development of an inflammatory response to bacterial agents has been studied, but there are no data on its association with the development of relapses of erysipelas, which requires further research.

Thus, despite the well-studied pathogenesis of erysipelas, the issue of preventing relapses remains relevant and unresolved, the search for a "universal" marker of intoxication did not give the desired results. There is no exhaustive information about lactoferrin and ceruloplasmin, the dependence of changes in the level of these blood enzymes as anti-inflammatory factors, with the development of relapses of erysipelas, the period of the disease, the frequency of the course, the presence of an unfavorable premorbid background and complications.

Annotation.

The aim is to study the state of research on clinical, epidemiological and immunological features of erysipelas, to determine the directions for solving the problem of preventing relapses of the disease.

Materials and methods – meta-analysis of databases with scientific publications (Pubmed / Medline, Scopus, Ebsco, Index Copernicus) was carried out, and a bibliographic and semantic research method was used.

Erysipelas is an infectious and allergic disease caused by beta-hemolytic Streptococcus with the development of erythematous, bullous or hemorrhagic inflammation and is an urgent issue today. A significant role in its development is played by provoking factors and belonging of the patient to the risk group: diabetes mellitus, lymph and circulatory disorders, inactivity, bad habits and mycoses. Recently, there has been an increase in the number of clinical cases that are accompanied by a severe course and complications (the predominance of intoxication syndrome, the occurrence of hemorrhagic forms, a tendency to relapse), which in turn lead to disability of working-age patients and an increase in mortality among the elderly. Intoxication syndrome develops due to an increase in the level of endogenous toxins. Medium-molecular peptides are considered a universal marker of endogenous intoxication, the level of which reflects the degree of protein catabolism and correlates with the main clinical and prognostic criteria for metabolic disorders.

Accordingly, excessive intensity of lipid peroxidation of biological membranes may be the result of increased activity of the pro-oxidant system or antioxidant insufficiency, as well as a combination of these factors.

The role of ceruloplasmin as the main blood antioxidant that binds superoxide radicals and prevents lipid peroxidation of cell membranes was studied. The relationship of disorders of the balance of free radical oxidation, the antioxidant defense system and endotoxicosis with each other in the pathogenesis of erysipelas requires further study.

The importance of lactoferrin in the development of an inflammatory response to bacterial agents was studied. It is a biologically active protein that plays an important role as a pro-inflammatory factor, but there are no data on its association with the development of relapses in erysipelas, which requires further research.

Thus, despite the well-studied pathogenesis of erysipelas, the issue of preventing relapses remains relevant and unresolved, the search for a "universal" marker of intoxication did not give the desired results. There is no exhaustive information about lactoferrin and ceruloplasmin, the dependence of changes in the level of these blood enzymes as anti-inflammatory factors, with the development of relapses of erysipelas, the period of the disease, the frequency of the course, the presence of an unfavorable premorbid background and complications.

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