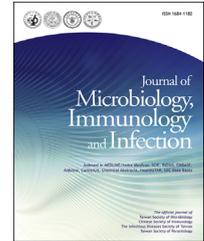




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ORIGINAL ARTICLE

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



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## KEYWORDS

cellulitis;  
penicillin;  
prophylaxis

**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  $\geq 18$  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.

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## 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.<sup>1,2</sup> In Taiwan, it is also a bothersome condition frequently encountered in our daily practice.<sup>3</sup> 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%.<sup>4</sup> Around 7% of patients need hospitalization, resulting in significant medical costs.<sup>5</sup> Moreover, up to 50% of cases have recurrent diseases<sup>6</sup> 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  $\beta$ -hemolytic streptococci,<sup>7</sup> most of the prophylaxis strategies are active against these streptococcal species with a penicillin-based regimen, including oral phenoxymethylpenicillin 250 mg twice daily,<sup>6</sup> intramuscular benzathine penicillin G 1.2 million international units (MIU)/mo,<sup>3</sup> and intramuscular benzathine penicillin G 2.4 MIU at 14-day intervals.<sup>8</sup> 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.<sup>6</sup> Wang et al<sup>3</sup> 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,<sup>8</sup> 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.<sup>9,10</sup>

Because benzathine penicillin has been consistently active to Group A streptococcus in Taiwan,<sup>11</sup> it has been suggested for secondary prevention of rheumatic fever,<sup>12</sup> and has shown some evidence of effectiveness on prevention of recurrent cellulitis,<sup>3</sup> 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.<sup>3,10</sup> 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

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