The effectiveness of erysipelas prophylaxis depends on the cumulative dose of benzathine penicillin G

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Abstract

Erysipelas is an acute infection due to S. pyogenes and is characterized by a high risk of relapses. The number of patients suffering from one or more recurrences varied depending on the study and accounted for between 16% and 47% of the total number of those affected. Antibiotic prophylaxis with the use of penicillin can reduce the risk of recurrence by 47%. A number of 873 patients with erysipelas treated at the Hospital for Infectious Diseases in Warsaw from 2010 to 2018 was enrolled in the study. Benzathine-penicillin G was given intramuscularly at a dose of 1.2 MU or 2.4 MU or 3.6 MU. The earliest moment that prophylactic treatment was administered was the first episode of erysipelas recurrence. The decision to administer the antibiotic and the dose to use was discretionally made by the examining physician. Altogether 104 (11.9%) persons experienced at least one episode of erysipelas recurrence during the study period. A total of 2976 doses of benzathine-penicillin G (BP) were administered. The most common dose was that of 2.4 MU (2380, 80%). The dose of 1.2 MU was given 567 times (19%). The highest dose, *i.e.* 3.6 MU, was administered to only 5 patients (8 applications, 0.2%). No effect was shown by either the number of benzathine-penicillin G administered doses (p=0.07) or the median dose (p=0.65), whereas patients without relapse received a statistically higher cumulative dose of the antibiotic (p=0.047). Age was a risk factor of recurrence only in the group of diabetic patients (p=0.03). Benzathine penicillin G given in an appropriate cumulative dose is effective in preventing erysipelas recurrence.

Introduction

Erysipelas is due to S. pyogenes and is characterized by an acute onset of a bright red and painful swelling with a border sharply demarcated from healthy skin. Uncomplicated cellulitis has very similar features to clinical erysipelas with localized pain, erythema, swelling and heat.[1,2] Both conditions are burdened with the risk of recurrence. The number of patients suffering from one or more recurrences varied depending on the study and accounted for from 16% to 47% of the cases.[1]

Leg edema, venous insufficiency, lymphatic insufficiency and obesity are potential risk factors for the recurrence of erysipelas.[1,3,4]

Antibiotic prophylaxis shows a statistically significant benefit for preventing of recurrent cellulitis compared to no antibiotic prophylaxis.[5,6] The use of penicillin can reduce the risk by 47%.[7] However, some papers indicate that despite antibiotic prophylaxis, cellulitis still recurs. Postulated reasons for failure of preventive therapy include noncompliance; incorrect antibiotic; other causative micro-organisms; or insufficient antibiotic concentrations.[6]

In this study we analyzed the rate of the recurrence of erysipelas and uncomplicated cellulitis, among the patients of the Hospital for Infectious Diseases in Warsaw, Poland, certain risk factors for the infection relapse, and the effectiveness of the benzathine penicillin G administration in the prevention of the infection recurrence.

Materials and methods

Study population

We reviewed the records of 873 patients with erysipelas and uncomplicated cellulitis who were hospitalized in two of five wards for adult patients in the Hospital for Infectious Diseases in Warsaw, Poland from 01.01.2010 to 31.12.2018.

Data collection

The Optimed database (Esa Project, Poland) was searched for adult patients (≥18 years) with any (principal or secondary) discharge diagnosis code for erysipelas according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

The principal diagnosis indicated the main reason for hospitalization according to the assessment of the discharging clinician. Erysipelas was the secondary diagnosis if another disease entity was acknowledged as the main reason for hospitalization.

Essential information including age, sex was extracted from Optimed. Then the patients' medical documentation was

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reviewed by the clinicians in search for underlying conditions, such as diabetes mellitus, obesity, a history of thrombophlebitis, information confirming a recurrence and the dose of benzathine-penicillin G that had been administered.

Case definition

Erysipelas recurrence was defined as local erythema associated with pain and edema. In uncertain situations the basic inflammatory parameters, namely leucocyte count and CRP concentration were examined.

In our study patients with the diagnosis of erysipelas and uncomplicated cellulitis were assigned to the "erysipelas" group, since in the Hospital for Infectious Disease in Warsaw, Poland the management of those two conditions does not vary.

Follow-up

Patients were given benzathine-penicillin G intramuscularly at a dose of 1.2 MU or 2.4 MU or 3.6 MU. The hospital's standard allowed to introduce prophylactic treatment from the first episode of erysipelas recurrence. The decision to administer the antibiotic and the dose specification was discretionally made by the examining physician.

Statistical calculation

Statistical calculations were made for the entire study group and for groups of patients with diabetes, obesity and a history of vein thrombosis comparing patients with erysipelas recurrence and without it.

The distribution of discrete variables was analyzed with the chi-square test. For continuous variables the Mann-Whitney u-test was used to compare the groups.

Results

Over the study period, 873 (459 women and 414 men) patients were included for analysis. The median age of the researched population was 63 (average 62), the minimum age was 18, while the maximum 98 years (Table 1).

Diabetes mellitus was diagnosed in 221 patients (25%), obesity in 355 persons (41%), 17 patients had a history of thrombophlebitis (2%).

Benzathine penicillin G (BP) was given to 422 (48.3%) patients. A total of 2976 doses were administered.

The most common dose was that of 2.4 MU (2380 doses, 80 %). The dose of 1.2 MU was given 567 times (19.1%). The highest dose, *i.e.* 3.6 MU was administered to only 5 patients (8 applications, 0.2%) (Table 1).

Altogether 104 (11.9 %) persons experienced at least one erysipelas recurrence during the study period. To be exact, one relapse occurred in 81 patients, two in 15 patients, three in 6 patients, four in 2 persons (Table 1).

Of this number 37 (35.6%) persons suffered from diabetes mellitus, 28 (26.9%) from obesity and 5 (4.8%) had history of thrombophlebitis (Table 1).

Neither of the above-mentioned underlying conditions nor sex were associated with higher erysipelas recurrence rate.

In case of age statistically significant difference was found only in the group of diabetic patients. Those with infection relapse were statistically younger (p=0.03) (Figure 1).

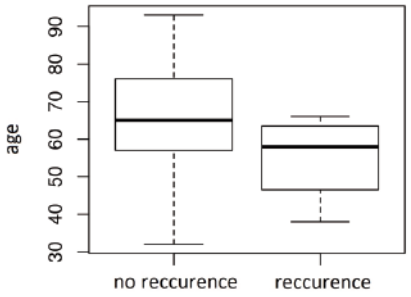

Figure 1. Age as a risk factor in the group of diabetic patients.

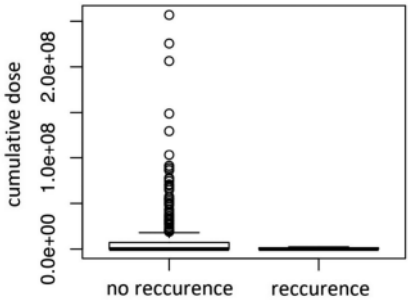

Figure 2. Impact of cumulative dose of benzathine penicillin G on the risk of erysipelas recurrences.

Table 1. Study population.

No of patients	Total 873. Women 459 (53%). Men 414 (47%)
Median (average) age	63(62)
Minimum age, maximum age (years)	18, 98
Benzathine penicillin G administration, n. of patients (% of whole study population)	Yes 422 (48.3%). No 440 (50.4%). Lack of data 11 (1.3%)
No of benzathine penicillin G doses	2976
No of 2.4 MU doses (% of all doses)	2380 (80.0%)
No of 1.2 MU doses	567 (19.1%)
No of 3.6 MU doses	5 (0.2%)
Lack of data on the BP dose	21 (0.7%)
No of patients with recurrences (% of whole study population / % of population with recurrence)	Total 104 (11.9%). One recurrence 81 (9.3%/77.9%). Two recurrences 15 (1.7%/14.4%) Three recurrences 6 (0.7%/5.8%). Four recurrences 2 (0.2%/1.9%)
Diabetes mellitus (no of patients, % of whole study population/no of patients with recurrences, % of patients with recurrence)	221 (25%)/37 (35.6%)
Lack of data on diabetes mellitus diagnosis	12
Obesity (no of patients, % of whole study population/no of patients with recurrences, % of patients with recurrence); lack of data on the risk factor	355 (41%) / 28 (26.9%)
Lack of data on obesity diagnosis	18
Thrombophlebitis (no of patients, % of whole study population/no of patients with recurrences, % of patients with recurrence); lack of data on the risk factor	17(2%) /5 (4.8%)
Lack of data on thrombophlebitis diagnosis	21

Table 2. The distribution of discrete variables: sex, BPG administration, underlying condition (chi-square test).

Variable (unit)	Total	P value
Female/male ratio (%)	459 (53%) / 414(47%)	0.523693177
Diabetes mellitus (no of patients/no of patients with recurrence)	221/37	0.306864988
Obesity (no of patients/no of patients with recurrence)	355/28	0.085936132
Thrombophlebitis (no of patients/no of patients with recurrence)	17/5	0.671305156

Table 3 The distribution of continuous variables: median and cumulative dose of BPG and number of BPG doses (Mann-Whitney u-test).

Variable (unit)	P value	Median – patients without recurrence	Median – patients with recurrence
Benzathine penicillin G (median dose, MU)	0.645935728	1994074.074	1885714.286
Benzathine penicillin G (no of doses)	0.066968625	3.489411765	0.45
Benzathine penicillin G (cumulative dose, MU)	0.047166114	6988235.294	660000

No effect was shown by either the number of benzathine-penicillin G administered doses (p=0.07) or the median dose (p=0.65), whereas patients without relapse received a statistically higher cumulative dose of the antibiotic (p=0.047) (Tables 2 and 3, Figure 2).

Discussion

The present study examined 873 (459 women and 414 men) patients with erysipelas and uncomplicated cellulitis. Multiple recurrences were observed in 104 persons (11.9%). One relapse accounted for the most common number of episodes and was seen in 81 (77.9%) persons. The results vary from other findings, which show a higher relapse percentage and a higher number of recurrences. The different methods applied, mostly prophylactic measures, must certainly have had an impact on the dissimilarity.[3,7-10]

Benzathine penicillin G and other penicillins reduce the incidence rate of recurrent cellulitis.[5-7] In our study no effect was shown by either the number of benzathine penicillin G administered doses (p=0.07) or the median dose (p=0.65), whereas patients without relapse received a statistically higher cumulative dose of the antibiotic (p=0.047). The effective cumulative dose was about 7 MU. Although the number of doses did not reach statistical significance it closely approached it, indicating 3.5 doses as sufficient. On the other hand, when 2.4 MU was the most common penicillin dose, we can assume that the administration of 2.9 such doses could prevent the relapses of infection.

In the study of Rob F and Hercogova J, 1.2 MU of benzathine penicillin G administered once every 3 weeks was found to be an effective method for preventing the relapse of erysipelas. Patients were given 10 doses, which gives 12 MU, but the lowest cumulative dose was not examined.[4] Similarly in the study of Chen HM, patients who received benzathine penicillin at the dose of 2.4 MU every 4 weeks at least 3 times, experienced fewer recurrence episodes than patients in the non-prophylactic period. The given dose aggregated to at least 7.2 MU.[12]

Benzathine penicillin G given intramuscularly shows a lack of accumulation over time in either the serum or the peripheral tissues. The concentration 4 weeks after the sixth dose is similar to the concentration 4 weeks after the first dose.[13] Most strains of *Streptococcus pyogenes* express the fibronectin-binding proteins F1 and F2, which promote bacterial adherence to and entry into human cells and can be responsible for the failure of antibiotic treatment to eradicate *Streptococcus pyogenes*.[14] In patients with erysipelas, there is frequently a history of preceding streptococcal sore throat in case of face involvement or suggestive evidence that a local skin infection can play the role of a reservoir for β-hemolytic streptococci that initiates episodes of erysipelas or cellulitis of the lower extremities.[15] It can be assumed that BPG prevents erysipelas relapses if it is administered repetitively over an appropriate time to reach the adequate dose.

Local disorders, such as leg edema, venous insufficiency, lymphatic insufficiency, as well as underlying chronic conditions, namely obesity, diabetes mellitus, a history of malignant disease are possible risk factors for erysipelas.[2,4,16]

In our study we analyze obesity, diabetes mellitus, and the history of thrombophlebitis as a possible cause of chronic edema or venous insufficiency. Neither of the factors were associated with higher erysipelas recurrence rate, similarly as in the results obtained by Rob F and Vignes S.[4,10]

Interestingly, younger diabetic patients (55 *vs* 66 years, p=0.03) were more likely to suffer from the relapse of the infection. Recurrent episodes of erysipelas, despite prophylactic treatment, were found in non-compliant patients.[17] In Poland the retirement age for women starts from 60 years and for men from 65.[18] Diminished compliance of professionally active persons and increased risk for infection among diabetic patients can explain this result.[19]

Conclusions

Benzathine penicillin G given in an appropriate cumulative dose is effective in preventing erysipelas recurrence.

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