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Comorbidities as Risk Factors for Acute and Recurrent Erysipelas

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Abstract

BACKGROUND: Erysipelas is a common infectious skin disease. A typical feature of erysipelas, especially on the lower limbs, is the tendency to reoccur and the study aimed to define the comorbidities associated with it.

AIM: We aimed to investigate systemic and local comorbidities in patients diagnosed with erysipelas on the lower limbs.

MATERIAL AND METHODS: We conducted a retrospectively-prospective, population-based cohort study which included all patients diagnosed with erysipelas on the lower limbs, during two years. Patients were divided into two groups: patients with first episode and patients with recurrent erysipelas. These two groups were compared, with particular emphasis on systemic and local comorbidities.

RESULTS: The study included 313 patients, of which 187 with the first episode of erysipelas and 126 with a recurrent. Regarding the analyzed systemic risk factors, the recurrent erysipelas was significantly associated with obesity ($p < 0.0001$), insulin dependent diabetes mellitus ($p = 0.0015$), history of malignant disease ($p = 0.02$) and tonsillectomy ($p = 0.000001$). For a p-value < 0.0001, significantly more frequent finding of peripheral arterial occlusive disease, chronic oedema/lymphoedema, fungal infections of the affected leg and chronic ulcer was confirmed in recurrent erysipelas. Neuropathy had 23% of the recurrent cases and 8.6% in patients without recurrence, and the difference was found to be significant for $p = 0.0003$. The only dissection of the lymph nodes was found more frequently in recurrent erysipelas ($p = 0.017$), but no associations with other analysed local surgery on the affected leg. Patients with recurrent erysipelas had ipsilateral coexisting dermatitis $p = 0.00003$ significantly more frequent. Minor trauma often preceded the first episode of erysipelas $p = 0.005$.

CONCLUSION: Identification and treatment of modifiable risk factors are expected to reduce the risk of a subsequent episode of erysipelas on the lower limbs.

Introduction

Erysipelas is an acute bacterial nonpurulent infection of the superficial layer of the skin, with significant inflammation of the lymphatic vessels (lymphangitis), whose main clinical feature is demarcated elevated, warm erythema with pronounced systemic symptoms [1], [2]. Cellulitis is a soft tissue infection that affects the deep dermis and subcutaneous tissue [2], [3], [4]. The historical distinction between cellulitis and erysipelas based on a different bacterial aetiology, and therefore therapeutic modalities, is outdated with the growth of evidence suggesting overlapping of these two entities [5], [6]. Epidemiological studies show an increase in the incidence of erysipelas [7], [8], [9]. It is thought to be 200 per 100,000 people per year, and there is no gender difference. The highest incidence was observed in the oldest age groups [9]. The most common anatomical localisation of erysipelas are the lower limbs [9]. Women are at greater risk for erysipelas on the trunk, and men are erysipelas on the lower limbs [9]. These infections are caused by

streptococci, most commonly in Group A, but also from the groups B, C, F, or G. The diagnosis is primarily clinical and is based empirically on the cutaneous manifestations, and systemic signs of infection [10]. Typically for erysipelas, especially the lower limbs, is the tendency to recur. The incidence of recurrent erysipelas varies from study to study. Namely, 10-30% of patients who have had erysipelas, will have relapses at different time intervals, several weeks to years [11], [12]. The relapse rate is 8% to 20% per year [13]. In studies with a longer follow-up period, the rate of relapse is significantly higher, so in a retrospective three-year study it is more than 45% [14]. The recurrent erysipelas of the lower limbs is thought to be a result of the repetitive bacterial invasion of the skin through injuries to its protective barrier [14]. Accordingly, the potential points of entry of the infection were analyzed as risk factors for relapse in several clinical studies-disruption of the cutaneous barrier (ulcer, trauma), coexisting dermatoses of the lower limbs, lymphoedema, surgical interventions of the lymphatic/venous system, peripheral arterial occlusive disease, chronic venous insufficiency [8], [12], [15]. General risk factors include obesity, history of malignant disease and diabetes mellitus and smoking [12], [13], [14], [15], [16], [17], [18]. Treatment for an initial and recurrent episode of erysipelas do not differ and are described in several existing protocols [19], [20], [21], [22]. These protocols reinforce the significance of long-term antibiotic prophylaxis as a method for the reduction of recurrent erysipelas [23], [24], [25], but proclaim as well rigorous control of predisposing risk factors [13], [14], [16], [17].

We aimed to investigate systemic and local comorbidities in patients diagnosed with erysipelas on the lower limbs.

Methods

We conducted a retrospectively-prospective, population-based cohort study, conducted in a dermatology department in two years. All patients aged ≥ 18 years were recruited, with a diagnosis of acute erysipelas on the lower limbs. All types of necrotising skin and soft tissue infections (SSTI) have been excluded, skin infections in severely immunocompromised patients, and infectious complications of severe injuries to soft tissues. Patients with a first episode of erysipelas on the lower extremities were followed for at least one year from the initial episode, for the development of a recurrent one.

Upon completion of the study and the follow-up period, patients were divided into two groups, cohorts. First group (no recurrence group – NE)-patients with the first episode of erysipelas defined only on clinical findings which included the area of erythema, swelling, warmth and pain, fever was not needed to meet the definition and did not experience a recurrent episode during the follow-up period. Second group-patients with recurrent erysipelas (RE), defined as a second/multiple episodes of erysipelas that meets the criteria of the first episode, at the same anatomical localisation, at least 1 month to one year from the initial diagnosis. This group will also include all patients with at least a second episode that has occurred during the study and out of the study (through anamnestic data or medical documentation for it). These two groups will be compared with particular emphasis on general and local risk factors/comorbidities. The required data for all recruited patients was obtained through clinical examination and patient interview, as well as medical records. The analysed variables were classified in local and general risk factor/comorbidities. Obesity is defined if BMI ≥ 30 [26]. Alcohol abuse is considered if the consumption of 14 units of alcohol per week is exceeded-in men and 7 units weekly for women [27].

Point of entry was detected by clinical examination (wound, chronic ulcer, coexisting chronic pruritic dermatoses and fungal infections of the ipsilateral extremity). Chronic oedema/lymphoedema defined as chronic progressive swelling of the affected lower limb longer than 3 months [28] present on clinical examination or in the medical records. The following variables will be considered present if pointed in an interview or medical records-history of regional surgery; neurological diseases, history of phlebitis, diabetes mellitus, chronic renal failure, hepatic cirrhosis, cardiovascular diseases, history of malignancy, rheumatic and autoimmune diseases, peripheral arterial occlusive disease (PAOD), chronic venous insufficiency (CVI). Regarding statistics, the Kolmogorov-Smirnov test was used to test the distribution of data. The categorical variables are represented by distribution on frequencies. Quantitative variables with symmetric distribution are shown with mean values, and the media was used to display quantitative data with asymmetric distribution. Pearson Chi-square test, Yates Pearson Chi-square test (Student t-test for independent samples and Mann-Whitney test) were used to compare groups with first and recurrent erysipelas. The statistical significance was defined on the level of $p < 0.05$.

Results

Comparison of general and local risk factors between

The study included 313 subjects, of which 187 were with a first episode of erysipelas (NE), and 126 with recurrent erysipelas (RE).

Table 1: Comparison of comorbidities – general risk factors

Variable	Ne group	Re group	P-level
Bmi			
Mean ± SD	30.01 ± 16.5	31.49 ± 6.5	P = 0.34
Min - max	20.8 – 247	22.7 – 53.8	
Obesity	65 (34.76)	73 (57.94)	P < 0.0001
Diabetes mellitus			
Insulin dependant	39 (20.86)	48 (38.10)	P = 0.0015
On oral hypoglycemic agents	38 (20.32)	27 (21.43)	
Chronic kidney disease	9 (4.81)	8 (6.35)	P = 0.56
Cirrhosis hepatis	4 (2.14)	5 (3.97)	P = 0.34
History of malignancy	10 (5.35)	16 (12.7)	P = 0.02
Autoimmune disease	4 (2.14)	5 (3.97)	P = 0.34
Tonsilectomy	4.8 (9)	23.8 (30)	P = 0.000001
Alcohol excess	28 (14.97)	16 (12.7)	P = 0.57
I.v. drug use	0	3 (2.38)	P = 0.13
Actueal smoking	42 (22.46)	35 (27.78)	P = 0.28
Cerebro vascular disease	4 (2.14)	5 (3.97)	P = 0.34
Copd	10 (5.35)	11 (8.73)	P = 0.24
Congesticve heart failure	42 (22.46)	33 (26.19)	P = 0.45
Ischaemic heart disease	21 (11.23)	23 (18.25)	P = 0.08

All the analyzed systemic risk factors (Table 1), with the exception of alcoholism, were more commonly reported in RE patients, but a significant difference between the two groups was confirmed regarding this risk factors-obesity (p < 0.0001), diabetes mellitus (p = 0.0015), history of malignant disease (p = 0.02) and tonsillectomy (p = 0.000001) (Figure 1).

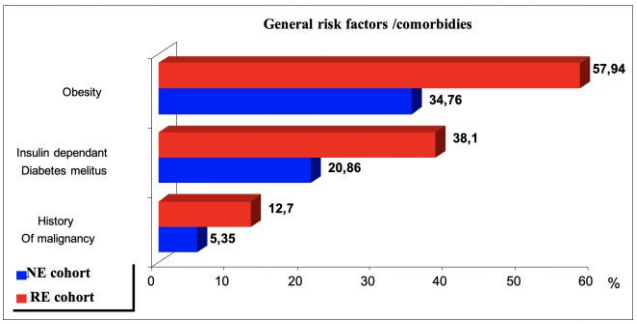

Figure 1: Graphic representation of general risk factors in the two cohorts

About 34.8% of patients with NE were obese, and 57.9% were patients with RE. Insulin-dependent DM had 20.9% of patients in the NE group and 38.1% with RE. 5.35% of the NE patients had a history of the malignant disease and 12.7% in the RE group. Tonsillectomy was performed in 4.8% of patients without and 23.8% of patients with RE.

Table 2: Comparison of comorbidities – local risk factors

Variable	NE group	RE group	p-level
CVI	92 (49.2)	65 (51.59)	P = 0.68
PAOD	41 (21.93)	52 (41.27)	P < 0.0001
Chronic oedema/lymphoedema	64 (34.22)	109 (86.51)	P < 0.0001
History of an ulcer	24 (12.83)	64 (50.79)	P < 0.0001
History of flebitis	44 (23.53)	35 (27.78)	P = 0.39
Neuropathy	16 (8.56)	29 (23.02)	P = 0.0003
The surgical intervention of the blood and lymph. Vessels			
Saphenectomy	6 (3.21)	11 (8.73)	P = 0.08
Endovascular and other surgical intervention of the blood and lymph.Vessels	26 (13.9)	20 (15.87)	
Local orthopaedic surgery			
Endoprotesis of knee and hip joint	8 (4.28)	7 (5.56)	P = 0.051
Fractures or other orthopaedic interventions	14 (7.49)	20 (15.87)	
Dissection of regional lymph nodes	1 (0.53)	7 (5.56)	P = 0.017
Surgery of the skin and soft tissue			
Skin grafting	1 (0.53)	5 (3.97)	
incision, drainage and other procedures	1 (0.53)	4 (3.17)	
Fungal infection			
Onichomycosis	7 (3.74)	25 (19.84)	P < 0.0001
Tinea pedis	21 (11.23)	41 (32.54)	
Preceding trauma	54 (28.88)	19 (15.08)	P = 0.005
Chronic ulcer	29 (15.51)	48 (38.1)	P < 0.0001
Ipsilateral coexisting dermatitis	49 (26.2)	62 (49.21)	P = 0.00003

Peripheral arterial occlusive disease (PAOD), chronic oedema/lymphoedema, history of an ulcer, neuropathy, lymph node dissection, preceding trauma, chronic ulcer fungal infections and coexisting dermatitis on the ipsilateral are local risk factors with significantly different representation in both cohorts (Table 2). For p < 0.0001 values, significantly more frequent finding of PAOD was confirmed in RE (51.6% vs 49.2%) in NE patients, chronic edema/ lymphoedema (86.5% vs 34.2%), fungal infections of the affected limb t (52.4% vs 15%), and chronic ulcer (38.1% vs 15.5%). Consecutive. With p < 0.0001 significance, patients with recurrent erysipelas had a significantly more frequent history of an ulcer, compared with patients with NE (50.8% vs 12.8%). Neuropathy had 23% of patients with RE, and 8.6% in a patient with no recurrence and the difference was confirmed as significant for p = 0.0003. Dissection of lymph nodes had 8 patients, one without relapse and 7 with recurrent erysipelas (p = 0.017). Patients with RE had significantly more frequent ipsilateral coexisting dermatitis (49.2% vs 26.2%, p = 0.00003). Minor trauma significantly preceded NE, (28.9% vs 15.1%, p = 0.005).

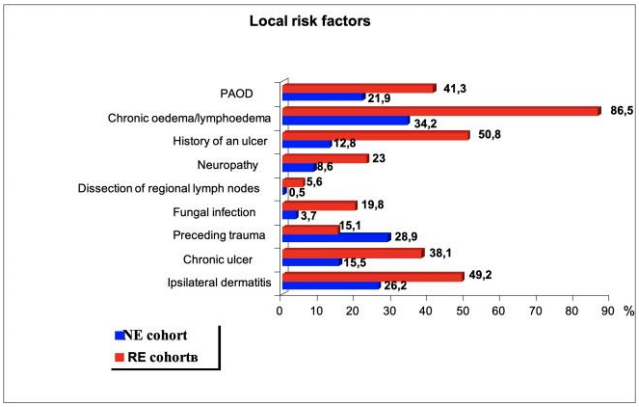

Figure 2: Graphic representation of local risk factors in the two cohorts

Discussion

The recurrence rate of erysipelas is almost 30% in a 2-4-year period [29]. There are only a few studies that analyze the risk factors in recurrent erysipelas, some of the results of our study are consistent with them [12], [13], [14], [15], [16], [17], [18], [30].In this study, we included 313 patients throughout two years, of which 187 were the first episode of erysipelas, and 126 with recurrent erysipelas. The study was a retrospective-prospective population-based cohort, and the collected data are with particular emphasis on systemic and local risk factors and with the primary goal to compare patients with first (NE) and recurrent erysipelas (RE). The

study included all patients with erysipelas on the lower extremities, hospitalised and outpatient, avoiding bias in patient selection; however, hospitalised patients are more likely to be older and have more comorbidities. In our cohort of RE, significantly more frequent systemic risk factors were-obesity, history of malignant disease, which correlates to other studies [8], [13], [14], [15]. Diabetes in the RE is present with 38.1% vs 20.9% in NE group ($p < 0.001$) and was strongly associated with recurrent erysipelas. In other studies [14], [17] this association has not been established. However, Harris et al. suggested an association with glucose intolerance [31]. Diabetes affects the healing process [32]. Hyperglycemia reduces the function of neutrophils and monocytes through impairment in the immune system cascade, primarily chemotaxis, adherence, and phagocytosis [33], [34]. People with diabetes are generally at greater risk of infection with certain microorganisms, in particular, group A and B streptococci and Staphylococcus aureus [35]. This study confirms tonsillectomy ($p = 0.000001$) as a risk factor for relapse, previously suggested by a study by Karppelin et al., from 2013 [18]. The ability of the streptococcus to survive intracellularly is suggested as a mechanism in recurrent tonsilitis and is likely the reason for the recurrent nature of erysipelas [36], [37], [38]. The most significant risk factors are local-Chronic oedema/lymphedema, history of ulcer, coexisting ipsilateral dermatitis, PAOD, chronic ulcer, fungal infections of the ipsilateral limb-all significant in other studies [12], [13], [14], [15], [16], [17]. In most of the patients who were involved in our study, the point of entry could be identified. The disruption of the cutaneous barrier is repeatedly referred to as a risk factor, namely in relation to fungal infections it is considered that they do not cause erysipelas, but in many cases of erysipelas of the lower limbs, the responsible streptococci are residents in the interdigital spaces, when they are macerated, presented with regards and fissures [39], [40], [41]. Recurrent episodes [40] have been discontinued the treatment of tinea pedis as a point of entry. Sometimes, the streptococcal reservoir is the anal canal or vagina, especially in patients with previous gynaecological carcinoma treated with surgical and radiotherapy [42]. However, only the disruption of the skin barrier usually does not lead to the onset of infection. It is considered that there must precede damage to the subcutaneous tissue and lymphatics. The authors agree that damage to the lymphatic system plays a key role in the development of acute cellulite on the lower limbs. In particular, damage to the venous and lymphatic system predisposes to the creation of an environment suitable for bacterial colonization for infections caused by β-haemolytic streptococci [12], [13], [43]. The lymphatic system plays a central role in the host's defence against skin infections and soft tissue. The damaged lymphatic clearance for microbial antigens and inflammatory mediators is proposed as a mechanism leading to a self-sustaining vicious circle of inflammation [44], [45].

In our study, the significance of CVI was not confirmed as a predictive risk factor, which is the case of multiple studies [12], [14], [30]. We've concluded that the reason is that the institution in which this study was conducted is specialised in the treatment and care of chronic wounds. All patients with first episode of erysipelas and CVI, were educated about the benefits and use of the appropriate compressive stockings/bandage (for each patient with CVI a compression bandage was applied during hospitalization) as well as skin care especially for lipodermatosclerosis and stasis dermatitis that is common in these patients and acts as point of entry.

Surgical interventions of blood and lymphatic vessels, as well as orthopaedic surgery, have not been proven as significant risk factors, unlike in other studies [15], [41] except for local lymph node dissection. This is consistent with the risk factor history of malignant disease. Malignity can be complicated by venous and lymphatic compromise, directly due to tumour effects or indirectly due to radiotherapy, and it predisposes to streptococcal infection [43]. These results indicate that erysipelas should be considered as a recurrent, potentially chronic disease [4]. In all patients with acute erysipelas the lower extremities preventive measures are required to reduce the high incidence of recurrent disease. The extent of the required prophylaxis is unknown. However, prolonged antibiotic prophylaxis in patients at high risk has a role in preventing the recurrence [24]. The crucial element in prevention of recurrent infection is elimination of risk factors such as avoiding mechanical trauma, treatment of point of entry (chronic ulcers, tinea pedis, onychomycosis, pruritic dermatitis, and CVI), use of compressive stockings/bandages, lowering Body Mass Index (BMI) and rigorous glycemic control in diabetic patients.

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