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# Recurrent erysipelas despite antibiotic prophylaxis: an analysis from case studies

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## ABSTRACT

**Background:** Erysipelas is a distinctive type of superficial cellulitis of the skin with prominent lymphatic involvement, generally caused by group A streptococci. A substantial proportion of patients experience recurrences of erysipelas, and this may be a reason to install prophylactic antibiotic treatment. Despite such prophylaxis, further recurrences are occasionally encountered.

**Objectives:** To investigate recurrences of erysipelas during prophylactic antibiotic treatment and to delineate the reasons for such failure.

**Methods:** Retrospective chart review of 117 adult patients with episodes of erysipelas known in our institution between 1990 and 2004.

**Results:** Recurrent episodes of erysipelas, despite prophylactic treatment, were found in eight patients. Our analysis indicated noncompliance, incorrect selection and insufficient dosing of antibiotics, and causative pathogens other than streptococci as demonstrable causes of the recurrence of erysipelas. In three patients, a reason for failure could not be identified.

**Conclusions:** In a minority of cases, erysipelas recurs despite antibiotic prophylaxis. Based on these cases, we first recommend that all efforts are made to (re)confirm the diagnosis of erysipelas and search for the causative micro-organism. Based on this information, the right antibiotic with adequate dosing and timing can be selected. The issue of compliance with the prophylactic treatment should be addressed and finally, the clinician should be aware that prophylaxis does not prevent erysipelas in all cases.

## KEYWORDS

Antibiotic prophylaxis, erysipelas, prevention, recurrent erysipelas

## INTRODUCTION

Erysipelas is an acute inflammation of the skin, with marked involvement of cutaneous lymphatic vessels. It is a clinically recognisable entity, with sudden onset of fever and a painful erythematous swollen lesion, sharply demarcated from the normal skin. Erysipelas is most commonly caused by  $\beta$ -haemolytic streptococci of group A, less so by group B, C, or G streptococci, and occasionally by *Staphylococcus aureus*.<sup>1,2</sup> In many patients, factors are present that facilitate the development of erysipelas. The major risk factors in erysipelas are disruption of the skin and lymphoedema.<sup>3</sup> Erysipelas can be treated successfully with narrow-spectrum penicillins, such as benzylpenicillin and feneticillin. Patients who are allergic to penicillin may be treated effectively with macrolides.

The recurrence rate of erysipelas is high: nearly 30% has been noted within a two to four year period.<sup>4</sup> Unfortunately, once erysipelas occurs, damage to the cutaneous lymph vessels often leads to susceptibility for further relapses. To prevent a vicious circle of recurrent erysipelas and vulnerability to subsequent episodes, long-term antibiotic prophylaxis is advocated. Studies have suggested an effect of such prophylaxis, using various antibiotic regimens.<sup>4-7</sup> A neglected aspect in studies on prophylaxis for erysipelas is that a few patients still have attacks of erysipelas during antibiotic prophylaxis.<sup>7,8</sup> In line with this notion, we have encountered patients with recurrent erysipelas despite antibiotic prophylaxis. In this paper, we review these cases and examine the reasons for failure of prophylaxis.

## PATIENTS AND METHODS

Patients with one or more episodes of erysipelas during antibiotic prophylaxis were identified and retrospectively analysed to examine the incidence of recurring erysipelas

despite prophylactic antibiotic treatment and the factors associated with this failure. Patients were identified by searching two databases for the clinical diagnosis of erysipelas: the first database contains data on infectious disease consultations performed in our university medical centre between 1990 and 2004; the second contains the diagnoses of patients at the outpatient clinic for internal medicine from 1999 until 2003. In addition, infectious disease specialists were asked whether they were aware of additional patients.

From the charts of patients with attacks of erysipelas during antibiotic prophylaxis, the following data were collected: 1) personal characteristics: gender, age, weight; 2) underlying diseases and/or factors predisposing for erysipelas; 3) attacks of erysipelas before prophylactic treatment; 4) results of diagnostic tests, such as cultures, antistreptolysin titres and anti-DNAse B; 5) treatment of the episodes of erysipelas; 6) prophylactic regimens; 7) the effect of the antibiotic prophylaxis.

## RESULTS

In this study, 117 patients with erysipelas were identified. Five patients had an attack despite antibiotic prophylaxis. Three more patients were retrieved from infectious diseases specialists. The characteristics of these eight patients, the sites of erysipelas, and underlying conditions are provided in *table 1*.

The phenomenon of recurrent erysipelas under antibiotic prophylaxis will further be described on the basis of three illustrative cases.

### Patient C

This 29-year-old male had suffered from several episodes of erysipelas affecting the right leg since the age of 17. At 15 years, he underwent an epiphysiodesis of the femur and tibia of his right leg to correct a difference in length.

He had been treated with benzathine penicillin 1.2 MU intramuscularly every four weeks as prophylaxis. Despite this treatment, frequent attacks of erysipelas recurred. It turned out that relapses occurred shortly before the next injection was planned.

At the age of 20, the patient was hospitalised for another episode of erysipelas, which was treated with penicillin G. On this occasion, interdigital mycosis was found as a potential portal of entry. In an attempt to reduce the risk of another attack, antimycotic treatment and elastic stockings were prescribed, but despite this, episodes of erysipelas still recurred. The attacks responded well to therapy with roxitromycin.

The patient was first seen at our department at the age of 22. He was put on a prophylactic regimen of benzathine penicillin 1.2 MU every two weeks and this preventive treatment was successfully continued for two years. Six months after stopping, a new episode occurred, and the two-weekly preventive regimen was reinstated. Despite the prophylaxis, a new attack occurred three months later. This episode probably occurred because the penicillin injection was delayed until 3.5 weeks after the previous dose.

The next episode of erysipelas developed 16 days after the injection of benzathine penicillin. After treatment, a prophylactic regimen of injections strictly administered every two weeks was installed. This prevented recurrences for 2.5 years. On the patient's request, the frequency of administration was again reduced to every three weeks and this led to new episodes of erysipelas. Antibiotic prophylaxis every two weeks has prevented further attacks of erysipelas, for one year of follow-up.

### Patient E

This 24-year-old female experienced a minor trauma of her chin at the age of five. The first episode of erysipelas at the age of 14 affected her chin and lower lip. During the following years she had several attacks of erysipelas. After her second hospitalisation at the age of 18, she received

**Table 1.** *Patients characteristics*

Patient	Age (years)	Sex	Weight (kg)	Location	Underlying condition	Site of entry	Age at first episode (years)	Age at start of prophylaxis (years)
A	45	m	113	Right and left leg	Trauma: spinal cord lesion, multiple fractures left leg	Intertrigo	33	39
B	56	m	-	Left leg	Spinal muscular atrophy, fracture left femur		47	52
C	29	m	108	Right leg	Epiphysiodesis right leg	Dermatomycosis	17	19
D	53	f	86	Left arm	Post-breast cancer surgery	Eczema	44	47
E	24	f	72	Face	Trauma chin		14	18
F	38	m	74	Right and left leg	Short-bowel syndrome, arterial insufficiency right leg	Intertrigo	34	35
G	55	f	62	Right arm	Post-breast cancer surgery	Skin lesion	45	53
H	39	f	63	Face, neck	Recurrent herpes simplex	Herpetic lesions	29	30

prophylactic treatment, consisting of benzathine penicillin 1.2 MU intramuscularly every four weeks.

She remained free from episodes of erysipelas for 11 months until a new attack at the same site occurred during antibiotic prophylaxis. During this episode, the serology was suggestive for a streptococcal origin: aspartate aminotransaminase (AST) (332 U ml<sup>-1</sup>) and anti-DNAse (B 879 U ml<sup>-1</sup>) were both elevated, whereas the antistaphylolysin titre was 0.71 U ml<sup>-1</sup>. She was referred to our clinic.

The prophylactic regimen was changed to clindamycin 300 mg three times a day. Five months after starting with this regimen, another episode of erysipelas occurred. As the patient was not critically ill, we felt confident to try and see whether it was a dose or a resorption problem. So we switched to intravenous clindamycin 3 x 600 mg. The response to therapy with intravenous clindamycin was rapid. Hereafter, the dose of prophylactic treatment was raised to 300 mg four times a day. Measurement of serum clindamycin showed concentrations of 1.69 and 4.12 mg l<sup>-1</sup>, which are considered appropriate. Even with the higher oral dose of clindamycin, another episode of erysipelas occurred three months later. Prophylaxis was stopped, and nine months later, she again developed erysipelas.

#### Patient G

This 55-year-old female was healthy until the age of 44, when breast cancer was diagnosed. A modified radical mastectomy with axillary lymph node dissection was performed. A year later, a tumour was found in her other breast, and a mastectomy with axillary lymph node dissection was performed followed by radiotherapy. Tamoxifen was continued for 2.5 years.

Since the second mastectomy, she experienced several episodes of erysipelas. These episodes would usually follow a small skin defect on the right hand and were characterised by a fiery red, sharply demarcated lesion on one side of the thorax and the right arm, high fever, and systemic toxicity. Response to treatment with either amoxicillin or flucloxacillin was rapid.

Five years after surgery, a reconstruction by a latissimus dorsi muscle flap combined with breast implants was performed, complicated by oedema of the right arm. The episodes of erysipelas increased in frequency. After multiple attacks, the patient was put on benzathine penicillin 1.2 MU intramuscularly every four weeks. The attacks decreased but were not completely prevented. Even injections given every two weeks did not prevent the episodes of erysipelas. There was no clear correlation between the time of injection and the occurrence of erysipelas.

After stopping the prophylactic treatment, the frequency of erysipelas increased to once every one or two months. She was put on a prophylactic regimen of clindamycin 600 mg twice daily, and several months later the dose was

decreased to 600 mg once daily. This treatment prevented further episodes of erysipelas for three months, but thereafter breakthroughs occurred.

An overview of the cases of recurrent erysipelas during antibiotic prophylaxis is provided in *table 2*. In most cases, it is not possible to judge whether these recurrent episodes represent relapses from foci within the body or exogenous reinfections.

In a number of cases, a plausible explanation for the failure of prophylaxis and subsequent recurrences could be given on the basis of chart review. These were: 1) noncompliance; 2) incorrect antibiotic; 3) other causative micro-organism; and 4) insufficient antibiotic concentration.

#### Noncompliance

Two patients experienced an episode of erysipelas when they extended the interval time of the prophylactic regimes. Patient C exceeded the prophylactic schedule by 1.5 weeks, when erysipelas recurred. Patient A had a new attack of erysipelas ten weeks after the last injection.

#### Incorrect antibiotic

Instead of benzathine penicillin, patient B received a combination of benzathine and procaine-benzylpenicillin. This agent only contains 0.6 MU of benzathine penicillin. Penicillin concentrations in serum are therefore only detectable for about one week.

#### Other causative micro-organism

Although no culture samples could be obtained, it is likely that the recurrences in patients D and B during antibiotic prophylaxis were not caused by group A streptococci, but by *Staphylococcus aureus*. Patient D developed a skin infection of the left arm four days after the injection of benzathine penicillin. The infection responded to flucloxacillin. Patient B developed an attack of erysipelas one week after the injection of benzathine penicillin 1.2 MU. The initial treatment consisted of feneticillin 1000 mg four times a day. Despite an initial improvement, treatment was unsuccessful. After two weeks, the treatment was changed to clindamycin 600 mg three times a day, which led to an improvement.

#### Insufficient antibiotic concentration

In three patients, the serum concentrations of the antibiotic agent were probably insufficient. Patient B received clarithromycin 250 mg daily to prevent further episodes of erysipelas. This did not prevent the episode 1.5 weeks later. The recommended therapeutic dose for an adult should be at least 250 mg twice daily. Patients C and H experienced several episodes during prophylaxis with benzathine penicillin 1.2 MU. The occurrence of episodes of erysipelas occurred just before the dose was to

**Table 2.** Recurrences during antibiotic prophylaxis

Patient	Re- currence	Antibiotic	Dosage	Time to recurrence	Treatment of erysipelas	Reasons for failure of prophylaxis				
						Non- compliance	Incorrect antibiotic	Other causative micro- organism	Insufficient antibiotic concentration	No explanation
A	1	benzathine penicillin	1.2 MU/4 wk	15 mo	penicillin, feneticillin	v				
B	1	procaine penicillin	1.2 MU/4 wk				v			
	2	clarithromycin	250 mg/day	1.5 wk					v	
	3	benzathine penicillin	1.2 MU/3 wk	1 wk	feneticillin failed			v		
C	1	benzathine penicillin	1.2 MU/4 wk	*					v	
	2	benzathine penicillin	1.2 MU/2 wk	3.5 wk		v			v	
	3	benzathine penicillin	1.2 MU/2 wk	2 wk	feneticillin					v
	4	benzathine penicillin	1.2 MU/3 wk		penicillin, feneticillin					v
D	1	benzathine penicillin	1.2 MU/4 wk	2 wk	flucloxacillin			v		
	2	benzathine penicillin	1.2 MU/3 wk	1.5 wk	amoxicillin					v
E	1	benzathine penicillin	1.2 MU/4 wk	9 mo	amoxicillin					v
	2	clindamycin	300 mg t.i.d.		clindamycin iv					v
	3	clindamycin	300 mg q.i.d.		clindamycin iv					v
F	1	benzathine penicillin	1.2 MU/4 wk							v
G	1	benzathine penicillin	1.2 MU/4 wk							v
	2	benzathine penicillin	1.2 MU/2 wk							v
H	1	benzathine penicillin	1.2 MU/4 wk	9 mo	penicillin **				v	

\* shortly before the next injection was planned; \*\* plus valaciclovir prophylaxis; wk = week; mo = month; t.i.d. = three times a day; q.i.d = 4 times a day.

be administered, which may indicate insufficient levels of the antibiotic during the last phase of the administration interval. Indeed, in patient B injections every two weeks and in patient H every three weeks prevented relapses.

#### No explanation

Recurrences of erysipelas during antibiotic prophylaxis in patients E, F, and G could not be explained. Furthermore, no explanation was available for one episode of erysipelas in patients C and D.

#### DISCUSSION

Our review of the literature and analyses of case reports clearly indicate that despite antibiotic prophylaxis, erysipelas still recurs.<sup>7,8</sup> Recurrent erysipelas despite

prophylaxis has gone unnoticed, because cases are rare. A survey in our tertiary care centre among 117 cases of erysipelas yielded eight such cases. It is not usually possible to judge whether these recurrent episodes represent relapses from foci within the body (e.g., within the lymphatic system) or exogenous reinfections.

The analysis of the reasons for failure of preventive therapy in our sample indicates that the recurrence of erysipelas had multiple causes: 1) noncompliance; 2) incorrect antibiotic; 3) other causative micro-organism; 4) insufficient antibiotic concentrations. Importantly, in half of the cases, no valid explanation could be obtained. Thus, the reasons for failure of prophylaxis in these cases remain unclear. We tend to conclude that in such cases, erysipelas may recur despite concentrations of antibiotics that are otherwise considered adequate. We have not been able to find many similar cases in the literature.

An important question is whether evidence exists that antibiotic prophylaxis is effective in preventing recurrences of erysipelas. In the older literature, case reports suggested that prolonged antibiotic prophylaxis successfully reduces the frequency of attacks in all patients with recurrent erysipelas.<sup>8,9</sup> In addition, several clinical studies have addressed this problem. In the study by Duvanel *et al.*<sup>5</sup> benzathine penicillin 2.4 MU every three weeks was given intramuscularly to 12 patients for six months, after the first attack of erysipelas. There were no recurrences during the period of prophylaxis, but after discontinuation of prophylaxis, three patients experienced a recurrence.

Jorup-Rönström *et al.*<sup>4</sup> included 143 patients with erysipelas; 29% had recurrences during a follow-up period of two to four years. Only nine patients received antibiotic prophylaxis, which prevented further episodes of erysipelas. After the second recurrence, the calculated cost of prophylaxis with phenoxymethylpenicillin or erythromycin was only marginally lower than the cost of therapy for erysipelas attacks.

Kremer *et al.*<sup>6</sup> studied erythromycin as a preventive antibiotic in 32 patients who had suffered two or more episodes of erysipelas or cellulitis during a follow-up period of 18 months. Only 11 of 36 patients were included because of recurrent erysipelas. There were no recurrences in the study group, compared with a relapse rate of 50% in the control group.

Sjöblom *et al.*<sup>7</sup> prescribed antibiotic prophylaxis to 20 patients with a history of two or more attacks of erysipelas. Phenoxymethylpenicillin was given in most cases. A few patients received erythromycin because of a known allergy to penicillin. Despite the antibiotic prophylaxis, two patients had a recurrence, compared with eight patients in the control group. The median follow-up period was 15 months.

Our study has a number of implications for clinicians dealing with recurrent erysipelas (summarised in table 3). First, we would recommend that the diagnosis is as certain as it can possibly be. Cultures and serology may be of help to ascertain the cause. Not only should the question be raised whether it is a streptococcal or a staphylococcal infection, but also more rare causes, such as *Campylobacter jejuni*, especially in patients with compromised host defences (e.g., hypogammaglobulinaemia) and *Campylobacter fetus* in patients with other underlying

illnesses,<sup>10-12</sup> should be considered. Secondly, the clinician should make sure that the correct antibiotic is selected, based on the most likely causative micro-organism. Thirdly, dosing and timing of antibiotic prophylaxis is of great relevance. A problem is that the penicillin concentrations needed for adequate prophylaxis are not known. From a theoretical point of view, it could be argued that the protective serum penicillin concentrations need to be maintained at levels equal or above the minimal inhibitory concentration (MIC) of the causative micro-organism. It is noteworthy that the majority of the patients in this study received benzathine penicillin 1.2 MU every four weeks as the first prophylactic regimen. With this schedule extremely low penicillin concentrations may be present at the end of the dosing interval.<sup>13</sup> From the literature and also the cases presented here, it is suggested that three-weekly schedules are more effective for preventing erysipelas. In some cases, even two-weekly schedules may be necessary. Another approach to provide protective plasma penicillin levels is increasing the dosage.<sup>14</sup> Doubling the dose prolongs the protective plasma penicillin levels by only one half-life, which in this case may be around seven days.

In addition, the deposition of benzathine penicillin after an injection in the buttocks has been questioned: the majority of injections have been reported to be intralipomatous rather than intramuscular.<sup>15</sup> Finally, the clinician should address the issue of compliance with the prophylactic treatment. If oral prophylaxis is being prescribed, patient information is a crucial issue. The importance of prophylactic treatment to prevent further damage of the lymph vessels and serious infections should be stressed. Importantly, in half of the cases no valid explanation could be obtained. Thus, the reasons for failure of prophylaxis in the cases remain unclear. The insight that prophylaxis does not allow the prevention of all episodes of erysipelas may lead to more systematic investigations of this topic.

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**Table 3. Recurrent erysipelas despite antibiotic prophylaxis**

1. Check compliance
2. Reconsider diagnosis (*Staphylococcus aureus*, *Campylobacter species*)
3. Consider shortening the dosing interval (benzathine penicillin) or raising the dose of oral prophylaxis
4. Change regimen, e.g., to clindamycin

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