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ORIGINAL ARTICLE

The experience of intramuscular benzathine penicillin for prophylaxis of recurrent cellulitis: A cohort study

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Abstract *Background/Purpose:* Recurrent cellulitis is an important clinical issue but the optimal strategy for prophylaxis is not determined. Intramuscular benzathine penicillin at a 4-week interval had been adopted in our hospital and the study was conducted to evaluate the efficacy.
Methods: From January 1, 2009 to May 31, 2013, all patients aged ≥ 18 year, with a history of recurrent cellulitis and having received at least three shots of intramuscular benzathine penicillin for prophylaxis were retrospectively recruited for analysis. Two treatment periods (prophylaxis period and nonprophylaxis period) were defined. The effects of benzathine penicillin prophylaxis and patient characteristics on the incidence rate of recurrent cellulitis were analyzed using Poisson regression model.
Results: A total of 72 patients were enrolled, including 26 (36.1%) men. The most common underlying conditions were past surgery at the proximal side of the affected limb (38, 52.8%), malignancy (31, 43.1%), and diabetes mellitus (24, 33.3%). The incidence rate of recurrent cellulitis in the prophylaxis period was 0.73 episode/patient-year, significantly lower than that of 1.25 episodes/patient-year in the nonprophylaxis period ($p < 0.001$). Tinea pedis was a significant factor associated with increasing incidence of recurrent cellulitis in our cohort.
Conclusion: Intramuscular benzathine penicillin at a 4-week interval may be an effective prophylactic strategy to reduce the incidence of cellulitis. Further studies are necessary to deter-

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mine the factors associated with failure of prophylaxis as well as optimal individualized dosage and dosing interval of the prophylactic agent.

Introduction

Cellulitis is a common problem that causes 1.1% of all hospital admissions and 1.3—3.0% of visits to the emergency department in North America.[1,2] In Taiwan, it is also a bothersome condition frequently encountered in our daily practice.[3] The clinical presentation can vary from an uncomplicated disease to an invasive infection, and once an invasive infection occurs, the mortality rate is as high as 18%.[4] Around 7% of patients need hospitalization, resulting in significant medical costs.[5] Moreover, up to 50% of cases have recurrent diseases[6] and this makes preventing recurrent cellulitis an important issue.

Given the observation that most recurrent cellulitis is mainly caused by Group A streptococcus and other groups of β-hemolytic streptococci,[7] most of the prophylaxis strategies are active against these streptococcal species with a penicillin-based regimen, including oral phenoxymethylpenicillin 250 mg twice daily,[6] intramuscular benzathine penicillin G 1.2 million international units (MIU)/mo,[3] and intramuscular benzathine penicillin G 2.4 MIU at 14-day intervals.[8] In the Prophylactic Antibiotics for the Treatment of Cellulitis at Home I (PATCH I) trial, oral penicillin 250 mg twice/d was effective in preventing subsequent attacks during prophylaxis, but the protective effect diminished progressively once drug therapy was stopped.[6] Wang et al[3] showed that administration of prophylaxis with 1.2 MIU intramuscular benzathine penicillin per month successfully reduced the recurrence rate among patients without predisposing factors but failed to prevent recurrence in those with predisposing factors. In a single arm study, Vignes and Dupuy,[8] retrospectively evaluated a cohort of female patients with secondary arm lymphedema, who were given intramuscular benzathine penicillin G 2.4 MIU at 14-day intervals for prophylaxis of recurrent erysipelas, the estimated rate of recurrence was 26% at 1 year and 36% at 2 years. Although these studies showed evidence of effectiveness of prophylaxis strategies, there were still limitations to make a conclusion on the optimal method for preventing recurrent cellulitis.[9,10]

Because benzathine penicillin has been consistently active to Group A streptococcus in Taiwan,[11] it has been suggested for secondary prevention of rheumatic fever,[12] and has shown some evidence of effectiveness on prevention of recurrent cellulitis,[3] intramuscular benzathine penicillin at a 4-week interval has been adopted as the prophylactic strategy for recurrent cellulitis in our hospital. However, the evidence to support our common practice was not robust.[3,10] This study was conducted to determine the efficacy of this strategy.

Methods

Patients and clinical settings

From January 1, 2009 to May 31, 2013, patients who were aged $\geq$ 18 years, had a history of recurrent cellulitis, and had received at least three shots of intramuscular benzathine penicillin for prophylaxis were included for analysis. Full review of medical records was performed and the characteristics of the patients, including age, sex, underlying conditions, cellulitis episodes, and the time and doses of benzathine penicillin prophylaxis were collected.

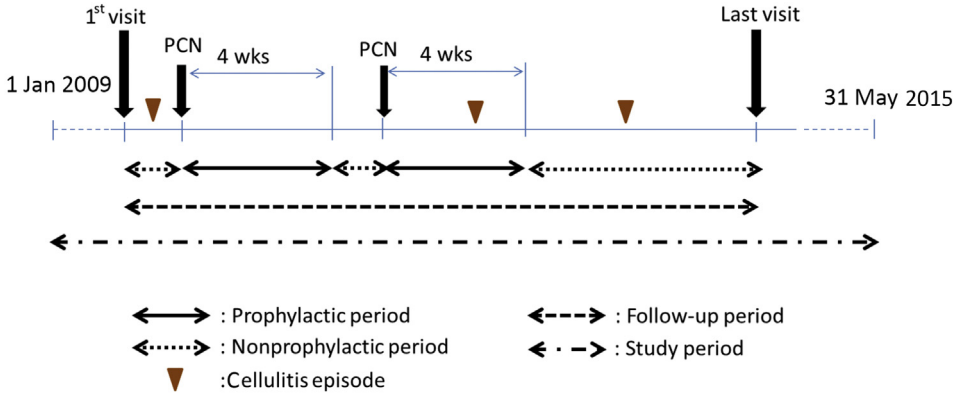
Benzathine penicillin was mostly administered intramuscularly with a dose of 2.4 MIU at a 4-week interval in our hospital, although a lower dose of 1.2 MIU and shorter or longer intervals may be occasionally adopted depending on the clinicians' clinical decision. Only four of the 72 patients received 1.2 MIU dose for prophylaxis and they were included for analysis since the result was not changed if they were excluded.

Definitions

A case of recurrent cellulitis was defined as a patient with a history of at least two episodes of clinically diagnosed cellulitis with documented treatment. For each patient, the follow-up period was defined as the time interval from the patient's first visit to the last visit in our hospital for any reason during the study period, the prophylaxis period was defined as the 4-week period after every shot of benzathine penicillin and nonprophylaxis period as the period not covered by the prophylaxis period during the follow-up period of the patient. The illustration of various time intervals is shown as Figure 1. When a patient had any recurrent episode of cellulitis during prophylaxis period, they were categorized as the prophylaxis failure group.

Outcome measure and statistics analysis

To determine the efficacy of benzathine penicillin prophylaxis and identify possible factors associated with recurrent cellulitis in our cohort, the incidence rate of recurrent cellulitis was used as the main outcome measure. The incidence rates of different treatment periods (prophylactic period and nonprophylactic period) and patient groups with different characteristics were compared by incidence rate ratio in the Poisson regression model. Univariate and multivariate analysis were performed to identify the factors with influence on the incidence rate of recurrent cellulitis. Factors with $p < 0.2$ in univariate analysis were



PCN = a shot of benzathine penicillin prophylaxis.

Figure 1. Illustration of the various time intervals of the study.

included in multivariate analysis. In comparison of characteristics of patients with and without prophylaxis failure, χ^2 test was used for categorical variables and Student *t* test was used for continuous variables.

Results

A total of 72 patients were included in the study. The mean age was 61.7 years old and the mean body mass index was 29.2 kg/m^2. Twenty-six (36.1%) of them were men. The clinical characteristics of the patients are summarized in Table 1.

Thirty-eight patients (52.8%) had a history of surgery at the proximal side of the affected limb, which was defined as any past surgeries performed > 2 weeks before the onset of cellulitis. Among these patients, 15 had operations for cervical cancer, six had operations for endometrial cancer, four had arthroplasty for degenerative disease, three had operations for breast cancer, three had proximal site fixation for fractures (which were not on the site of cellulitis), two had history of debridement for necrotizing fasciitis, one had repair for inguinal hernia, one had operation for skin cancer, one had surgery for varicose vein, one had hysterectomy for uterine myoma, and one had skin graft. Malignancy (31, 43.1%) was the second most common underlying condition. Among the patients, 21 had cervical or endometrial cancers, four had breast cancers (1 of them also had endometrial cancer), three had cancers of gastrointestinal tract, two had skin cancers, one had a hepatocellular carcinoma, and one had a tongue cancer. Only six of the 31 patients with malignancies were in active status.

Table 1 Demographic data of the study cohort.

Characteristics	Patients (n = 72)
Age (y)	61.7 ± 15
Sex (male)	26 (36.1)
BMI (kg/m^2)	29.5 ± 6.7
Underlying conditions	
Surgery at the proximal side of the affected limb [a]	38 (52.8)
Malignancy	31 (43.1)
Diabetes mellitus	24 (33.3)
Chronic kidney disease [b]	21 (29.2)
Tinea pedis	18 (25.0)
Cirrhosis	10 (13.9)
Impaired venous return [c]	10 (13.9)
Ulceration on cellulitis	10 (13.9)
Gout	8 (11.1)
Previous fracture around cellulitis	7 (9.7)
Heart failure	1 (1.4)

Data are presented as *n* (%) or mean ± standard deviation.
BMI = body mass index.
[a] The surgery must be > 2 weeks before the first cellulitis occurred.
[b] Chronic kidney disease was defined as the estimated glomerular filtration rate < 30.0 mL/min/1.73 m^2.
[c] Impaired venous return included varicose vein and deep venous thrombosis.

The episodes of recurrent cellulitis for each patient during the follow-up periods ranged from zero to 16, with incidence rates ranging from 0/patient-year to 4.74/patient-year in the prophylactic period and 0/patient-year to 107/patient-year in the nonprophylactic period. For the entire cohort, total follow-up duration was 216.2 patient-years, consisting of 71.7 patient-years in the prophylactic period and 144.5 patients-years in nonprophylactic period. The total episodes of recurrent cellulitis were 52 in prophylactic period and 180 in nonprophylactic period. The incidence of cellulitis was 0.73/patient-year in prophylactic period and 1.25/patient-year in the nonprophylactic period. The incidence rate of prophylactic period was significantly lower than that of nonprophylactic period (incidence rate ratio = 0.53, 95% confidence interval = 0.39–0.72, $p < 0.001$; Table 2).

In univariate analysis, patients with tinea pedis and cirrhosis had significantly higher incidence rates of recurrent cellulitis (incidence rate ratio = 1.69 and 1.79, respectively) while penicillin prophylaxis was a factor favoring lower incidence. In multivariate analysis, penicillin prophylaxis was still a strong factor associated with lower incidence and tinea pedis was a significant factor for higher incidence (Table 3).

A total of 52 episodes of cellulitis occurred in 30 patients during the prophylaxis periods. An attempt to identify

Table 2 The comparison of incidence of recurrent cellulitis in periods with and without benzathine penicillin prophylaxis.

	Prophylaxis period	Nonprophylaxis period	Incidence rate ratio (95% CI)	*p*
Total time of follow-up (y)	71.7	144.5	0.53 (0.39–0.72)	<0.001
No. of cellulitis episodes	52	180		
Incidence rate (episodes/patient-y)	0.73	1.25		

CI = confidence interval.

factors associated with prophylaxis failure was performed (Table 4). Male sex was noted to have a trend toward prophylaxis success and tinea pedis had a trend toward to prophylaxis failure but neither was statistically significant.

Discussion

Our study revealed a significantly positive result of penicillin prophylaxis at a 4-week interval. The incidence of recurrent cellulitis decreased from 1.25 episodes/patient-year to 0.73 episodes/patient-year ($p < 0.001$) and 42 of the 72 patients had no recurrent cellulitis during the prophylactic period. Although a previous study failed to demonstrate the effectiveness of prophylaxis with monthly 1.2 MIU penicillin prophylaxis in patients with predisposing factors,[3] most of the patients in our study had predisposing factors for recurrent cellulitis and the benzathine penicillin prophylaxis still showed its effectiveness. This difference probably resulted from a 2.4 MIU prophylactic dosage in our study and the different dosage might result in different concentration in blood.[13]

Previous studies had identified some predisposing factors for recurrent cellulitis, including diabetes mellitus, impaired venous drainage, congestive heart failure, liver disease, obesity, pregnancy, previous fracture, total knee replacement, aging, and previous myocardial infarction.[3,6,13] In our cohort, the most common underlying conditions were history of surgery at the proximal side of the affected limb (52.8%), malignancy (43.1%), and diabetes mellitus (33%). However, in the multivariate analysis, only patients with tinea pedis had increased incidence rate of recurrent cellulitis. There were several reasons: first, the effect of each risk factor on the recurrence of cellulitis might be diluted by others because many of the patients had multiple risk factors concomitantly. Second, the effectiveness of benzathine penicillin prophylaxis on prevention of recurrent cellulitis might differ in patients. It was possible that the effects of surgery at the proximal side of the affected limbs, malignancy and diabetes mellitus on the incidence of recurrent cellulitis were offset by penicillin prophylaxis more than that of tinea pedis. Third, the classification might be too rough to show a difference. For example, some types of malignancy might be strongly associated with recurrent cellulitis while others might not be. Finally, the sample size might not be large enough to see the difference.

Thirty of the 72 patients had recurrent cellulitis during the prophylactic periods. In Thomas et al's[6] report, three or more previous cellulitis episodes, edema, and body mass index > 33 kg/m^2 were predictive for prophylaxis failure. However, we failed to identify risk factors associated with prophylaxis failure in our cohort. This might be because most of our patients had these risks and there relatively few cases in our study, so some factors could not be further categorized. The dosage and interval of benzathine penicillin might also be important in a concern of prophylaxis failure. Most of our patients received monthly prophylaxis with 2.4 MIU benzathine penicillin as previously mentioned. Recent research has shown that the concentration of benzathine penicillin was not enough after 2 weeks of injection with 1.2 MIU or 2.4 MIU.[14,15] To determine the actual cause in these patients with recurrence, tests of serum penicillin concentration are needed. Another possible cause of prophylaxis failure was that the pathogens responsible for the recurrent episodes might not be penicillin-sensitive streptococci. However, it is hard to determine the causative pathogens for cellulitis clinically since many of the patients had neither pus nor discharge for microbiological studies.

Table 3 Univariate and multivariate analysis for factors associated with increased incidence of cellulitis.

Characteristics	Incidence rate ratio, per patient-year (95%CI)	*p*
Univariate		
Age (y)	0.99 (0.98–1.00)	0.234
BMI	1.01 (0.98–1.03)	0.598
Male	0.97 (0.65–1.45)	0.975
Penicillin prophylaxis	0.53 (0.39–0.72)	0.000*
Ulceration on cellulitis	0.89 (0.47–1.69)	0.716
Previous fractures	1.01 (0.40–2.52)	0.985
Tinea pedis	1.69 (1.14–2.50)	0.008*
DM	1.07 (0.69–1.66)	0.757
CHF	0.95 (0.78–1.15)	0.572
Cirrhosis	1.79 (1.05–3.05)	0.034*
CKD	1.29 (0.91–1.83)	0.154
Gout	1.09 (0.70–1.68)	0.709
Malignancy	1.03 (0.70–1.50)	0.898
Surgery at proximal side of the affected limb	1.23 (0.84–1.79)	0.293
Impaired venous return	0.93 (0.61–1.41)	0.742
Multivariate		
Tinea pedis	1.54 (1.06–2.24)	0.025*
Cirrhosis	1.57 (0.89–2.8.)	0.122
Penicillin prophylaxis	0.55 (0.41–0.75)	0.000*
CKD	1.13 (0.76–1.69)	0.556

*$p < 0.05$ is significant.
BMI = body mass index; CHF = congestive heart failure; CI = confidence interval; CKD = chronic kidney disease; DM = diabetes mellitus.

Table 4 Comparison of characteristics of patients with and without prophylaxis failure.

Factors	Patients with prophylaxis failure (n = 30)	Patients without prophylaxis failure (n = 42)	p
Male	7 (23.3)	19 (45.2)	0.082
Age (y)	61.5 ± 14.1	61.9 ± 17.3	0.909
BMI	30.6 ± 7.1	28.7 ± 6.3	0.230
Ulceration on cellulitis	2 (6.7)	8 (19.0)	0.178
Fracture	1 (3.3)	6 (14.3)	0.227
Tinea pedis	10 (33.3)	8 (19.0)	0.182
DM	9 (30.0)	15 (35.7)	0.800
CHF	0 (0.0)	1 (2.4)	1.000
Cirrhosis	5 (16.7)	5 (11.9)	0.732
CKD	8 (26.7)	13 (30.9)	0.795
Gout	4 (13.3)	4 (9.5)	0.711
Malignancy	15 (50)	16 (38.1)	0.344
Surgery proximal to affected limbs	18 (60)	20 (47.6)	0.345
Impaired venous return	4 (13.3)	6 (14.3)	1.000

Data are presented as n (%) or mean ± standard deviation.
BMI = body mass index; CHF = congestive heart failure; CKD = chronic kidney disease; DM = diabetes mellitus.

There were some limitations in our study. First, this was a retrospective study and there is no objective principle to decide whether the patient should have benzathine penicillin prophylaxis or not. However, it was expected that the frequency and severity of recurrent cellulitis might be milder when the physician decided not to administer prophylaxis for the patient. This situation might lessen the effectiveness of prophylaxis in our study. Second, the history of antibiotic therapy for cellulitis was not collected and the antibiotic therapy may have influence on the incidence rate of recurrent cellulitis in both study periods. Third, we would not record the occurrence of cellulitis if the patient visited other hospitals or clinics. Nevertheless, our study demostrated the efficacy of intramuscular benzathine penicillin at a 4-week interval by comparing the incidence rates of the defined periods (prophylaxis and nonprophylaxis) in the same cohort of patients with recurrent cellulitis and the selection bias might be minimized since the recorded characteristics of our patients didn't change during follow-up.

In conclusion, intramuscular benzathine penicillin at a 4-week interval reduced the incidence rate of recurrent cellulitis in our cohort. It is a more convenient way than the daily administered oral penicillin regimen to ensure compliance. A 4-week interval prophylaxis was less time-consuming than a 2-week interval, especially in rural areas such as Changhua County. Further studies are needed to determine the factors associated with prophylaxis failure as well as optimal individualized dosage and dosing interval of prophylactic agents.

Conflicts of interest

All authors have no conflicts of interest to declare.

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