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

Agnieszka Bednarska,1,2 Iwona Sosińska-Bryła,2 Paweł Grąbczewski,2 Regina Podlasin,2 Marcin Paściorek,1,2 Dominik Bursa,1,2 Małgorzata Hackiewicz,2 Michał Makowiecki,2 Andrzej Horban,1,2
1Department of Adults’ Infectious Diseases, Medical University of Warsaw; 2Hospital for Infectious Diseases in Warsaw, Poland

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%. 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.

Correspondence: Agnieszka Bednarska, Hospital for Infectious Diseases, 01-301 Warsaw, Wolska 37, Poland.
Tel: +48 22 3355372.
E-mail: abednarska@zakazny.pl

Key words: Erysipelas, Recurrence, Benzathine penicillin G, Cumulative dose.

Contributions: All authors have read and approved the manuscript AB main author, DB, IS-B, PG, MH, MM data collection and analysis, RP, MP manuscript revising, AH final approval of the version to be published.

Conflict of interest: The authors declare no potential conflict of interest.

Funding: The study was supported by Fundacja Rozwoju Nauki w Województkim Szpitalu Zakaźnym (Foundation for the Development of Infectious Diseases at the Voivodship Infectious Diseases Hospital) through financial support for data collection and article publishing charge.

Ethics approval: Since the study has retrospective character local ethics committee ruled that no formal ethics approval was required.

Consent for publication: Not applicable for this article.

Availability of data and material: All data generated or analyzed during this study are included in this published article.

©Copyright: the Author(s), 2022 Licensee PAGEPress, Italy Dermatology Reports 2022; 14:9429 doi:10.4081/dr.2022.9429

Publisher’s note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

[ Dermatology Reports 2022; 14:9429 ]
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 discretional 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.](image)

![Figure 2. Impact of cumulative dose of benzathine penicillin G on the risk of erysipelas recurrences.](image)

### Table 1. Study population.

|                          | Total 873. Women 459 (53%). Men 414 (47%) |
|--------------------------|--------------------------------------------|
| No of patients           |                                            |
| Median (average) age     | 63(62)                                     |
| Minimum age, maximum age | 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 (%)   | 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        | 221 (25%)/37 (35.6%)                      |
| Lack of data on diabetes mellitus diagnosis | 12                                         |
| Obesity                  | 355 (41%)/28 (26.9%)                      |
| Lack of data on obesity diagnosis | 18                                        |
| Thrombophlebitis         | 17(2%)/5 (4.8%)                           |
| Lack of data on thrombophlebitis diagnosis | 21                                        |
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

### 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 | 0.306684988 |
| Obesity (no of patients/no of patients with recurrence) | 355/28 | 0.08596132 |
| 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) | 0.069698625 | 3.48941765 | 0.45 |
| Benzathine penicillin G (cumulative dose, MU) | 0.04166114 | 6388235.294 | 660000 |

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) (Tables 2 and 3, Figure 2).

Conclusions

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

References

1. Chlebicki MP, Oh CC. Recurrent Cellulitis: Risk, Factors, Etiology, Pathogenesis and Treatment. Curr Infect Dis Rep 2014;16:422.
2. Kasper DL, Fauci AS. Harrison’s Infectious Diseases. 3rd ed. McGraw-Hill Education; 2017.
3. Leclerc S, Teixeira A, Mahe E, et al. Recurrent Erysipelas: 47 Cases. Dermatology 2007;2014:52-7.
4. Rob F, Hercogova J. Benzathine penicillin G once-every-3-week prophylaxis for recurrent erysipelas: a retrospective study of 132 patients. J Dermatol Treat 2018;29:39-4.
5. Dalal A, Eskin-Schwartz M, Mimouni D et al. Interventions for the prevention of recurrent erysipelas and cellulitis. Cochrane Database Syst Rev 2017;6:CD009758.

6. Oh CC, Hung Ko HC, Lee HY, et al. Antibiotic prophylaxis for preventing recurrent cellulitis: a systematic review and meta-analysis. J Infect 2014;69:26-34.

7. U.K Dermatology Clinical Trials Network's PATCH Trial Team. Prophylactic antibiotics for the prevention of cellulitis (erysipelas) of the leg: results of the U.K. Dermatology Clinical Trials Network's PATCH II trial. Br J Dermatol 2012;166:169-78.

8. Jorup-Ronstrom C, Britton S. Recurrent erysipelas: predisposing factors and costs of prophylaxis. Infection 1987;15:105-6.

9. Bartholomeeusen S, Vandenbergroucke J, Truyers C, et al. Epidemiology and comorbidity of erysipelas in primary care. Dermatology 2007;215:118-22.

10. Vignes S, Dupuy A. Recurrence of lymphoedema–associated cellulitis (erysipelas) under prophylactic antibiotic therapy: a retrospective cohort study. J EADV 2006;20:818-22.

11. Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis. N Engl J Med 2013;368:1695-703.

12. Chen HM, Li YL, Liu YM, et al. The experience of intramuscular benzathine penicillin for prophylaxis of recurrent cellulitis: A cohort study. J Microbiol Immunol Infect 2017;50:613-8.

13. Neely M, Kaplan EL, Blumer JL, et al. A Population Pharmacokinetic Modeling Approach Shows that Serum Penicillin G Concentrations Are Below Inhibitory Concentrations by Two Weeks after Benzathine Penicillin G Injection in the Majority of Young Adults. Antimicrob Agents Chemother 2014;58:6735–41.

14. Passali D, Lauriello M, Passali GC, et al. Group A Streptococcus and its antibiotic resistance. Acta otorhinolaryngologica italiana 2007;27:27-32

15. Stevens DL, Bryant AE. Impetigo, Erysipelas and Cellulitis. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. Streptococcus pyogenes: Basic Biology to Clinical Manifestations [Internet].Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016.

16. Brishkoska-Boshkovski V, Kondov-opuzovska I, Damevska K et al. Comorbidities as Risk Factors for Acute and Recurrent Erysipelas. Open Access Macedon J Med Sci 2019;7:937-42.

17. Koster JB, Kulberg BJ, van der Meer JWM. Recurrent erysipelas despite antibiotic prophylaxis: an analysis from case studies. Neth J Med 2007;65:89-94.

18. Ustawa z dnia 16 listopada 2016 r. o zmianie ustawy o emeryturach i rentach z Funduszu Ubezpieczeń Społecznych oraz niektórych innych ustaw.

19. Carey IM, Critchley JA, DeWilde S, et al. Risk of Infection in Type 1 and Type 2 Diabetes Compared with the General Population: A Matched Cohort Study. Diabetes Care 2018;41:513-21.