PROSPERITAS VESTRA FINIS NOSTRA!

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**"PROF. DR. PARASKEV STOYANOV"**

**FACULTY OF MEDICINE**

**DEPARTMENT OF INFECTIOUS DISEASES, PARASITOLOGY AND DERMATOVENEREOLOGY**

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# A study of haemostasis in erysipelas

**Author`s dissertation summary**

For the acquisition of educational and scientific degree of **"doctor of philosophy"**
in the field of higher education №7 Public Health and Sports,
professional trend № 7.1; Medicine and scientific specialty of Dermatovenereology

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**Varna**

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The dissertation contains 98 tpe-written pages and is illustrated with 20 tables and 7 figures. The reference list includes a total of 85 primary sources, of which there are 24 in Cyrilic and 61 in Latin.

The dissertation has been discussed and forwarded to a public defence by the extended departmental council of the Department of Infectious Diseases, Parasitology and Dermatovenereology of the Medical University "Prof. Paraskev Stoyanov" of Varna, based on Report with reference №……by ……Head of the Department of Infectious Diseases, Parasitology and Dermatovenereology, Medical University of Varna.

Public defense of the dissertation will be held on 05. 10. 2021, based on Order № R-109-323 of Prof. Valentin Lyubomirov Ignatov, MD, PhD, Rector of the Medical University "Prof. Paraskev Stoyanov" of Varna.

Dissertation-related materials have been published on the Internet site of the Medical University "Prof. Paraskev Stoyanov" of Varna and are at the disposal in the Research Department of the Medical University "Prof. Paraskev Stoyanov" of Varna.

## ABBREVIATIONS USED

**AK –** Anticoagulants

**aPTT -** Activated partial thromboplastin time

**CMV** – Cytomegalovirus

**CVI** – Chronic venous insufficiency

**CHF –** chronic heart failure

**DVT –** Deep venous insufficiency

**EBV** – Epstein – Bar virus

**HTLV-1** – Human-T-lymphotropic virus type 1

**PCT –** Procalcitonin

**PT –** Prothrombin time

**RE –** Recurrent erysipelas

**Well`s score -** Well`s criteria for pulmonary embolism

**CONTENTS**

## 1. INTRODUCTION

Erysipelas is an acute, non-necrotizing bacterial dermo-hypodermatitis caused mainly by group A β-hemolytic streptococcus. The modern epidemiology of the disease shows an increased frequency of the disease, change of the predilection site from the face to the lower limb resulting in subsequent structural and functional changes of the affected limb. The recurrent form can be considered as the most common complication of the primary erysipelas, and according to the multiplicity and course - as a chronic, recurrent disease. Recurrent erysipelas (RE) creates a comorbidity background and favors the development of vascular accidents. A current problem in patients with erysipelas is the high recurrence rate, reaching 40%, compared to 15% in the last century. In RE there is a stable localization of the infection. Rarely RE, with up to 3 recurrences per year, is considered an exogenous infection, while often RE (with more than 3 recurrences per year) is considered an endogenous reactivation of already inoculated *S. pyogenes*. The main risk factors for the development of RE are residual inflammatory changes from erysipelas. From systemic diseases - only obesity (BMI> 30) has a proven effect on the increased incidence of the disease. The presence of severe concomitant diseases such as chronic heart failure, chronic renal failure, diabetes mellitus and chronic venous insufficiency have an indirect role in the development of RE by slowing the recovery process, longer persistence of inflammation, its penetration into depth and creating conditions for intracellular existence of streptococcus. RE is a complication of primary erysipelas, occurring with structural and functional changes in the affected limb. So far, the gold standard for relapse prevention is long-term use of depot penicillins. The latter prolongs the period free of relapses, but in case of stopping, and in isolated cases during prophylaxis, such may occur. Therefore, antibiotic prophylaxis has no protective effect against relapses. This phenomenon cannot be explained by penicillin resistance, as it has been shown to be absent. Currently, the cause of RE remains unclear, given the lack of resistance to penicillins.

A study from 2020 demonstrates a new discovery in the biological behavior of *S. pyogenes* and its ability for intracellular persistence and survival.

It is assumed that this mechanism of coexistence with the host is the cause of the so-called "intracellular reservoirs" of streptococci, sources of intermittent bacteremia.

It is this phenomenon that allows us to assume that the intracellular persistence and survival of streptococci is the cause of the development of RE.

Another current problem of the disease is the lack of unified statements and criteria for the usage of anticoagulants (AK) in the treatment of patients with erysipelas. Their unjustified use for the purpose of prevention of vascular accidents, in the absence of established criteria, is a risk factor both for the dissemination of streptococci and for the creation of "intracellular reservoirs"

Targeted study of specific haemostatic indices, in combination with the pro-inflammatory marker procalcitonin (PCT) will help to better understand the disease-related changes in the hemostatic system in erysipelas and will contribute to a deeper understanding of the need for justified, effective and safe administration of anticoagulants without the risk of creating an intracellular source of bacteremia.

To date, studies have not considered the use of anticoagulants in the context of the risk of recurrence.

## 1. PURPOSE AND TASKS

### 2.2. PURPOSE OF THE STUDY

The purpose of this study is to determine whether and what changes occur in the coagulation system in patients with erysipelas. In addition, changes in PCT levels were monitored, as well as some epidemiological, demographic and clinical characteristics, aimed at identifying specific patterns of erysipelas and its course. The study is retrospective, multicenter and includes patients hospitalized in the Department of Infectious Diseasesm Parasitology and Dermatovenereology at University Hospital "St. Marina" - Varna and the Department of Skin and Venereal Diseases at the Ministry of Interior - Sofia, for a period of 2 years (07. 2018 - 07. 2020).

### 2.2. TASKS OF THE STUDY

The tasks for accomplishment of this purpose are the following:

1. Epidemiologic and clinical study in patients with erysipelas by three criteria: sex, age and seasonality for a period of 2 years, based on hospital medical records.
2. A comparative analysis of some demographic and clinical features of the erysipelas between men and women, based on hospital medical records.
3. Determination of the clinical characteristics of erysipelas by 5 criteria - location, frequency, severity, nature of local manifestations and outcome of the disease, based on hospital medical records.
4. Determination of the comorbid background, the entrance door of the infection and the performed penicillin prophylaxis in recurrent and primary erysipelas with residual manifestations, based on the hospital medical documentation.
5. Establishing the level of some hemostasis indices - platelets, fibrinogen, PT and aPTT in patients with erysipelas and in a control group of patients with other skin diseases from the hospital medical records.
6. Determination of PCT levels in patients with erysipelas and in patients with other skin diseases, based on hospital medical records.
7. Search for a correlation between the severity of the disease and changes in hemostasis and / or PCT.
8. Analysis of the correlation between the level of hemostasis and PCT and the clinical characteristics of erysipelas (severity and nature of local changes).

## 2.3. WORKING HYPOTHESIS

M. Frick et al. (2006) found that upon contact of coagulation factors with the surface of *S. pyogenes*, antimicrobial peptides activating the contact system are formed and released. As a result, a fibrin network is formed, which covalently crosslinks the neighboring fibrin chains and turns the newly formed clot into insoluble. Through this mechanism, the efflux of plasma and blood cells is prevented and the invasion of pathogens into the systemic circulation is prevented. The activation of the contact system is associated with the activation of factor XIII on the streptococcal surface. Factor XIIIa covalently entangles bacteria in the fibrin network and limits their dissemination, helping to destroy them by antimicrobial peptides. The ultimate goal in activating the coagulation system in infections is the formation of thrombin, which converts fibrinogen to fibrin, and the activation of coagulation factor XIII. Fibrin deposition reduces the chance of survival and dissemination of streptococcus by limiting vascular invasion and hematogenous dissemination. Fibrinogen restricts bacterial hematogenous dissemination, stimulates the inflammatory response against streptococcus, and serves as a molecule that attaches streptococcus to procoagulant microvesicles. In patients with erysipelas, with a mild to moderate inflammatory response, streptococci become intracellular and persist and form an "intracellular" reservoir. Under "favorable" conditions, endogenous reactivation occurs, clinically occurring as a relapse. According to recent literature data, milder forms of erysipelas are riskier with respect to RE. Findings in the biological behavior of streptococcus and its ability to enter, survive, and persist intracellularly are a rational explanation for the high incidence of RE, despite antibiotic prophylaxis.

Observations on this problem are insufficient, which creates the need to continue and deepen research in this direction. The intracellular localization of streptococci makes them "inaccessible" to antibiotics and the immune system, which is why they survive and persist for a long time in the host. The intracellular location of streptococci is determined by the severity of the infection. The most significant is the level of intracellular pathogens in primary infection, with mild to moderate inflammatory manifestations and low bacterial load. Completely extracellular or combined extra- / intracellular are streptococci in severe inflammatory tissue changes. Intracellular survival of *S. pyogenes* has been established in vitro, despite therapeutic antibiotic concentrations. Discontinuation of antibiotic therapy is followed by significant extracellular, bacterial proliferation. Invasion of endothelial cells by streptococci is thought to facilitate neighborhood dissemination. Upon entering the endothelial cells, streptococci are protected by the endothelial barrier and become a source of transient bacteremia.

It is assumed that a key role for RE is played by the "preventive" use of AK in the acute phase of erysipelas, which helps to destroy the "limiting" streptococcal fibrin network.

At present, the need for AK inclusion in erysipelas patients due to the risk of vascular accidents is unclear.

Treatment with AK, evaluated only by hemostatic indices carries a risk of dissemination of streptococci and creation of an intracellular reservoir with subsequent intermittent bacteremia.

The present study examines the need for AK inclusion by assessing changes in APTT, PT, fibrinogen, platelet count, and procalcitonin.

Hemostatic indices provide information about the basic condition of the coagulation system, and PCT level - information about the presence, activity and severity of the infection, as well as the risk of developing sepsis.

## 3. MATERIALS AND METHODS

### 3.1 BASE FOR REALIZATION OF THE DISSERTATION

1. Department of Infectious Diseases, Parasitology and Dermatovenereology, University Hospital "St. Marina" - Varna

2. Department of Skin and Venereal Diseases of the Ministry of Interior - Ministry of Interior, Sofia

3. Clinical Laboratory and Clinical Immunology at the University Hospital "St. Marina" - Varna

4. Department of Social Medicine and Health at MU "Prof. Dr. Paraskev Stoyanov ", Varna

The current retrospective, multicenter study was conducted in the Department of Skin and Venereal Diseases of , University Hospital "St. Marina" - Varna, Department of Skin and Venereal Diseases of the Ministry of Interior - Sofia, and includes 138 patients hospitalized for a period of 2 years - 07. 2018 - 07. 2020.

To perform the set tasks, the medical documentation of 138 patients was studied, divided mainly into two groups - patients with erysipelas (89) and patients with other, non-infectious skin diseases (control group, controls - 49).

### 3.2 Including criteria - patients with erysipelas

1. Persons over 18 years of age.

2. Acute change in the skin color, accompanied by objective local and systemic manifestations of acute inflammation, not due to other nosological units.

3. Clinical finding for acute infectious skin disease - erysipelas - asymmetric, localized erythemo-edema with clearly demarcated borders from the surrounding tissues ± bullous and hemorrhagic lesions.

4. Absence of other infectious diseases during hospitalization.

5. Patients without congenital and acquired coagulation diseases, cardiovascular diseases requiring long-term use of anticoagulants, chronic and acute liver diseases, autoimmune platelet diseases, hematological diseases, CMV, EBV, HTLV-1 - infections, patients receiving drugs with haematotoxic effect (methotrexate, azathioprine, chloramphenicol, thiazidime, antiepileptic drugs), patients undergoing active radiation / chemotherapy for or after neoplastic disease.

**3.3. Excluding criteria - patients with erysipelas**

1. Persons over 18 years of age.

2. Skin disease with unconvincing clinical finding - lack of objective and subjective clinical data on skin infection.

3. Presence of other, active infections during hospitalization.

4. Patients who need long-term treatment with AK, patients with congenital or acquired coagulation diseases, chronic and acute liver diseases, autoimmune blood diseases (platelets), CMV, EBV, HTLV-1 - infections, taking myelotoxic drugs. Patients during or after chemotherapy / radiation.

**3.4. Including criteria - controls**

1. Persons over 18 years of age.

2. Patients with non-infectious skin disease.

3. No other active infection, accompanied or not by a skin finding.

4. Patients without congenital and acquired coagulation diseases, cardiovascular diseases requiring long-term use of anticoagulants, chronic and acute liver diseases, autoimmune platelet diseases, hematological diseases, CMV, EBV, HTLV-1 - infections, patients receiving drugs with haematotoxic effect (methotrexate, azathioprine, chloramphenicol, thiazidime, antiepileptic drugs), patients undergoing active radiation / chemotherapy for or after neoplastic disease.

**3.5. Excluding criteria - controls**

1. Persons over 18 years of age.

2. Patients with a skin finding due to another disease not classified as cutaneous [allergies, dermatoses provoked by exogenous factors (trauma, burns)].

3. Patients with another active infection, with or without a skin finding.

4. Patients with skin disease, but suffering from disease states requiring long-term use of AK. Patients suffering from congenital or acquired coagulation diseases, chronic and acute liver diseases, autoimmune diseases of the bloodstream (platelets), CMV, EBV, HTLV-1 - infections, taking myelotoxic drugs. Patients during or after chemotherapy / radiation.

**3.6. Clinical methods**

Examination of the medical documentation from the time of the patients hospitalization.

* Determining objective and subjective complaints of the patient and their grouping, according to the observed indicators.

* Evaluation of the clinical finding for the diagnosis of "erysipelas" - the presence of asymmetric, localized erythema-edema with clearly demarcated edges from peripheral tissues ± bullous and hemorrhagic elements.

* Comparison of demographic and clinical characteristics of patients with erysipelas according to patient`s sex - location, frequency, severity, nature of local manifestations and outcome of the disease, comorbid background, front door, depopenicillin prophylaxis, outcome of the disease.

### 3.7. Determining the risk profile of patients

The following risk factors were identified and assessed in both groups of patients:

**- Invariable risk factors -** age and sex;

**- Variable comorbid risk factors -** comorbidities, other than the excluding criteria - diabetes, hypertension, coronary heart disease, gastritis, asthma, COPD.

## 4. LABORATORY STUDY

The study included 138 patients who were tested for levels of APTT, PT, platelets, fibrinogen and PCT.

- **Measurement of platelets level in peripheral venous blood - devices Sysmex XN 1000 and / or Advia 2120i were used.**

The Sysmex XN 1000 device works by an impedance method using electrical pulses. Advia 2120 works by optical method with scattered light.

**- Measurement of the level of fibrinogen, aPTT and prothrombin time - Sysmex CS2500 and ACL TOP550 devices were used.**

**- Procalcitonin level** - performed using an automatic biochemical analyzer SIEMENS ADVIA 1800; with a linearity of 0.2 to 52 ng / ml; detection limit - 0.16 ng / ml, reproducibility - L1-SD 0.068 / CV 5.8%, L2- 0.899, CV 4.9%.

## 5. STATISTICAL ANALYSIS OF THE DATA

The collected data were analyzed using the following statistical methods:

### 5.1. Descriptive analysis

- Alternative analysis of qualitative variables - calculation of absolute and relative frequencies.

- Variation analysis of quantitative variables - calculation of mean value, standard deviation, standard error of mean value, 95% confidence interval.

### 5.2. Parametric methods

- t - Student's test - for comparison of two arithmetic mean values.
- Analysis of variance (ANOVA) - for comparison of more than two averages.
- Pearson’s r correlation analysis - to detect associative relationships between quantitative and qualitative variables.

### 5.3. Nonparametric methods

- Pearson's criterion $\chi 2$ for analysis of categorical variables.
- Spearman’s $\rho$ correlation analysis - to detect associative relationships between two ordinal variables.

The data are organized and presented through simple and complex multidimensional tables, as well as through bar and pie charts.

Results with significance level $p < 0.05$ were considered statistically significant. Statistical data processing was performed using the statistical package IBM SPSS for Windows, version 25.0.

## 6. OWN RESULTS

### 6.1. Age comparison between two groups of patients

The current study includes 138 patients, 89 patients with erysipelas and 49 patients with other skin conditions (controls).

Among erysipelas patients, the male: female ratio was 1: 1 (47 men: 42 women), with no statistically significant difference in gender distribution: $\chi 2 = 0.79$; $p = 0.37$; (Table 2).

The mean age of the patients with erysipelas from the general sample was 61.73 years, and of the control group - 66.08 years (Table 1).

The mean age of men with erysipelas is 57.62 years, and of women - 66.33 years (Table 2).

Among patients-controls - the ratio of men:women is 1: 1 (22 men: 27 women). The average age for male control patients was 64.59 years, and for females - 67.30 years (Table 3).

**General sample**

**Table 1**

| | Patients | Number | Mean | Std. Deviation (±) | t | p |
|---|---|---|---|---|---|---|
| **Age** | **erysipelas** | 89 | 61.73 | 12.995 | -1.863 | 0.065 |
| | **controls** | 49 | 66.08 | 13.202 | | |

***Tab. 1. Age comparison between the two groups of participants - with erysipelas and controls***

**Patients with erysipelas**

**Table 2**

| | Sex | Number | Mean | Std. Deviation (±) | t | p |
|---|---|---|---|---|---|---|
| **Age** | **men** | 47 | 57.62 | 12.234 | -3.334 | 0.001 |
| | **women** | 42 | 66.33 | 12.385 | | |

***Tab. 2. Sex distribution in patients with erysipelas***

**Patients - control group**
**Table 3**

| | Sex | Number | Mean | Std. Deviation (±) | t | p |
|---|---|---|---|---|---|---|
| **Age** | **male** | 22 | 64.59 | 13.500 | -0.707 | 0.483 |
| | **female** | 27 | 67.30 | 13.082 | | |

***Tab. 3. Sex distribution in the control group of patients***

### 6.2. Distribution of patients by season and sex

Table 4 presents the distribution of patients with erysipelas according to season and sex. 26.2% of women and 17.0% of men suffer from erysipelas in the spring. 38.1% of women and 46.8% of men - in the summer. 23.8% of women and 31.9% of men suffer from erysipelas in the fall. 11.9% of women and 4.3% of men - in winter. The obtained results show that there is no statistically significant difference in the distribution by season between the two sexes: $\chi 2 = 3.44$; $p = 0.329$.

**Table 4**

| | | | **Sex** | | **Total** |
|---|---|---|---|---|---|
| | | | **women** | **men** | |
| **Season** | **Autumn** | **Count** | 10 | 15 | 25 |
| | | **% within Season** | 40.0% | 60.0% | 100.0% |
| | | **% within sex** | 23.8% | 31.9% | 28.1% |
| | **Winter** | **Count** | 5 | 2 | 7 |
| | | **% within season** | 71.4% | 28.6% | 100.0% |
| | | **% within sex** | 11.9% | 4.3% | 7.9% |
| | **Summer** | **Count** | 16 | 22 | 38 |
| | | **% within season** | 42.1% | 57.9% | 100.0% |
| | | **% within sex** | 38.1% | 46.8% | 42.7% |
| | **Spring** | **Count** | 11 | 8 | 19 |
| | | **% within season** | 57.9% | 42.1% | 100.0% |
| | | **% within sex** | 26.2% | 17.0% | 21.3% |
| **Total** | | **Count** | 42 | 47 | 89 |
| | | **% within season** | 47.2% | 52.8% | 100.0% |
| | | **% within sex** | 100.0% | 100.0% | 100.0% |
| **a. Participants = patients with erysipelas** | | | | | |

*Tab. 4. Distribution of patients by season and sex*

Fig.1 illustrates the distribution of erysipelas patients by sex and seasonality.

In both sexes the disease occurs with summer-autumn seasonality and predilectional involvement of the lower limb in summer / autumn and face and trunk - in winter / spring.

**Figure 1**

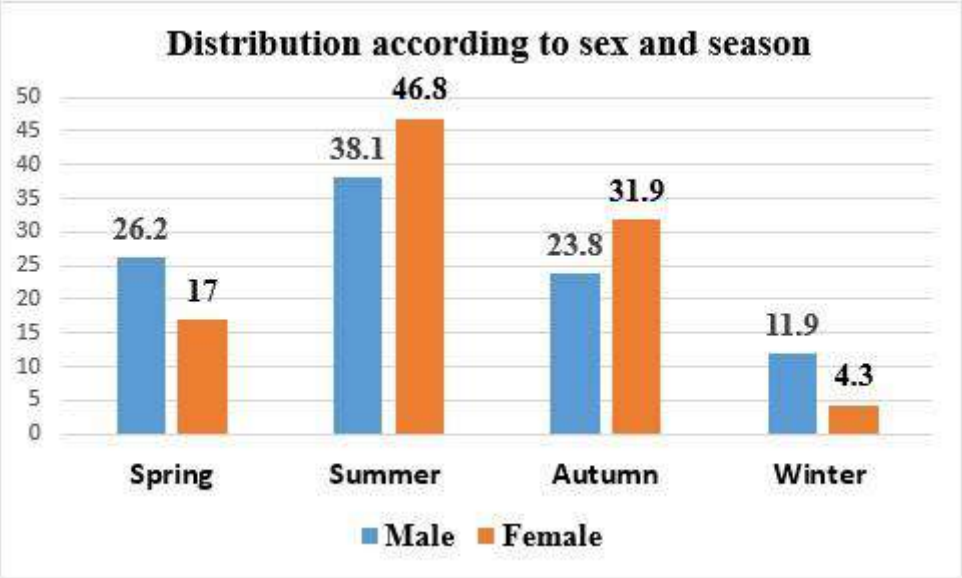


***Fig. 1. Distribution of patients according to sex and season***

## 6.3. Distribution of patients according to the location of erysipelas

In 47.80% of patients the disease involves various aspects of the left lower limb, in 36.2% - right lower limb, in 5.5% right upper limb and right half of the torso, in 1.1% - left arm. From the facial erysipelas - in 4.4% the right facial half and right auricle are affected, and in 5.0% - the left facial half and the left auricle (Fig. 2).

Comparative analysis of the localization between the two sexes does not establish a statistically significant difference in the distribution of localization between the two sexes: $\chi 2 = 28.25$; $p = 0.39$.

**Figure 2**

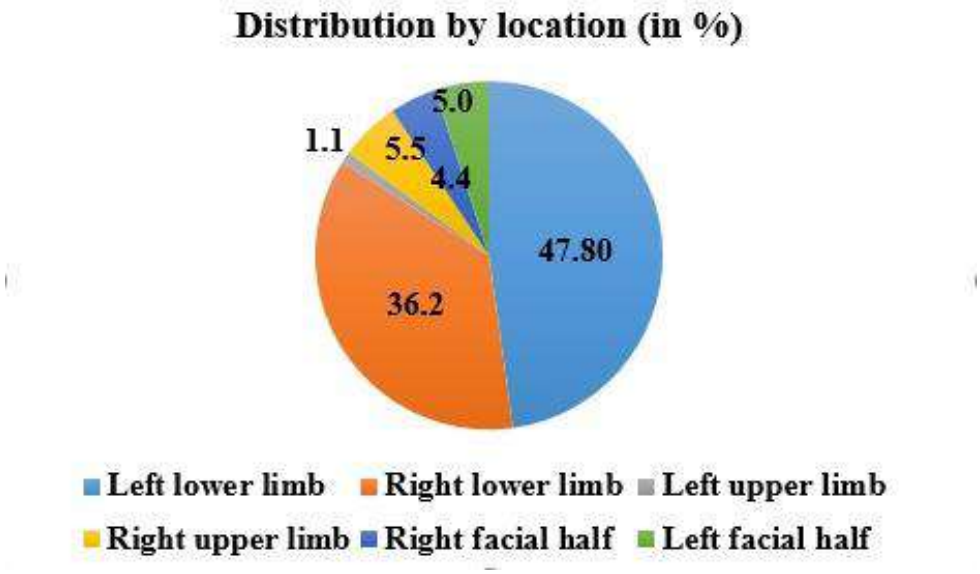


***Fig. 2 Distribution of patients according to the location of erysipelas***

### 6.4. Structural distribution of erysipelas according to localization

The structural distribution of the types of erysipelas according to the localization shows that the main part of the diagnosed cases of erysipelas are localized on the lower extremities - 83.1% (n = 74); significantly less on the face - 10.1% (n = 9) and even less on the upper limb (4.5%; n = 4) and trunk (2.2%; n = 2).

### 6.5 Distribution of patients by multiplicity of erysipelas

The distribution of patients by multiplicity of the disease is presented in fig. 3.

The distribution of patients by multiplicity and sex indicates that primary erysipelas occurs in 47.9% of women (n = 23) and 52.1% of men (n = 25). Its frequency in the total sample reaches 56.1% of patients.

Rarely recurrent erysipelas accounts for 19.1% of women (n = 8) and 14.9% of men (n = 7).

Repeatedly occuring erysipelas was found in 9% of patients - 7.1% in women (n = 3) and 10.6% in men (n = 5).

Often recurrent erysipelas is common in 7.2% of women (n = 3) and 2.1% of men (n = 1).

Late recurrent erysipelas - 9.5% of women (n = 4) and 14.8% of men (n = 7).

Comparative analysis of the frequency of disease occurrence between the two sexes did not establish a statistically significant difference in the multiplicity between the two sexes: $\chi 2 = 12.9$; $p = 0.52$

**Figure 3**

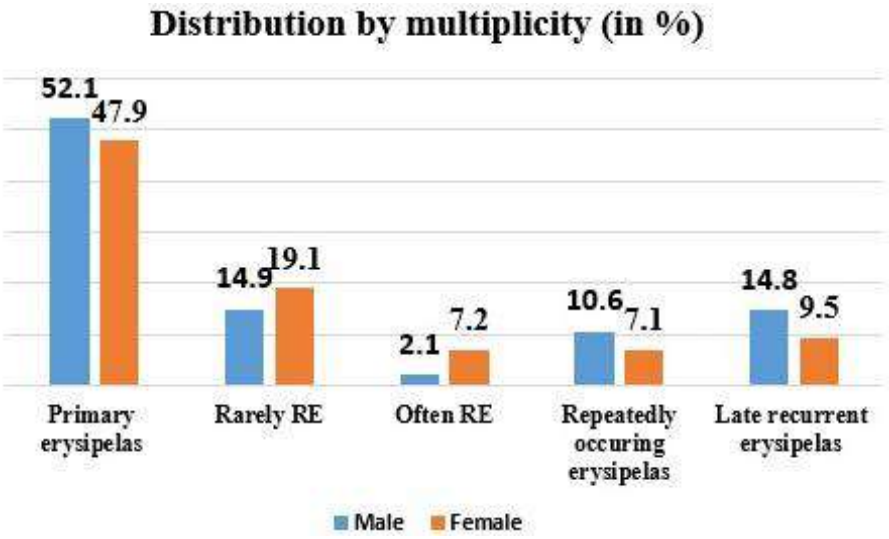


***Fig. 3. Distribution of patients by multiplicity***

### 6.6. Distribution of patients by erysipelas severity

In Fig. 4 shows the distribution of patients according to the severity of erysipelas. Patients with a moderately severe form of the disease predominate 46.0%, followed by a mild form – 29.0% and a severe form – 25.0%.

Comparative analysis of the severity of the course between the two sexes did not establish a statistically significant difference in the distribution of severity between the two sexes: $\chi 2 = 1.71$; $p = 0.64$.

**Figure 4**

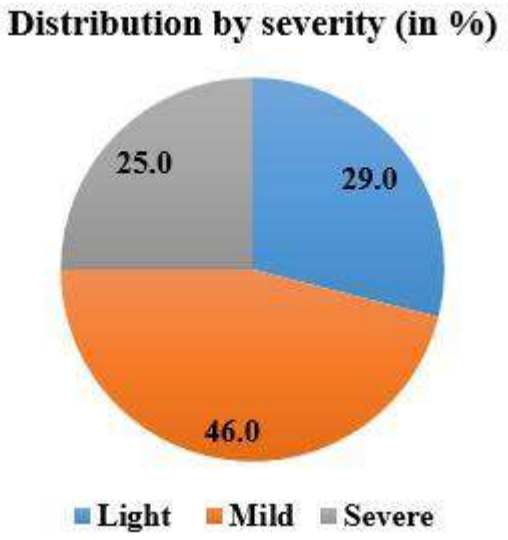


***Fig. 4. Distribution of patients by severity of the disease***

### 6.7. Distribution of patients according to the local manifestations

Table 5 presents the distribution of patients according to the local manifestations. The nature of the local changes is determined by the clinical skin finding. In the present study, local changes were determined according to the current classification for erysipelas and are as follows: erythematous, erythemo-bullous, erythemo-bullous-hemorrhagic and erythemo-hemorrhagic. The predominant frequency is the erythemo-hemorrhagic form of erysipelas – 48.3%, followed by the erythematous – 29.2%, the erythemo-bullous-hemorrhagic – 19.1% and the erythemo-bullous – 3.4%.

Comparative analysis between the two sexes did not establish a statistically significant difference in the distribution according to the nature of the local manifestations between the two sexes: $\chi 2 = 1.89$; $p = 0.59$.

**Table 5**

| **Type of local manifestations** | | | | | |
|---|---|---|---|---|---|
| | | **Frequency** | **Percent** | **Valid Percent** | **Cumulative Percent** |
| **Valid** | **Erythematous** | 26 | 29.2 | 29.2 | 29.2 |
| | **Erythemo-bullous** | 3 | 3.4 | 3.4 | 32.6 |
| | **Erythemo-bullo-hemorrhagic** | 17 | 19.1 | 19.1 | 51.7 |
| | **Erythemo-hemorrhagic** | 43 | 48.3 | 48.3 | 100.0 |
| | **Total** | 89 | 100.0 | 100.0 | |
| a. Participants = patients with erysipelas | | | | | |

**Tab. 5. Distribution of patients according to the local manifestations**

**Figure 5**

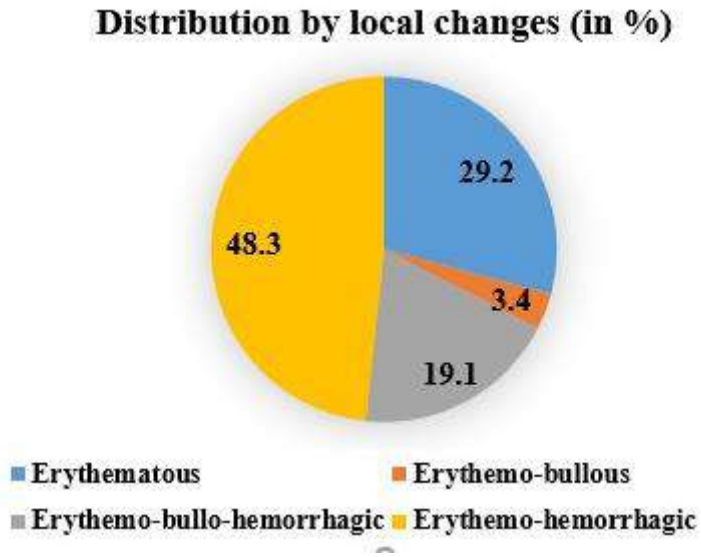


***Fig. 5. Distribution of patients according to the nature of local changes***

### 6.8. Distribution of patients according to the outcome of the disease (with / without complications)

Fig. 6 shows the distribution of patients according to the outcome of the disease. In 39.3% the disease proceeds without complications, in 60.7% with complications, of which - relapses - 30.4%, post-erysipelas syndrome - 20.4% and lymphostasis - 9.1%. A small percentage (1.1%) fall on other complications, including lethal respiratory failure, necrotizing fasciitis, abscess, limb deformity, facial nerve palsy. Comparative analysis between the outcome of the disease and gender did not establish a statistically significant difference in the distribution according to the outcome of the disease between the two sexes: $\chi 2 = 19.42$; $p = 0.195$.

**Figure 6**

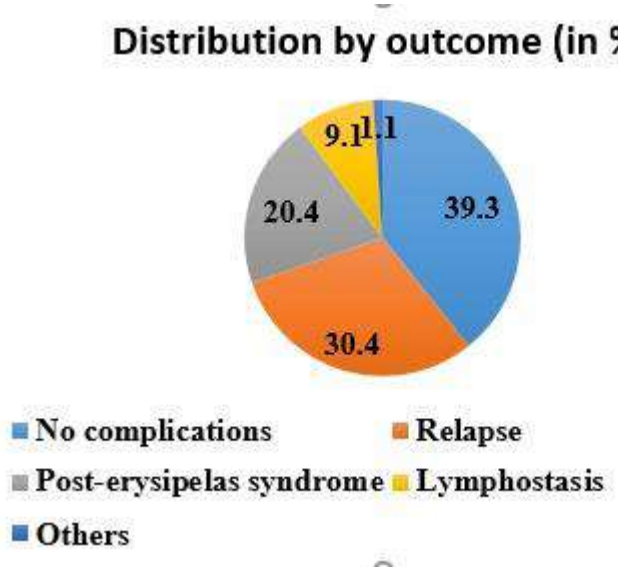


***Fig. 6. Distribution of patients according to the outcome of the disease (with / without complications)***

### 6.9. Distribution of patients by sex and obesity

Table 6 presents the distribution of patients with erysipelas by sex and obesity. Obesity was found in 37.8% of women and 62.2% of men. There was no statistically significant difference in the distribution of patients with erysipelas by sex and obesity: $\chi 2 = 3.23$; $p = 0.07$;

**Table 6**

| | | | Obesity | | Total |
|---|---|---|---|---|---|
| | | | Yes | No | |
| Sex | Women | Count | 17 | 25 | 42 |
| | | % within sex | 40.5% | 59.5% | 100.0% |
| | | % within obesitas | 37.8% | 56.8% | 47.2% |
| | Men | Count | 28 | 19 | 47 |

| | | | | | |
|---|---|---|---|---|---|
| | | **% within sex** | 59.6% | 40.4% | 100.0% |
| | | **% within obesitas** | 62.2% | 43.2% | 52.8% |
| **Total** | | **Count** | 45 | 44 | 89 |
| | | **% within sex** | 50.6% | 49.4% | 100.0% |
| | | **% within obesitas** | 100.0% | 100.0% | 100.0% |

***Tab. 6.* Distribution of patients by sex and obesity**

### 6.10. Distribution of patients by sex and diabetes mellitus

Table 7 shows the distribution of patients with erysipelas by sex and diabetes mellitus. Among them, 38.9% are women and 61.1% - men. There was no statistically significant difference in the distribution of patients with erysipelas by sex and diabetes mellitus: $\chi 2 = 1.267$; $p = 0.19$.

**Table 7**

| | | | **Diabetes** | | **Total** |
|---|---|---|---|---|---|
| | | | **yes** | **no** | |
| **Sex** | **female** | **Count** | 14 | 28 | 42 |
| | | **% within sex** | 33.3% | 66.7% | 100.0% |
| | | **% within diabetes** | 38.9% | 52.8% | 47.2% |
| | **male** | **Count** | 22 | 25 | 47 |
| | | **% within sex** | 46.8% | 53.2% | 100.0% |
| | | **% within diabetes** | 61.1% | 47.2% | 52.8% |
| **Total** | | **Count** | 36 | 53 | 89 |
| | | **% within sex** | 40.4% | 59.6% | 100.0% |
| | | **% within diabetes** | 100.0% | 100.0% | 100.0% |

**Tab. 7. Distribution of patients by sex and obesity**

### 6.11. Distribution of patients with erysipelas by sex and CVI

Table 8 shows the distribution of patients with erysipelas by sex and manifestations of CVI. In 15.8% of women and 84.2% of men, CVI is documented. There was a statistically significant difference in the distribution of patients with erysipelas by sex and manifestations of CVI: $\chi 2 = 9.56$; $p = 0.002$.

**Table 8**

| | | | Chronic venous Insufficiency (CVI) | | Total |
|---|---|---|---|---|---|
| | | | yes | no | |
| **Sex** | **female** | **Count** | 3 | 39 | 42 |
| | | **% within sex** | 7.1% | 92.9% | 100.0% |
| | | **% within CVI** | 15.8% | 55.7% | 47.2% |
| | **male** | **Count** | 16 | 31 | 47 |
| | | **% within sex** | 34.0% | 66.0% | 100.0% |
| | | **% within CVI** | 84.2% | 44.3% | 52.8% |
| **Total** | | **Count** | 19 | 70 | 89 |
| | | **% within sex** | 21.3% | 78.7% | 100.0% |
| | | **% within CVI** | 100.0% | 100.0% | 100.0% |

***Tab. 8. Distribution of patients with erysipelas by sex and CVI***

### 6.12. Distribution of patients with erysipelas according to the portal of entry

Fig. 7 shows the distribution of erysipelas patients according to the front door. In 22.4% of patients interdigital mycosis is found as a portal of entry, in 14.5% - erosions, excoriations, chronic eczema, in 14.6% - trauma, in 4.5% - stasis dermatitis, in 4.4% - otitis and / or rhinitis, in 3.4% - mastectomy. In 36.2% of patients a portal of entry is not established.

Comparative analysis between the front door and the sex of the patients did not establish a statistically significant difference in the distribution according to the portal of entry between the two sexes: $\chi 2 = 26.87$; $p = 0.58$.

**Figure 7**

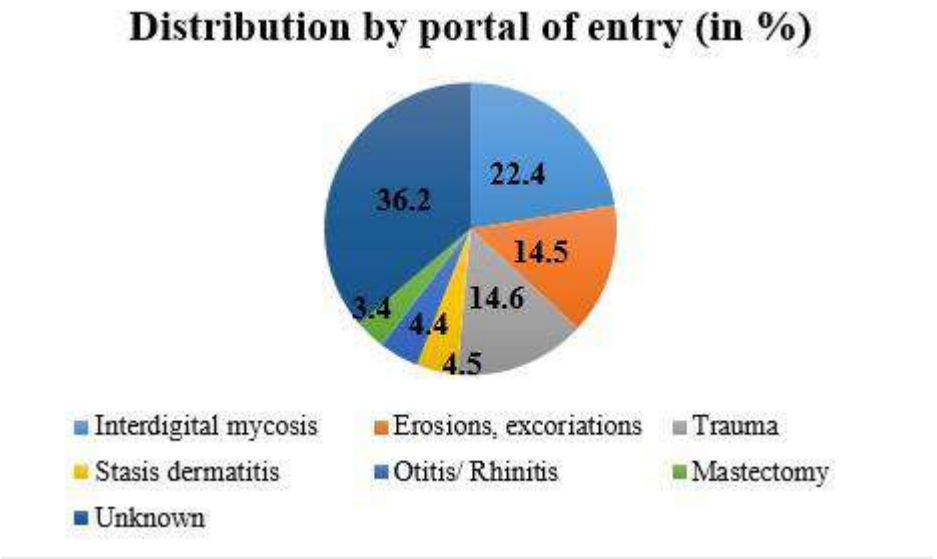


***Figure 7. Distribution of patients by portal of entry***

### 6.13. Distribution of patients by sex and performed depot-penicillin prophylaxis

53.8% of women underwent depot-penicillin prophylaxis, compared to 46.2% of men. There was no statistically significant difference in the distribution of patients by sex and performed depopenicillin prophylaxis: $\chi 2 = 0.27$; $p = 0.603$ (Table 9).

**Table 9**

| | | | Depot-Penicillin Prophylaxis | | Total |
|---|---|---|---|---|---|
| | | | yes | no | |
| **Sex** | **female** | **Count** | 7 | 35 | 42 |
| | | **% within sex** | 16.7% | 83.3% | 100.0% |
| | | **% within prophylaxis** | 53.8% | 46.1% | 47.2% |
| | **male** | **Count** | 6 | 41 | 47 |
| | | **% within sex** | 12.8% | 87.2% | 100.0% |
| | | **% within prophylaxis** | 46.2% | 53.9% | 52.8% |

| | | | | |
|---|---|---|---|---|
| **Total** | **Count** | 13 | 76 | 89 |
| | **% within sex** | 14.6% | 85.4% | 100.0% |
| | **% within prophylaxis** | 100.0% | 100.0% | 100.0% |

***Tab. 9. Distribution of patients by sex and performed depopenicillin prophylaxis***

## 7. CLINICAL AND LABORATORY STUDY

### 7.1. Comparative analysis of haemostatic indices between patients with erysipelas compared to controls (Independent Samples T-Test)

The clinical and laboratory study of patients with erysipelas was performed using a comparative analysis of hemostasis between patients with erysipelas and a control group (patients with other skin diseases). The presented comparative analysis was performed by Independent Samples T-Test.

The comparative analysis of the haemostatic indices between the patients with erysipelas in comparison with the controls is presented in table. 10.

The mean platelet count for erysipelas was 239.71 (± 102.7) x 109, compared to 251.43 (± 73.4) x 109 in the control group at reference values: 140-440 x 109 * (t = 0.71; p = 0.48).

The mean value of fibrinogen in erysipelas was 5.08 (± 1.64) g / L, compared to 3.57 (± 0.77) g / L in the control group, at reference values 2.38 - 4.98 g / L (t = 7.33; p <0.0001).

The mean value of aPTT in patients with erysipelas was 31.03 (± 6.27) sec., Compared to 30.01 (± 5.44) in the control group, at reference values - 25.4 - 36.9 sec. * (T = 0.96; p = 0.34).

The mean activity value of PT was 85.45 (± 21.64) %, compared to 93.60 (± 20.62)% in the controls, at reference values 70-130% * (t = -2.16; p = 0.033).

From the conducted comparative analysis, a statistically significant difference was found when comparing the indicators fibrinogen (t = 7.33; p <0.0001) and PT activity (t = -2.16; p = 0.033).

**Table 10**

| | **Patients** | **Number** | **Mean (±sd)** | **t** | **p** |
|---|---|---|---|---|---|
| **Platelets** | **erysipelas** | 89 | 239.71 (±102.7) | 0-.71 | 0.48 |
| | **controls** | 49 | 251.43 (±73.4) | | |
| **Fibrinogen (g/ L)** | **erysipelas** | 89 | 5.08 (±1.64 | 7.33 | <0.0001 |
| | **controls** | 49 | 3.57 (±0.77) | | |

| | | | | | |
|---|---|---|---|---|---|
| **APTT (sec)** | **erysipelas** | 89 | 31.03 (±6.27) | 0.96 | 0.34 |
| | **controls** | 49 | 30.01 (±5.44 | | |
| **APTT ratio** | **erysipelas** | 89 | 1.97 (±9.27 | 0.77 | 0.44 |
| | **controls** | 49 | 0.94 (±0.16) | | |
| **PT activity (%)** | **erysipelas** | 89 | 85.45 (±21.64) | -2.16 | 0.033 |
| | **controls** | 49 | 93.60 (±20.62) | | |
| **PT time (sec)** | **erysipelas** | 89 | 16.03 (±6.56) | 1.34 | 0.18 |
| | **controls** | 49 | 14.71 (±3.03) | | |

***Tab. 10. Comparative analysis of haemostatic indices between patients with erysipelas compared to controls (Independent Samples T-Test)***

### 7.2. Comparative analysis of haemostasis parameters between patients with primary erysipelas compared with recurrent (Independent Samples T-Test)

The comparative analysis of hemostatic indices between patients with primary erysipelas compared with recurrent was performed by Independent Samples T-Test.

The results are presented in table. 11. The mean platelet count in patients with primary erysipelas was 221.04 (± 76.34) x 109, compared with recurrent - 263.64 (± 126.1) x 109, at reference values: 140-440 x 109 (t = -1.972; p = 0.052).

The mean value of fibrinogen in patients with primary was 4.86 (± 1.44) g / L, compared with recurrent erysipelas: 5.35 (± 1.85), at reference values 2.38 - 4.98 g / L (t = -1.377; p = 0.173). The mean aPTT value in primary erysipelas is 30.35 (± 4.21) sec, and in recurrent: 31.89 (± 8.17) sec, at reference values - 25.4 - 36.9 sec. (t = 1,151; p = 0.253).

The mean PT activity in primary erysipelas was 86.34 (± 21.39) % and in recurrent - 84.30 (± 22.17), at reference values - 70-130% (t = 0.438; p = 0.662). The comparative analysis of haemostatic indices between patients with primary and recurrent erysipelas did not establish a statistically significant difference between haemostatic indices in patients with primary and recurrent erysipelas.

## Table 11

| | **Multiplicity** | **Number** | **Mean (±sd)** | **t** | **p** |
|---|---|---|---|---|---|
| **Platelets** | **primary** | 50 | 221.04 (±76.34) | -1.972 | 0.052 |
| | **recurrent** | 39 | 263.64 (±126.1) | | |
| **Fibrinogen g/L** | **primary** | 50 | 4.86 (±1.44) | -1.377 | 0.173 |
| | **recurrent** | 39 | 5.35 (±1.85) | | |
| **APTT sec** | **primary** | 50 | 30.35 (±4.21) | -1.151 | 0.253 |
| | **recurrent** | 39 | 31.89 (±8.17) | | |

| | | | | | |
|---|---|---|---|---|---|
| **APTT ratio** | **primary** | 50 | 2.71 (±12.37) | 0.861 | 0.391 |
| | **recurrent** | 39 | 1.01 (±0.26) | | |
| **PT activity %** | **primary** | 50 | 86.34 (±21.39) | 0.438 | 0.662 |
| | **recurrent** | 39 | 84.30 (±22.17) | | |
| **PT time sec** | **primary** | 50 | 15.05 (±4.47) | -1.626 | 0.108 |
| | **recurrent** | 39 | 17.30 (±8.41) | | |

**Tab. 11. Comparative analysis of haemostatic indices between patients with primary erysipelas compared with recurrent erysipelas**

### 7.3. Comparative analysis of hemostasis in patients with varying severity of erysipelas (ANOVA - Scheffe Post-hoc Test)

In the table. 12 and 13 are presented the results of the comparative analysis of haemostatic indices in patients with different severity of erysipelas. A statistically significant difference in the mean values of haemostasis between the individual degrees of erysipelas severity was found only in fibrinogen: in mild erysipelas - 4.2662 ± 1.078 g / L, while in severe - 5.9377 ± 1.65 g / L ($p < 0.001$).

**Table 12**

| | | **Брой** | **Mean** | **±sd** | **Std. Error** | **95% CI** | | **Mini mum** | **Maxi mum** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | from | to | | |
| **Platelets** | **light** | 26 | 238.58 | 63.62 | 12.48 | 212.88 | 264.27 | 129 | 365 |
| | **mild** | 41 | 237.00 | 81.02 | 12.65 | 211.43 | 262.57 | 59 | 462 |
| | **severe** | 22 | 246.09 | 163.96 | 34.96 | 173.39 | 318.79 | 96 | 845 |
| | **Total** | 89 | 239.71 | 102.7 | 10.89 | 218.06 | 261.36 | 59 | 845 |
| **Fibrinogen g/ L** | **light** | 26 | 4.2662 | 1.078 | 0.21 | 3.83 | 4.7015 | 2.44 | 6.68 |
| | **mild** | 41 | 5.1259 | 1.71 | 0.27 | 4.59 | 5.67 | 2.47 | 8.70 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **severe** | 22 | 5.9377 | 1.65 | 0.35 | 5.21 | 6.67 | 2.34 | 8.66 |
| | **Total** | 89 | 5.0754 | 1.64 | 0.17 | 4.72 | 5.42 | 2.34 | 8.70 |
| **APTT sec** | **light** | 26 | 31.5817 | 8.2 | 1.60 | 28.29 | 34.88 | 22.00 | 67.00 |
| | **mild** | 41 | 30.5143 | 4.4 | 0.67 | 29.12 | 31.90 | 21.00 | 44.80 |
| | **severe** | 22 | 31.3300 | 6.91 | 1.47 | 28.27 | 34.39 | 23.75 | 49.00 |
| | **Total** | 89 | 31.0278 | 6.27 | 0.66 | 29.71 | 32.35 | 21.00 | 67.00 |
| **APTT ratio** | **light** | 26 | 1.0023 | 0.26 | 0.051 | .8976 | 1.11 | .76 | 2.15 |
| | **mild** | 41 | 3.1107 | 13.65 | 2.13 | -1.19 | 7.42 | .76 | 88.40 |
| | **severe** | 22 | .9686 | 0.18 | 0.04 | 0.89 | 1.05 | .71 | 1.48 |
| | **Total** | 89 | 1.9653 | 9.27 | 0.98 | 0.02 | 3.92 | .71 | 88.40 |
| **PT activity %** | **light** | 26 | 86.8385 | 24.17 | 4.74 | 77.08 | 96.60 | 21.40 | 140.00 |
| | **mild** | 41 | 86.5841 | 21.26 | 3.32 | 79.9 | 93.29 | 25.00 | 129.00 |
| | **severe** | 22 | 81.6773 | 19.63 | 4.19 | 72.97 | 90.38 | 27.00 | 106.00 |
| | **Total** | 89 | 85.4455 | 21.64 | 2.29 | 80.89 | 90.01 | 21.40 | 140.00 |
| **PT time sec** | **light** | 26 | 15.3231 | 4.78 | 0.94 | 13.40 | 17.25 | 11.20 | 36.40 |
| | **mild** | 41 | 15.6024 | 4.87 | 0.76 | 14.07 | 17.14 | 11.10 | 37.70 |
| | **severe** | 22 | 17.6818 | 10.21 | 2.17 | 13.16 | 22.20 | 12.00 | 56.40 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Total** | 89 | 16.0348 | 6.56 | 0.69 | 14.65 | 17.42 | 11.10 | 56.40 |

***Табл. 12. Comparative analysis of haemostatic indices between patients with primary erysipelas compared with recurrent erysipelas***

**Table 13**

| **Scheffe** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Dependent Variable** | **(I) Severity** | **(J) Severity** | **Mean Difference (I-J)** | **Std. Error** | **Sig.** | **95% Confidence Interval** | |
| | | | | | | **Lower Bound** | **Upper Bound** |
| **Platelets** | **light** | **mild** | 1.577 | 26.046 | 0.998 | -63.30 | 66.46 |
| | | **severe** | -7.514 | 30.096 | 0.969 | -82.48 | 67.46 |
| | **mild** | **light** | -1.577 | 26.046 | 0.998 | -66.46 | 63.30 |
| | | **severe** | -9.091 | 27.457 | 0.947 | -77.49 | 59.31 |
| | **severe** | **light** | 7.514 | 30.096 | 0.969 | -67.46 | 82.48 |
| | | **mild** | 9.091 | 27.457 | 0.947 | -59.31 | 77.49 |
| **Fibrinogen g/L** | **light** | **mild** | -.85970 | .38551 | 0.089 | -1.8200 | .1006 |
| | | **severe** | -1.67157* | .44545 | 0.001 | -2.7812 | -.5620 |
| | **mild** | **light** | .85970 | .38551 | 0.089 | -.1006 | 1.8200 |
| | | **severe** | -.81187 | .40639 | 0.142 | -1.8242 | .2005 |
| | **severe** | **light** | 1.67157* | .44545 | 0.001 | .5620 | 2.7812 |
| | | **mild** | .81187 | .40639 | 0.142 | -.2005 | 1.8242 |
| **APTT sec** | **light** | **mild** | 1.06746 | 1.58519 | 0.798 | -2.8812 | 5.0162 |
| | | **severe** | .25173 | 1.83166 | 0.991 | -4.3109 | 4.8144 |
| | **mild** | **light** | -1.06746 | 1.58519 | 0.798 | -5.0162 | 2.8812 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | **severe** | -.81573 | 1.67105 | 0.888 | -4.9783 | 3.3469 |
| | **severe** | **light** | -.25173 | 1.83166 | 0.991 | -4.8144 | 4.3109 |
| | | **mild** | .81573 | 1.67105 | 0.888 | -3.3469 | 4.9783 |
| **APTT ratio** | **light** | **mild** | -2.10842 | 2.33485 | 0.666 | -7.9246 | 3.7077 |
| | | **severe** | .03367 | 2.69789 | 1.000 | -6.6868 | 6.7541 |
| | **mild** | **light** | 2.10842 | 2.33485 | 0.666 | -3.7077 | 7.9246 |
| | | **severe** | 2.14210 | 2.46132 | 0.686 | -3.9891 | 8.2733 |
| | **severe** | **light** | -.03367 | 2.69789 | 1.000 | -6.7541 | 6.6868 |
| | | **mild** | -2.14210 | 2.46132 | 0.686 | -8.2733 | 3.9891 |
| **PT activity %** | **light** | **mild** | .25432 | 5.45937 | 0.999 | -13.3450 | 13.8536 |
| | | **severe** | 5.16119 | 6.30822 | 0.716 | -10.5526 | 20.8750 |
| | **mild** | **light** | -.25432 | 5.45937 | 0.999 | -13.8536 | 13.3450 |
| | | **severe** | 4.90687 | 5.75508 | 0.696 | -9.4290 | 19.2428 |
| | **Severe** | **light** | -5.16119 | 6.30822 | 0.716 | -20.8750 | 10.5526 |
| | | **mild** | -4.90687 | 5.75508 | 0.696 | -19.2428 | 9.4290 |
| **PT time sec** | **light** | **mild** | -.27936 | 1.64511 | 0.986 | -4.3773 | 3.8186 |
| | | **Severe** | -2.35874 | 1.90089 | 0.466 | -7.0939 | 2.3764 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **mild** | **light** | .27936 | 1.64511 | 0.986 | -3.8186 | 4.3773 |
| | | **severe** | -2.07938 | 1.73421 | 0.490 | -6.3993 | 2.2406 |
| | **Severe** | **light** | 2.35874 | 1.90089 | 0.466 | -2.3764 | 7.0939 |
| | | **mild** | 2.07938 | 1.73421 | 0.490 | -2.2406 | 6.3993 |
| *** The mean difference is significant at the 0.05 level** | | | | | | | |

**Tab. 13. Comparative analysis of hemostasis in patients with varying severity of erysipelas**

### 7.4. Comparative analysis of PCT values in patients with varying severity of erysipelas (ANOVA - Scheffe Post-hoc Test)

The comparative analysis of PCT values in patients with different severity of erysipelas was performed using ANOVA - Scheffe Post-hoc Test. From the presented results it is not possible to establish a statistically significant difference in the average values of PCT between the different degrees of severity of erysipelas (p> 0.05) (Tables 16, 17).

**Table 16**

| **PCT (ng/ml)** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Number** | **Mean** | **±sd** | **Std. Error** | **95% CI** | | **Minimum** | **Maximum** |
| | | | | | **от** | **до** | | |
| **Light** | 5 | 0.26 | 0.16 | 0.07 | 0.05 | 0.46 | 0.06 | 0.46 |
| **mild** | 13 | 0.91 | 2.26 | 0.62 | -0.46 | 2.27 | 0.06 | 8.37 |
| **severe** | 8 | 1.06 | 2.40 | 0.85 | -0.93 | 3.06 | 0.06 | 6.98 |
| **Total** | 26 | 0.83 | 2.04 | 0.39 | 0.01 | 1.65 | 0.06 | 8.37 |

***Tab. 16. Comparative analysis of PCT values in patients with varying severity of erysipelas***

**Table 17**

| (I) Severity | (J) Severity | PCT Mean Difference (I-J) | Std. Error | p | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | from | To |
| **Light** | **Mild** | -0.65 | 1.10 | 0.841 | -3.54 | 2.23 |
| | **severe** | -0.81 | 1.19 | 0.799 | -3.93 | 2.32 |
| **Mild** | **light** | 0.65 | 1.10 | 0.841 | -2.24 | 3.54 |
| | **severe** | -0.15 | 0.94 | 0.987 | -2.62 | 2.31 |
| **Severe** | **light** | 0.81 | 1.19 | 0.799 | -2.32 | 3.93 |
| | **severe** | 0.15 | 0.94 | 0.987 | -2.31 | 2.62 |

**Tab. 17. Comparative analysis of PCT values in patients with varying severity of erysipelas**

### 7.5. Comparative analysis of PCT values between erysipelas patients and controls (Independent Samples T-Test)

There was no statistically significant difference in procalcitonin values between erysipelas patients and controls (p = 0.21) (Table 18).

**Table 18**

| | Patients | Number | Mean (±sd) | Mediana | t | p |
|---|---|---|---|---|---|---|
| **PC (ng/ml)** | erysipelas | 82 | 0.47 (1.18 | 0.17 | 1.26 | 0.21 |
| | Controls | 29 | 0.19(0.43) | 0.11 | | |

**Tab. 18. Comparative analysis of PCT values between erysipelas patients and controls**

### 7.6. Correlation analysis of hemostasis and PCT in patients with erysipelas

In the table 19 are presented the results of the correlation analysis of hemostasis and PCT in patients with erysipelas. The obtained results showed a positive moderate and statistically significant correlation when comparing procalcitonin with PT time (sec) (Pearson's r = 0.497; p = 0.010).

**Table 19**

| | | | Platelets | Fibrinoge ng/ L | APTT sec | APTT ratio | PT activity % | PT time sec |
|---|---|---|---|---|---|---|---|---|
| **PCT (ng/l)** | **Pearson Correlation** | | -0.005 | 0.253 | -0.233 | -0.044 | -0.331 | 0.497** |
| | **p** | | 0.982 | 0.213 | 0.251 | 0.831 | 0.098 | 0.010 |
| | **Number** | | 26 | 26 | 26 | 26 | 26 | 26 |

**Tab. 19. Correlation analysis of hemostasis and PCT in patients with erysipelas**

### 7.7. Correlation analysis of hemostasis and PCT in controls

The correlation analysis of the hemostasis parameters and PCT in the patients from the control group did not establish a statistically significant correlation dependence (Table 20).

**Table 20**

| | | Platelets | Fibrinogen g/ L | APTT sec | APTT ratio | PT activity % | PT time sec |
|---|---|---|---|---|---|---|---|
| **PCT (ng/l)** | **Pearson Correlation** | -.116 | -.004 | -.248 | -.215 | -.213 | -.040 |
| | **p** | .706 | .991 | .414 | .482 | .485 | .898 |
| | **Number** | 13 | 13 | 13 | 13 | 13 | 13 |

**Tab. 20. Correlation analysis of hemostasis and PCT in controls**

## 8. Discussion

Erysipelas is a well-known skin disease, but its epidemiological and clinical characteristics may change under the influence of the rapidly evolving and dynamic lifestyle of modern man.

The established incidence of erysipelas in Europe is 19-24: 10,000 people (Inghammar M et al. 2014), and among the Bulgarian population - 2.18% of all hospitalized patients and 21.66% of all patients with pyoderma (Marina C and et al. 1992). Thus, erysipelas retains its place among the socially significant diseases in dermatology, the reasons for which are the protracted course in severe forms (accompanied by structural and functional changes of the affected limb) and the risk of developing various forms of recurrent erysipelas.

In Bulgaria, studies on erysipelas are conducted by P. Verbev, I. Tolev, L. Daskarev, I. Dikov, S. Marina, T. Petkova, D. Gospodinov, I. Yungareva, R. Yankova, S. Pavlov, M. Gospodinova and etc. Most studies have shown a predominance of female involvement. The studies of S. Marina et al. (1992), T. Petkova et al. (2011), M. Gospodinova (2009) and S. Pavlov et al. (2004) confirm this among the Bulgarian population. In the present study, this trend persists but cannot be statistically justified due to a number of inclusion and exclusion criteria affecting gender distribution. According to the presented criteria necessary for inclusion of patients in the study, the present study does not show predominance in a given sex.

Unlike other streptococcal infections, erysipelas does not have the characteristic spring-autumn seasonality. Most authors find summer-autumn morbidity, with a predominance of cases in the second half of summer and early autumn. Most authors find summer-autumn morbidity, with a predominance of cases in the second half of summer and early autumn. According to S. Marina et al. (1992) and I. Yungareva (2014) the role is played by the seasonal change of the body's reactivity, the influence of cyclic changes on the immune response, as well as the activation of concomitant diseases.

Erysipelas occurs with summer-autumn seasonality, probably due to increased physical activity of patients, poor protective clothing and unfavorable conditions for work and outdoor sports, predisposing to outdoor microtrauma. In the present study, there is a predominant involvement of patients in summer and autumn. They reported trauma due to the lack of protective clothing, shoes and equipment or the presence of such, but led to mechanical irritation of the skin, serving as a portal of entry.

S. Marina et al. (1992) and I. Yungareva (2014) discuss the displacement of the predilection site of infection from the lower limb to the face during the autumn-winter season, probably due to acute respiratory diseases, otitis and rhinitis. In the present study, all patients with erysipelas on the face are hospitalized during the autumn-winter period. The presented trend requires preventive measures to reduce the risk of recurrence.

Erysipelas is a disease that affects all ages, but S. Marina et al. (1992) and I. Jungareva (2014) establish engagement of the creative age. A number of authors draw attention to the more common disease among men up to 40 years, and women after this age. Rare cases have also been described in children (Cherkasov V et al. 1985). This trend is maintained in the current study, with no cases of children with erysipelas. On the one hand, this is explained by the inclusion criteria (persons over 18 years of age) and on the other hand by the distribution of patients in an emergency room for adults and children.

Another reason is the increased hygiene of the umbilical cord in newborns and the growing education of mothers in skin care for children in early childhood.

Erysipelas rarely occurs on its own, without concomitant diseases, given the age of the patients affected. According to S. Marina et al. (1992), S. Pavlov (2003), S. Pavlov et al. (2004), M. Gospodinova (2009), T. Petkova et al. (2011) and I. Yungareva (2014) these diseases serve as a gateway or contribute to a protracted course of skin infection, delayed recovery of affected tissues and risk of recurrence.

The data which diseases are predisposing and which are risk factors for the appearance of erysipelas are contradictory. With the exception of open skin injuries, the main risk factors for the development of RE are residual changes from erysipelas, and from systemic diseases - only obesity (Body Mass Index> 30) has a proven effect on the increased incidence of the disease. The presence of serious concomitant diseases such as CHF, CKD, DM and CVI have an indirect role in the development of RE by slowing the recovery process, longer persistence of inflammation, its penetration into depth and creating conditions for intracellular existence of streptococcus. I. Yungareva (2014) emphasizes the role of common predisposing factors - alcoholism, immunosuppression (drug or HIV-associated), use of corticosteroids and chemotherapy.

According to S. Marina et al. (1992) obesity is a risk factor for both erysipelas and recurrence. In their studies, S. Marina et al. found that obesity is the second most common comorbidity and is almost 4 times more common in RE.

Being overweight is considered an indicator of a more severe course and is a prerequisite for hospital treatment. It causes lymphedema due to blockage of lymph vessels and subsequent reduced tissue oxygenation, predisposing to the development of infections.

J. Smolle et al. (2000) found that the presence of severe comorbidities, including liver and kidney disease, gout and diabetes in erysipelas of the lower extremities, are a prerequisite for a more severe course of infection and a risk of complications such as necrotizing fasciitis. According to L. Daskarev (1980) RE has diagnostic significance for the detection of diabetes.

With regard to concomitant diseases, the present studies show an identical frequency of obesity and diabetes in both sexes.

In the literature, predisposing factors are interdigital mycosis, intertrigo, CVI, followed by lymphedema and trophic disorders after mastectomy (Marina S et al. 1992), (Yungareva I. 2014).

According to studies by S. Marina et al. (1992) in 116 patients with primary and 90 with frequently recurrent erysipelas, trauma and microtrauma preceded in 79.3% the primary and rarely recurrent forms and only in 3.3% of the frequently recurrent ones.

If the nature of the provoking factors allows to judge the type of infection (endogenous or exogenous), then the accompanying diseases in patients are risk factors for the development of the disease. They are responsible for functional and morphological defects of the skin at the site of erysipelas, as well as contribute to the formation of focal, streptococcal infection.

In the present study, CVI occurs in 84.2% of men and 15.8% of women. There is a statistically significant difference in the distribution of CVI.

In the present dissertation, some of the risk factors considered are described as a gateway, including interdigital mycosis, erosions and excoriations, trauma and mastectomy. There was

no statistically significant difference in the front door between the two sexes. In all patients with erysipelas of the upper limb and trunk, there is a previous partial or total mastectomy, which confirms the role of disturbed lymphatic drainage in the occurrence of erysipelas.

S. Marina et al. (1992), I. Yungareva (2014) and A. Erovichenkov et al. (2017) demonstate a change in the predilection site of erysipelas from the face to the lower limb compared to data from the last century. The reason for this topographic change is not fully understood, but the role of concomitant diseases is discussed. Probably, the presence of diabetes and obesity contribute to impaired functionality and tissue trophism. The increased frequency of the two diseases, the sedentary lifestyle, the easy access to high-calorie food, as well as the hectic daily life, predisposing to the consumption of harmful food, are debatable.

S. Marina et al. (1992), T. Petkova et al. (2011) and I. Jungareva (2014) found a predominant involvement of the lower limbs, compared to the upper limbs, face and torso. S. Marina et al. (1992) found more frequent involvement of the left lower limb due to compression of the v. iliaca communis sinistra from art. iliaca communis dextra, the location of most of the plexus pampiniformis to the left of the abdomen, the infusion of v. testicularis sinistra at right angles in v. renalis sinistra and subsequent venous stasis. The present study confirmed a predominant frequency of lower limb involvement (83.1% (n = 74)), with a predominance of the left lower limb. Significantly lower frequency is the localization on the face - 10.1% (n = 9), upper limbs (4.5%; n = 4) and torso (2.2%; n = 2). This confirms the previous observations on the topographic location of the erysipelas. The study confirms the trend of more frequent left lower limb involvement among men, but cannot be statistically justified due to a number of inclusion and exclusion criteria in the study. The latter leads to the absence of a statistically significant difference in the distribution of localization between the two sexes in the present paper. The inclusion and exclusion criteria adopted by us make it possible to determine the characteristics of patients with a different from the observed sample, namely patients who lack congenital and acquired coagulation diseases, cardiovascular diseases requiring long-term AK, chronic and acute liver diseases, platelet autoimmune diseases, hematological diseases, CMV, EBV, HTLV-1 - infections, patients taking drugs with hematotoxic effect at the cellular and bone marrow level (methotrexate, azathioprine, chloramphenicol, thiazide drugs, antiepiles) conducting active radiation / chemotherapy for or after neoplastic disease.

Most often, erysipelas occurs as a primary, followed by frequent recurrence and early and late recurrent erysipelas (Marina S et al. 1992). Most publications indicate that inpatients are mostly patients with primary erysipelas, slightly less often with recurrent and very rarely with recurrent erysipelas. The authors also emphasize the increase in the frequency of RE compared to previous decades (Marina S et al. 1992, Pavlov S et al. 2004, Gospodinova M. 2009, Petkova T et al. 2011, Yungareva I. 2014). This paper confirms this pattern of predominance of the primary erysipelas, followed by the often recurrent one. An assessment of the multiplicity by sex does not indicate male or female predominance.

It is difficult to determine the predominant form of erysipelas, as patients with moderate and severe forms are hospitalized, and those with mild forms undergo home outpatient treatment (Marina C et al. 1992). This problem still exists today. In addition, patients with erysipelas are often admitted to wards / clinics for vascular or purulent-septic surgery, which is

a factor influencing the actual incidence of the disease, assessed in the wards for skin and venereal diseases.

In this study, primary erysipelas was found in 47.9% of women and 52.1% of men, rarely recurrent erysipelas in 24.1% of women and 16.9% of men. Recurrent erysipelas is found in 8.1% of women and 12.6% of men. Frequent recurrent erysipelas occurs in 11.4% of women and 3.6% of men, and late recurrent erysipelas in 8.5% of women and 14.8% of men.

Comparative analysis of the frequency of disease occurrence between the two sexes did not establish a statistically significant difference in the multiplicity between the two sexes: $\chi 2 = 12.9$; $p = 0.52$.

In the retrospective study, the predominant form of erysipelas according to severity is moderate to severe, and according to local manifestations of the disease is erythemo-hemorrhagic. Assessment by sex shows no significant difference in the distribution according to the nature of local manifestations.

In primary erysipelas 20.0% of cases occur as a mild degree of the disease, 52.0% - moderate and 28.0% - severe. In frequent RE - 38.5% are mild, 30.8% - moderate and 30.7% - severe. This indicates a more severe course of primary erysipelas and a milder course of PE. The obtained data confirm the regular course of the disease, according to the multiplicity, namely that in frequent RE the disease progresses more easily. According to S. Marina et al. (1992), some of the patients with frequent RE in relapse do not increase the temperature and may pass the infection on foot. This is explained by depletion of the immune system and a weaker immune response due to lack of lymphatic drainage, outside the area of swelling and antigen intolerance. Erysipelas can occur with local and systemic complications. Antibiotic treatment of erysipelas changes the type of complications in patients. Previously reported focal pneumonias and bronchopneumonias, pleurisy and pulmonary embolism, organic heart lesions such as endocarditis, myocarditis, pericarditis, hepatosplenomegaly, poststreptococcal diffuse glomerulonephritis, acute renal failure and renal failure (Erovichenkov A. 2003, Pavlov S et al. 2003, Yungareva I. 2014). Modern antibacterial treatment limits inflammation and mainly local complications such as tissue abscess or phlegmon, lymphangitis, phlebitis, thrombophlebitis, progressive lymphedema and the formation of posterior tibial syndrome have been reported (Marina S et al. 2003).

Complications were observed in 60.7% of patients with erysipelas, among which the most common were relapses - 30.4%, followed by posterior syndrome - 20.1% and lymphostasis - 9.1%. A small percentage (1.1%) are other complications, including severe - respiratory failure with fatal outcome, necrotizing fasciitis, abscess, limb deformity, paralysis of the facial nerve. No complications were found in 39.3%.

From the comparative analysis between the outcome of the disease and sex no statistically significant difference was found: $\chi 2 = 19.42$; $p = 0.195$. The gold standard for erysipelas prevention is long-term depot penicillin therapy. In the current study, 53.8% of women and 46.2% of men underwent depot penicillin prophylaxis.

Current data on the disease reveal an increase in RE against the background of ongoing or ongoing prevention. The increase in the incidence of RE cannot be explained by resistance to penicillins, as such has not been established. RE is a complication of erysipelas of a socially significant nature, concerning the ability to work and quality of life of patients, often at a

creative age. As a result, there is a need for more in-depth monitoring of the course of the infection.

The causes of RE are many and varied and could not be determined in a single study. In the present study, changes in hemostasis and PCT in erysipelas patients have been evaluated, which will help determine the need for AK in treatment.

According to I. Dikov (1976), V. Cherkasov (1989), S. Marina et al. (1992), V. Fazylov (1996), A. Erovichenkov (2003) and G. Genev et al. (2007) erysipelas proceeds with increased activation of coagulation. Hypercoagulability is the cause of occlusive vascular events, the occurrence of which is copied with the application of AK. The use of AK is not a rule in the treatment of erysipelas and is applied personally, based on hemostatic indices and the clinical picture. Observations on the use of heparin in patients with erysipelas were performed by R. Iankova et al. (1996). Currently, there are no data on studies on the role of applied AK in the risk of recurrence.

A 2019 study demonstrates a new discovery in the biological behavior of *S. pyogenes* and its ability for intracellular persistence and survival (Jendoubi F et al. 2019). It is assumed that this mechanism of coexistence with the host is the cause of the so-called "intracellular reservoirs" of streptococci, sources of intermittent bacteremia. It is this phenomenon that allows us to assume that the intracellular persistence and survival of streptococci is the cause of the development of RE.

It is known that the hemostasis and the immune system have a single evolutionary origin. These two systems function simultaneously in the lower and in the higher organisms it is differentiated into two separate systems. Therefore, the coagulation system not only plays a hemostatic role, but takes an active part in limiting the pathogen by forming a fibrin network.

The working hypothesis of the study is that the unwarranted use of AK in patients with erysipelas may lead to degradation of the fibrin network with dissemination of the etiological agent.

In this study, we aim to determine whether and what changes occur in the hemostasis system in patients with erysipelas. Together with this to study the relationship of the pro-inflammatory marker - PCT - with the severity of erysipelas and the studied hemostasis parameters. The comparative analysis of hemostasis parameters between patients with erysipelas and the control group found a statistically significant difference when comparing fibrinogen parameters and PT activity.

The comparative analysis revealed changes in the hemostasis system in fibrinogen values and PT activity. For example, the mean values of hemostatic indices between the individual degrees of severity of erysipelas show a statistically significant difference in fibrinogen - mild erysipelas - $4.27 \pm 1.078$ g / L, while in severe - $5.94 \pm 1.65$ g / L ($p < 0.001$) and PT (PT activity) ($t = -2.16$; $p = 0.033$).

Dysfibrinogenemia is discussed by I. Dikov (1976), S. Marina et al. (1992), A. Erovichenkov (2003) and G. Genev et al. (2007). Fibrinogen is known to be an acute phase protein whose value increases with an inflammatory response. An isolated rise in fibrinogen is not sufficient to assess hemostasis. The absence of a statistically significant difference between the values of the different hemostasis parameters with the type, severity and multiplicity of erysipelas allows us to hypothesize that the use of AK is not mandatory in all patients with

erysipelas. The presented data on the value of PCT and the severity of the disease are contradictory. S Noh et al. (2016) found a positive correlation between PCT, leukocytes and CRP with body temperature. The authors point out that PCT can be used as a useful marker for the severity of the disease and as a predictor of its prognosisR. Brindle et al. (2018) found low PCT levels in patients with lower extremity erysipelas. According to the authors, the indicator cannot be used both to confirm the diagnosis and the need for antibiotic treatment. A bad predictor is for early improvement. A Rast et al. (2015) found that PCT levels had greater diagnostic accuracy for differentiating erysipelas from DVT than routinely examined proinflammatory markers CRP and leukocytes. The marker has a high specificity for bacterial infections. Low PCT levels <0.1 μg / L do not rule out erysipelas, ie the indicator has a negative predictive value. This may explain the low PCT values in moderate, localized and non-systemic infections (such as early erysipelas). Erysipelas is a relatively easy diagnosis, but it is sometimes difficult to differentiate from deep vein thrombosis. In the latter, there are clinical cases in which the gold standard for deep vein thrombosis (haemostasis, D-dimers and Doppler ultrasonography of the affected limb) is insufficient. The use of PCT differentiates the inflammatory from vascular process (Aptula N et al. 2017). Normal PCT values correlate with vascular accident, while elevated values are an indicator of an inflammatory process. According to D. Miteva et al. 2016 even a slight deviation in PCT values is indicative of a local inflammatory process.

From our comparative analysis of PCT values between erysipelas patients and controls, it was found that the deviations in PCT values were mainly in erysipelas patients and not in the control group, although no statistically significant difference could be found ($p = 0.35$). This confirms the data of A. Rast et al. (2015) that PCT values were slightly elevated in patients with erysipelas in the initial phase of the disease, as PCT was examined on the 1st day of their hospitalization. The severity of the disease does not correlate with elevated PCT values. Comparative analysis of PCT parameters in patients with varying severity of erysipelas did not show a statistically significant difference in mean PCT values ($p > 0.05$). This is confirmed by the study of R. Brindle et al. (2018). A correlation analysis of hemostasis and PCT in patients with erysipelas revealed a positive moderate and statistically significant correlation of PCT compared with PT (sec) (Pearson's $r = 0.497$; $p = 0.010$). In a correlation analysis of hemostasis parameters and PCT in the control group of patients no statistically significant correlation was found.

The present study included patients selected by inclusion and exclusion criteria that would lead to inconsistencies with some of the epidemiological, clinical, or laboratory characteristics of erysipelas established in the literature available to date. Since the aim of the dissertation is to identify changes in the hemostasis system, it was necessary to define criteria that eliminate interfering factors such as the influence of AK and changes in hemostasis. The obtained results do not deny the regularities established so far, but consider the tendencies of the disease in patients selected according to specific criteria.

## 9. CONCLUDING REMARKS

1. Erysipelas affects middle-aged and elderly patients, and there is no significant difference in its characteristics and course between the sexes.
2. The disease occurs more often as a primary infection, manifesting as a moderate, erythemo-hemorrhagic form involving mainly the left lower limb.
3. The predominant involvement of the lower limbs, especially left lower limb, confirm the tendency for the changed topographic impact compared to the last century. There is no statistically significant difference in the distribution by location.
4. The summer-autumn seasonality of the disease for the lower limb and the spring-winter seasonality for the face and torso are confirmed. The presented trend requires preventive measures to reduce the risk of recurrence.
5. Among patients with RE, those who have performed depot-penicillin prophylaxis predominate.
6. Interdigital mycosis is found as the most common entrance door, followed by another type of violation of the integrity of the skin.
7. The most common complication after erysipelas is RE.
8. Among the main concomitant diseases in erysipelas are obesity, diabetes and CVI.
9. From the comparative analysis of the hemostasis parameters between the patients with erysipelas and the control group, a statistically significant difference was established when comparing the indicators of fibrinogen and activity of PT.
10. There is no statistically significant difference in the values of hemostatic indices in different severity forms of the disease, therefore the severity of the disease does not correlate with changes in the hemostasis system.
11. Elevated fibrinogen levels are due to the inflammatory response, and the change in PT levels is insufficient to assume hypercoagulability in patients with erysipelas.
12. The established statistically insignificant difference in the PCT values in the patients with erysipelas and the control group confirms the lack of significant influence of the coagulation system by the inflammatory response, regardless of its severity.
13. Low PCT values can be considered as an indicator of a moderate inflammatory response as well as limited involvement.

Based on the results presented above, a diagnostic-therapeutic algorithm for the use of AK in patients with erysipelas was developed. The purpose of the presented algorithm is to emphasize the need for careful and reasonable use of AK, given the likelihood of dissemination of the pathogen and the creation of intracellular "reservoirs" - a potential source of intermittent bacteremia.

Routine haemostasis tests - aPTT, PT, fibrinogen and platelets - are recommended in any patient with erysipelas for an overall assessment of coagulation status. Currently, the diagnosis of erysipelas is empirical and based on local clinical manifestations and general symptoms. The low specificity of microbiological tests and less than 5% positive blood cultures are inapplicable for diagnosis. Therefore, concurrent PCT testing will differentiate erysipelas from the vascular etiology of hemostasis changes.

## 10. CONCLUSION

Erysipelas is an acute, necrotizing bacterial dermo-hypodermatitis caused mainly by Streptococcus pyogenes, a group A β-hemolytic streptococcus. The modern epidemiology of the disease shows an increased frequency, change of the predilection site from the face to the lower limb and an increase in the frequency of frequently RE. The recurrent form can be considered as the most common complication of the primary erysipelas, and according to the multiplicity and nature of the course - as a chronic, recurrent disease.

A current issue in patients with erysipelas is the high recurrence rate, reaching 40%, compared to 15% in the last century, as well as the reason for retention and increase in the incidence of RE against the background of lack of resistance to penicillins.

Erysipelas is a disease of adults and rarely occurs on its own, in patients without concomitant diseases. Some of them have identified risk factors for the occurrence of RE. Residual changes after erysipelas are indicated as such, and from systemic diseases - obesity (Body Mass Index> 30) has a proven effect on the increased incidence of the disease. The presence of serious concomitant diseases such as CHF, CKD, diabetes mellitus and CVI have an indirect role in the development of RE by slowing the recovery process, longer persistence of inflammation, its penetration into the depths and creating conditions for intracellular existence of streptococcus. In addition, the role of some drugs, in particular AK, whose use may be interpreted as a risk factor for the possibility of dissemination of the pathogen, remains unclear. At present, the diagnosis of erysipelas is made empirically in the presence of clinical local and systemic manifestations of infection. The low specificity of microbiological tests and only 5% positive results in blood cultures do not allow them to be used in the diagnosis. Although erysipelas is an easy clinical diagnosis, it is sometimes a problem to differentiate it from deep vein thrombosis.

Targeted study of specific haemostasis parameters, in combination with the proinflammatory marker PCT, will help to better understand the disease-related changes in the haemostasis system in erysipelas, will contribute to a deeper understanding of the need for justified, effective and safe use of AK without the risk of creating an intracellular source of bacteremia and will help to differentiate inflammatory from vascular changes.

The aim of this dissertation is to determine whether and what changes occur in the coagulation system in patients with erysipelas. In addition, changes in procalcitonin levels were monitored, as well as some epidemiological, demographic and clinical characteristics, aimed at identifying specific patterns of erysipelas and its course.

138 patients were included, among 89 patients with erysipelas and 49 patients with other skin diseases (control group).

A retrospective study of some haemostasis parameters - aPTT, PT, fibrinogen, platelet count - and the proinflammatory marker PCT was performed.

A comparative analysis of the age of patients with erysipelas shows that it is a disease of creative age with average values of 57.62 years in men and 66.33 years in women. The seasonal distribution of patients with erysipelas establishes summer-autumn seasonality. In summer and autumn the lower limbs are affected more often, in particular the left lower limb, and in winter and spring the face. According to the multiplicity, erysipelas most often occurs as a primary,

followed by a rarely recurrent, late recurrent, recurrent and often recurrent erysipelas. According to the severity of the course, patients with moderate disease predominate, followed by mild and severe.

In primary erysipelas, the cases most often occur as a moderate to severe form, followed by severe and mild forms.

According to local changes, the predominant frequency is the erythemo-hemorrhagic form of erysipelas, followed by the erythematous, erythemo-bullous-hemorrhagic and erythemo-bullous.

According to the outcome - the disease passes without complications in 39.3%, and in 60.7% with complications, of which - relapses - 30.4%, post-erysipelas syndrome - 20.1% and lymphostasis - 9.1%. A small percentage (1.1%) are other complications, some of which are severe, such as acute respiratory insufficiency, necrotizing fasciitis, abscess, limb deformity and facial nerve palsy.

Obesity affects 37.8% of women and 62.2% of men with erysipelas.

DM is documented in 38.9% of women and in 61.1% of men.

CVI is found in 15.8% of women and 84.2% of men. There was a statistically significant difference in the distribution of patients with erysipelas by sex and manifestations of CVI: $\chi 2 = 9.56$; $p = 0.002$.

In 22.4% of patients interdigital mycosis is found as a gateway, in 14.5% - erosions, excoriations, chronic eczema, in 14.6% - trauma, in 4.5% - stasis dermatitis, in 4.4% - otitis and / or rhinitis, in 3.4% - mastectomy. No entrance door can be identified in 36.2% of patients.

Depot-penicillin prophylaxis was performed in 53.8% of women and 46.2% of men.

The comparative analysis of the hemostasis parameters between the patients with erysipelas and the control group established a statistically significant difference when comparing the indicators of fibrinogen and activity of PT.

The comparative analysis of hemostasis parameters between patients with primary and different forms of recurrent erysipelas did not reveal a statistically significant difference.

A statistically significant difference in the mean values of hemostatic indices between the individual degrees of erysipelas severity was found only in fibrinogen: in mild erysipelas - 4.27 ± 1.078 g / L and in severe - 5.94 ± 1.65 g / L ($p < 0.001$).

There was no statistically significant difference in PCT values between erysipelas patients and the control group ($p = 0.21$).

There was no statistically significant difference in mean PCT values between individual erysipelas severity levels ($p > 0.05$).

The correlation analysis of hemostasis and PCT in erysipelas patients shows a positive moderate and statistically significant correlation when comparing PCT with PT time (sec) (Pearson's $r = 0.497$; $p = 0.010$).

Correlation analysis of hemostasis and PCT in control patients did not establish a statistically significant correlation.

This study confirms the established features of erysipelas: socially significant disease with predominant involvement of patients in active, creative age; more frequent course as a primary infection, manifesting itself most often as a moderate, erythemo-hemorrhagic form involving mainly the left lower limb; the tendency for predominant involvement of the lower limbs is preserved, with a change of the predilection site from the face to the lower limb; the

summer-autumn seasonality of the disease with involvement of the lower extremities and the spring-winter seasonality of the face and trunk are confirmed.

The clinical-laboratory study did not find a statistically significant difference in the values of hemostatic indices in primary and different forms of PE. There is no statistically significant difference in the change of hemostasis parameters in relation to the shape, severity and multiplicity of erysipelas.

The lack of a statistically significant difference in the values of hemostatic indices in different forms of the disease shows that the severity of the disease does not correlate with the changes in the hemostasis system. The severity of erysipelas does not correlate with the degree of deviation of hemostatic indices.

The observed increase in fibrinogen is due to the inflammatory response, and the change in PT levels alone is insufficient to assume hypercoagulability in patients with erysipelas.

The results presented above allow us to conclude that it is not necessary to include AK in order to prevent vascular accidents in patients with erysipelas.

## 11. OWN DIAGNOSTIC-THERAPEUTIC ALGORITHM FOR USAGE OF ANTICOAGULANTS IN ERYSIPELAS

Patient with erysipelas

Laboratory examination of **aPTT, PT, fibrinogen, platelets, procalcitonin**

Coagulation status of the patient:

**1. Normal coagulation + PCT < 0. 05 ng/ ml**

Therapeutic approach, as in acute bacterial skin infection, according to microbiological examination, antibiogram and basic functional tests for renal and hepatic function. It is not necessary to turn on the AK.

**2. Normal coagulation + PCT ≥ 0.5 ng/ ml, but < 2 ng/ ml**

Dynamic monitoring of the patient's condition, changes in coagulation status and acute phase proteins. Re-examination of PCT after 24 hours. Therapy - as in acute bacterial skin infection, consistent with the risk of developing sepsis and multiple organ failure. AK - according to the patient's condition and coagulation status, monitored in dynamics.

**3. Hypercoagulability (PT < 99.0 sec., aPTT < 25.4 sec., Fibrinogen ≥ 4.98 g/L ) + PCT ≥ 0.5 ng/ ml + Well`s score (2-0):**

Therapeutic approach, as in acute skin infection. Inclusion of AK is recommended when moving the repeated coagulogram. Monitoring of coagulation status throughout the treatment period is recommended.

7. **Hypercoagulability + PCT ≥ 0.5 ng/ ml + Well`s score (1-2)**

Therapeutic approach, as in acute skin infection. Inclusion of AK in the indications of the second coagulogram. Monitoring of coagulation status is recommended.

8. **Hypercoagulability + PCT ≥ 0.5 ng/ ml + Well`s score (≧3)**

D-dimer + Doppler ultrasonography of the affected area * is required. It is recommended to include AK (benefit / risk).

** in erysipelas affecting lower or upper limb*

## 12. CONTRIBUTIONS TO THE DISSERTATION

***Confirmatory contributions***

1. The current demographic and clinical characteristics of erysipelas patients have been established.

2. A comparative analysis of the demographic and clinical characteristics of the disease in both sexes was performed. The lack of sex-related characteristics of the disease has been established.

3. The predominant comorbid background was found in patients with erysipelas.

9. The values of some hemostatic indices were determined - platelets, fibrinogen, PT and aPTT.

10. A correlation analysis was performed to establish the relationship between multiplicity, severity and type of erysipelas and changes in aPTT, PT, platelets, fibrinogen.

7. A correlation analysis was performed to establish a relationship between PCT and disease severity, as well as between PCT and platelets, fibrinogen, PT and aPTT.

8. Infection-induced changes in erysipelas haemostasis were found to be insignificant and did not require AK.

9. A moderately positive correlation was found between PCT and prothrombin time activity.

10. The established changes in the hemostatic changes as well as the lack of a significant statistical difference in the studied regularities, allow to assume that the patients with erysipelas have a relatively safe coagulation profile. The dynamic monitoring of the coagulation status and the acute phase proteins is of a recommendatory nature for the purpose of possible subsequent need for AK therapy.

***Original contributions***

1. For the first time, a comparative analysis of the demographic and clinical characteristics of erysipelas between the sexes was performed.

2. For the first time, a study of the relationship between the multiplicity, severity and shape of erysipelas and some hemostatic parameters (aPTT, PT, platelets, fibrinogen) was performed.

3. For the first time, a study was conducted to establish the relationship between hemostatic indices with a new, specific pro-inflammatory marker - PCT.

11. The relationship between PCT and aPTT, PT, platelets and fibrinogen was studied for the first time.

5. The role of AK in the pathogenesis of RE is being studied for the first time.

6. For the first time, a diagnostic-therapeutic algorithm has been developed with a recommendatory character for safe use of AK in patients with erysipelas.

## 13. SCIENTIFIC ARTICLES AND PARTICIPATIONS IN SCIENTIFIC FORUMS RELATED TO THE TOPIC OF THE DISSERTATION

**Co-authorship in textbook:**
1. S. Márina, V. Broshtilova, J. Dimitrova, F. Georgieva, **Ts. Kalinova**, Y. Velevska. Dermatology and Venereology. A textbook for students in medicine, dental medicine and pharmacy. Medical University – Varna. 2020: 144-148.

**II. Scientific articles:**

**1. Publications in international scientific journals**

**1. Kalinova Ts,** Velevska Y, Márina S. Hemostasis in erysipelas - modern concepts. Scripta Scientifica Medica. 2019; 51(3): 7-11.

**2. Publications in Bulgarian Journals**

1. **Kalinova Ts,** Márina S. Erysipelas or deep venous thrombosis – the role of procalcitonin. Medical Magazine. 2019; 68(8): 44-47.

2. **Kalinova Ts,** Márina S. Modern understanding of hemostatic changes in erysipelas. Dermatol. Venerol. 2020; 58(4): 9-14.

**3. Kalinova Ts,** Márina S. Intracellular persistence of *Streptococcus pyogenes* – a reason for recurrent erysipelas? Dermatol. Venerol. 2020; 1: 14-19.

**4. Kalinova Ts, Ungareva I**, Márina S. Pathophysiological role of hemostatic changes in erysipelas. MedInfo. 2020; 11: 106-111.

## III. Participation in scientific forums and congresses

### 1. Participation in international scientific forums

1. Kalinova Ts**,** Velevska Y, Márina S. Hemostasis in Erysipelas. 28-th Annual Assembly of International Medical Association Bulgaria (IMAB). 13-16 May, 2019, Varna, Bulgaria.

### III. 2. Participation in Bulgarian Scientific forums

**1. Kalinova Ts,** Velevska Y, Broshtilova V, Márina S. Fasciitis necrotisans. XX Annual National conference of BDS. 26-29 September 2019, Albena, Varna.
2. **Kalinova Ts**, Ungareva I, Broshtilova V, Márina S. Differential diagnosis of erysipelas. Spring Dermatological Days. Golden Sands, Varna. 18-21 April, 2019.
3. **Kalinova Ts,** Velevska Y, Georgieva S, Pavlov St. Necrotizing erysipelas in immunosuppressed patient with exitus letalis. Spring Dermatological Days. Golden Sands, Varna. 18-21 April, 2019.

## 14. APPENDICES

### Appendix 1.

**Modern classification of erysipelas according to S. Márina et al .:**

| Classification of erysipelas | |
|---|---|
| **Localisation** | - Face<br>- Scalp<br>- Upper limbs<br>- Lower limbs<br>- Trunk<br>- Genitalia<br>- Mucosal surfaces |
| **Multiplicity** | - Primary<br>- Repeated<br>- Recurrent (early and late, rare and frequently recurrent) |
| **Severity** | - Light<br>- Mild<br>- Severe |
| **Local changes** | - Erythematous<br>- Erythematous-bullous<br>- Erythematous-haemorrhagic<br>- Erythematous-bullous-haemorrhagic |
| **Type of local changes** | - Localised<br>- Disseminated (wandering and metastatic)<br>- |
| **Complications** | - No complications<br>- Coplications (local and systemic manifestations) |

**Appendix 2.**

**Interpretation of procalcitonin levels**

| PCT level | Interpretation |
|---|---|
| **Normal value** <0.05 ng / ml.<br>Healthy persons ≥ 3 days of age. | Normal procalcitonin value (95% CI). |
| **PCT < 0.5 ng/ ml.**<br>Measurable but clinically insignificant increase in PCT. | Local inflammation and local infection are possible.<br>Mild or insignificant systemic inflammatory response. |
| **PCT ≥ 0.5 ng/ ml, but < 2 ng/ ml.**<br>Significant but moderate inflammatory response. Infection is possible, but other reasons for the increase should be taken into account - trauma, major surgery, cardiogenic shock. | With a proven infection, a diagnosis of sepsis is present. Re-examine after 6-24 hours. |
| **PCT ≥ 2 ng/ ml, but < 10 ng/ ml.**<br>Severe systemic inflammatory response, most likely due to infection (sepsis), unless otherwise known. | High risk of developing organ dysfunction. If the value persists > 4 days, re-evaluate sepsis therapy. Possible unfavorable outcome. Daily PCT testing is recommended. |
| **PCT ≥ 10 ng/ ml.**<br>Significant systemic inflammatory response, most often due to severe sepsis or septic shock. | Most often - the presence of organ dysfunction. High risk of mortality. Daily PCT testing is recommended. |

**Appendix 3.**

**WELL`S SCORE (WELL`S CRITERIA) FOR DEEP VENOUS THROMBOSIS**

Well`s score (Well`s criteria) is a point system for assessment the risk of developing DVT in the lower limb. The result is calculated by summing specific indices. The sum of the points reflects the degree of risk of developing DVT.

| Criteria | Points |
|---|---|
| Active cancer (treatment in the last 6 months or palliative) | **+ 1** |
| Swelling of the lower limb ≥ 3 cm compared to the asymptomatic limb (measured 10 cm below the tuberositas tibiae) | **+ 1** |
| Oedematous unilateral superficial veins (non-varicose, in the affected limb) | **+1** |
| Unilateral pitting oedema (of the affected limb) | **+1** |
| Previous, proven DVT | **+ 1** |
| Swelling of the whole affected leg | **+ 1** |
| Localized pain in the deep venous system | **+ 1** |
| Paralysis, paresis or recent immobilization of the lower limbs | **+ 1** |
| Recent bed rest ≥ 3 days or major surgery requiring regional or general anesthesia in the last 12 weeks | **+ 1** |
| An alternative diagnosis is at least as likely | **- 2** |
| + D-dimers (≥ 0.5 mcg/mL or 1.7 nmol/L) | **-** |
| No lower limb injury | **-** |
| Male | **-** |
| Oral contraceptives | **-** |

**Results:**

**-2 - 0 points** - low probability of developing DVT

**1 – 2 points** - moderate probability of developing DVT

**3 – 8 points** – high probability of developing DVT