Infection and Drug Resistance

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ORIGINAL RESEARCH

The Impact of Monthly Prophylactic Antibiotics Use in Patients with Recurrent Cellulitis: A 20-Year Population-Based Cohort Study in a Medical Center

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Purpose: The vicious cycle of recurrent cellulitis ultimately results in a high risk of relapse, which facilitates the use of antibiotic prophylaxis with monthly intramuscular benzathine penicillin G (BPG) to prevent recurrence. However, several clinical situations hinder the guideline recommendations in daily practice. Therefore, intramuscular clindamycin has been used as an alternative in our institution for years. This study aims to elucidate the effectiveness of monthly intramuscular antibiotics in preventing further cellulitis recurrence and evaluate the applicability of intramuscular clindamycin as an alternative to BPG.

Patients and Methods: A retrospective cohort study was conducted at a medical center in Taiwan from January 2000 to October 2020. Adult patients with recurrent cellulitis were enrolled to receive monthly intramuscular antibiotic prophylaxis (including 1.2–2.4MU BPG or 300–600mg intramuscular clindamycin) or to be observed without prophylaxis. The decision to administer prophylaxis or observe was made at the discretion of the examining infectious disease specialists. Cox proportional-hazards regressions were performed to estimate hazard ratios (HR) and adjust for variables between groups. The Kaplan–Meier method was used to estimate survival curves.

Results: Enrollment in the study consisted of 426 patients, with 222 receiving BPG, 106 receiving intramuscular clindamycin, and 98 being observed without prophylaxis. Both types of antibiotics resulted in a significantly lower recurrence rate than observation alone (27.9% for BPG, 32.1% for intramuscular clindamycin, and 82.7% for observation, $P < 0.001$). After adjusting for multiple variables, antibiotic prophylaxis continued to significantly reduce the risk of cellulitis recurrence by 82% (HR 0.18, 95% CI 0.13 to 0.26), by 86% (HR 0.14, 95% CI 0.09 to 0.20) with BPG, and by 77% (HR 0.23, 95% CI 0.14 to 0.38) with intramuscular clindamycin.

Conclusion: Monthly intramuscular antibiotic prophylaxis was demonstrated to be effective in reducing cellulitis recurrence. Moreover, in the real-world practice, intramuscular clindamycin may serve as a reasonable alternative option to BPG.

Keywords: recurrent cellulitis, prophylactic antibiotic, intramuscular clindamycin, benzathine penicillin G

Introduction

The pathophysiology of recurrent cellulitis is characterized by skin defects, lymphatic dysfunction, and repeated bacterial invasions, ultimately resulting in a high risk of relapse and frequent hospitalization.[1] Over time, traditional emphasis on distinctions between cellulitis and erysipelas, including differences in bacterial pathogens, affected range of skin layer, or treatment options, has become obsolete due to the large overlap of clinical entities.[2] Vicious cycles occur after each recurrent episode due to fundamental pathogenic lymphatic system damage followed by inflammatory destruction.[3] Studies have shown that patients are at increasing risk of recurrence year by year due to repeated lymphatic system damage, with recurrent cellulitis accounting for 40–50% of all hospital admissions for cellulitis.[4,5] Therefore, more attention has been focused on evaluating factors related to treatment response[6,7] and elucidating predisposing factors of

Received: 27 March 2023
Accepted: 8 June 2023
Published: 15 June 2023

recurrence,[8,9] including fragile skin conditions such as tinea pedis, onychomycosis, maceration, and dermatitis, as well as cutaneous trauma, venous insufficiency, obesity, and lymphedema.[10,11]

Although culture data for cellulitis is not always attainable, the vast majority of cause of cellulitis is Streptococci and S. aureus. Therefore, antibiotics with activity against Streptococci and S. aureus[7,10] are favored candidates as prophylactic antibiotics, such as low-dose daily oral penicillin and monthly intramuscular benzathine penicillin G (BPG).[10,12] Antibiotic prophylaxis was found to be cost-effective,[13] and is recommended by the IDSA guidelines for patients with recurrent cellulitis and those at risk of recurrence. Among the recommended prophylactic options for recurrent cellulitis, BPG not only demonstrated a protective effect but also had a more convenient dosing frequency of once monthly compared to other daily oral antibiotics.[10] However, many clinical situations still prevent adherence to guideline recommendations in our daily practice, such as nonadherence to oral medications, global shortages of BPG, and hypersensitivity reactions to penicillin. Therefore, intramuscular clindamycin has been used as an option in our institution for years. This study aims to elucidate the effectiveness of monthly intramuscular antibiotic prophylaxis in preventing further recurrence and to evaluate the applicability of intramuscular clindamycin as an alternative option to BPG.

Materials and Methods

Design, Settings, Participants

This retrospective cohort study was conducted between January 2000 and December 2020 at a tertiary medical center in southern Taiwan. The study cohort consisted of adult patients aged >18 years who received monthly intramuscular BPG or monthly intramuscular clindamycin for prophylaxis of recurrent cellulitis, identified from the electronic healthcare database. Since most cellulitis cases are typically diagnosed based on a patient's medical history and physical examination without requiring for additional testing,[4] the definition of cellulitis in the present study is a clinical presentation characterized by acute onset of skin erythema, pain, swelling, and heat. Participants in the present analysis were retrieved from the cohort, including (1) patients with a history of two or more episodes of cellulitis at the same site and (2) patients with a history of one episode of cellulitis and known predisposing factors for recurrence. In order to accurately identify cellulitis episodes in electronic healthcare database, each episode of cellulitis attack should be prescribed with a therapeutic antibiotic course. To avoid overlapping interference between the effects of therapeutic antibiotics and prophylactic antibiotics, the cohort entry date was defined as the first day of administration of prophylactic antibiotics, which should be administered after completion of a therapeutic antibiotic course and confirmation of patient recovery. The decision to administer BPG prophylaxis, intramuscular clindamycin prophylaxis, or to observe without prophylaxis for eligible participants after the cohort entry date was made at the discretion of the examining infectious disease (ID) specialist.

Efficacy Interventions and Outcome Measures

BPG was administered at a dose of 1.2 to 2.4 MIU monthly, and intramuscular clindamycin was administered at a dose of 300 to 600 mg monthly. The dosing range was based on the regular dose at one time as indicated by guidelines, previous studies, or drug information. An ID specialist carefully selected a single dose from the dosing range that was appropriate for each patient. According to ID specialists' prophylaxis protocol, once a patient attained no recurrence for at least six months, the prophylaxis interval may extend to every two months depending on the ID specialist's and patient's decision. After further maintaining no recurrence for another six months or more, the prophylaxis interval may further extend to every three months depending on the ID specialist's and patient's decision. Stable control was defined as no recurrent cellulitis event (absence of clinical manifestations suggestive of active infection, such as erythema, warmth, edema, pain at the same infected site, and/or systemic fever), indicating that the patient's condition of recurrent cellulitis was under control. The primary outcome was defined as the occurrence of a recurrent event on the same limb during prophylactic periods. The definition of a recurrent event was made based on physicians' judgment during an outpatient visit, emergency department visit, or hospitalization, with a full course of completely treated therapeutic antibiotics administered at the same time. If no index event occurred, follow-up durations were cumulatively calculated. Follow-up durations were censored on the day of recurrence, nonadherent interruption of prophylaxis for over 90 days, or the end of the study period, whichever came first. Participants with cellulitis at different sites, culture data other than Streptococcus sp. and Staphylococcus sp., and treatments with broad-spectrum systemic antibiotics for other infections during

prophylactic periods were excluded. The study was approved by the institutional review board of the Chi Mei Medical Center (No. 10902-012).

The statistical software SPSS Statistics version 18.0 was utilized to conduct the chi-square test, Fisher's exact test for categorical variables, and *t*-test for continuous variables. To prevent outcome bias and illuminate the effectiveness of prophylactic antibiotics, known risk factors for recurrence and common covariates were adjusted. To determine the risk of recurrence, survival curves were estimated using the Kaplan–Meier method and the Log rank test. Furthermore, time-dependent Cox proportional hazards regressions were executed to calculate hazard ratios and adjust for multiple variables between the groups.

Results

During the study period, a total of 426 eligible participants were included in the present study cohort. The cohort comprised 65.3% men and 34.7% women, with a mean age of 62.6 ± 17.1 years old. Of the participants, 328 received antibiotic prophylaxis, 222 were assigned to receive prophylactic BPG with a median follow-up duration of 0.53 years (IQR, 0.28, 1.15), and 106 received intramuscular clindamycin prophylaxis with a median follow-up duration of 0.38 years (IQR, 0.16, 0.70), while 98 received no prophylaxis with a median follow-up duration of 0.22 years (IQR, 0.10, 0.65). The clinical characteristics of the participants are summarized in Table 1, and all characteristics were further adjusted in multivariable regression to avoid outcome bias.

During the entire follow-up period of 310.5 person-years for the study cohort, a total of 177 participants had a recurrence of index cellulitis that required therapeutic systemic antibiotic treatment (Table 2). In the antibiotic prophylaxis group, 96 out of 328 participants (29.4%) had a recurrence, while in the observation group, 81 out of 98

Table 1 Baseline Characteristics of the Study Cohort

	No. (%)						
	Total (n = 426)	Observation (n = 98)	Antibiotic Prophylaxis Group (n = 328)				
			Any Antibiotic	P-value[a]	BPG (n = 222)	IM Clindamycin (n = 106)	P-value[b]
Age, mean ± SD, year	62.6 ± 17.1	61.6 (17.2%)	63 ± 16.9	0.387	60.6 ± 17.4	68.9 ± 14.2	<0.001
Male	278 (65.3%)	78 (79.6%)	200 (61%)	0.04	130 (58.6%)	70 (66%)	0.33
Prophylaxis regimen							
Dose							
Regular dose	299 (70.2%)	-	299 (91.2%)	-	203 (91.4%)	96 (90.6%)	
Higher dose	29 (6.8%)	-	29 (8.8%)	-	19 (8.6%)	10 (9.4%)	1
Dosing interval							
Every 1 month	186 (43.7%)	-	186 (56.7%)	-	126 (56.8%)	60 (56.6%)	0.98
Every 2 month	65 (15.3%)	-	65 (19.8%)	-	44 (19.8%)	21 (19.8%)	1
Every 3 month	77 (18.1%)	-	77 (23.5%)	-	52 (23.4%)	25 (23.6%)	0.97
Lymphedema/ venous insufficiency	161 (37.8%)	39 (39.8%)	122 (37.2%)	0.68	76 (34.2%)	46 (43.4%)	0.12
Skin change with ulceration	26 (6.1%)	2 (2%)	24 (7.3%)	<0.001	13 (5.9%)	11 (10.4%)	0.06
Skin change with dermatitis	27 (6.3%)	5 (5.1%)	22 (6.7%)	0.48	15 (6.8%)	7 (6.6%)	0.95
Skin change with hyperpigmentation	36 (8.5%)	20 (20.4%)	16 (4.9%)	<0.001	11 (5%)	5 (4.7%)	0.91
DVT	41 (9.6%)	4 (4.1%)	37 (11.3%)	<0.001	14 (6.3%)	23 (21.7%)	<0.001
Vein surgery	19 (4.5%)	2 (2%)	17 (5.2%)	0.03	14 (6.3%)	3 (2.8%)	0.17
Other skin conditions	189 (44.4%)	44 (44.9%)	145 (44.2%)	0.92	99 (44.6%)	46 (43.4%)	0.86
Dermatitis	91 (21.4%)	24 (24.5%)	67 (20.4%)	0.41	40 (18%)	27 (25.5%)	0.08
Tinea pedis	181 (42.5%)	42 (42.9%)	139 (42.4%)	0.94	94 (42.3%)	45 (42.5%)	0.99
Skin breaks[c]	12 (2.8%)	2 (2%)	10 (3%)	0.48	9 (4.1%)	1 (0.9%)	0.12
Smoking	66 (15.5%)	22 (22.4%)	44 (13.4%)	0.06	22 (9.9%)	22 (20.8%)	<0.001
Obesity	36 (8.5%)	13 (13.3%)	23 (7%)	0.09	20 (9%)	3 (2.8%)	0.04

(*Continued*)

Table 1 (Continued).

	No. (%)						
	Total (n = 426)	Observation (n = 98)	Antibiotic Prophylaxis Group (n = 328)				
			Any Antibiotic	P-value[a]	BPG (n = 222)	IM Clindamycin (n = 106)	P-value[b]
Other comorbidities							
Diabetes mellitus	226 (53.1%)	55 (56.1%)	171 (52.1%)	0.59	99 (44.6%)	72 (67.9%)	<0.001
Hypertension	252 (59.2%)	40 (40.8%)	212 (64.6%)	<0.001	128 (57.7%)	84 (79.2%)	<0.001
Hyperlipidemia	40 (9.4%)	7 (7.1%)	33 (10.1%)	0.27	14 (6.3%)	19 (17.9%)	<0.001
Stroke	75 (17.6%)	9 (9.2%)	66 (20.1%)	<0.001	33 (14.9%)	33 (31.1%)	<0.001
CVD	112 (26.3%)	16 (16.3%)	96 (29.3%)	<0.001	60 (27%)	36 (34%)	0.18
PAOD	21 (4.9%)	5 (5.1%)	16 (4.9%)	0.92	6 (2.7%)	10 (9.4%)	<0.001
CKD	62 (14.6%)	5 (5.1%)	57 (17.4%)	<0.001	37 (16.7%)	20 (18.9%)	0.59
Liver cirrhosis	33 (7.7%)	19 (19.4%)	14 (4.3%)	<0.001	11 (5%)	3 (2.8%)	0.34
COPD	54 (12.7%)	19 (19.4%)	35 (10.7%)	0.05	28 (12.6%)	7 (6.6%)	0.09

Notes: [a]Compared between the observation group and antibiotic prophylaxis group. [b]Compared between the BPG prophylaxis group and intramuscular clindamycin prophylaxis group. [c]Including skin fissures, abrasions and lacerations.
Abbreviations: IM, intramuscular; SD, standard deviation; DVT, deep vein thrombosis; PAOD, peripheral arterial occlusive disease; CVD, cardiovascular disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Table 2 Number of Recurrent Cellulitis Events and Crude Incidence Rates Among the Study Arms

	Observation (n = 98)	Antibiotic Prophylaxis (n = 328)			Adjusted HR[a] (95% CI)
		Any Antibiotic (n = 328)	BPG (n = 222)	IM CLD (n = 106)	
Events, n (%)	81 (82.7)	96 (29.4)	62 (27.9)	34 (32.1)	–
Follow-up duration, p-yrs	43.5	267.1	197	70.1	-
Incidence,	1.86	0.36	0.31	0.49	-
Event/p-yr (95% CI)	(1.18, 2.94)	(0.25, 0.52)	(0.21, 0.49)	(0.26, 0.90)	
Antibiotic prophylaxis vs observation	-	-	-	-	0.18 (0.13, 0.26)*
BPG vs observation	-	-	-	-	0.14 (0.09, 0.20)*
IM CLD vs observation	-	-	-	-	0.23 (0.14, 0.38)*

Notes: [a]Multiple models adjusted by age, gender, lymphedema/venous insufficiency (including skin change with ulceration, deep vein thrombosis, skin change with dermatitis, skin change with hyperpigmentation, vein surgery), other skin conditions (including dermatitis, tinea pedis, skin break), smoking, obesity, and other comorbidities (diabetes mellitus, hypertension, hyperlipidemia, stroke, cardiovascular disease, peripheral arterial occlusive disease, chronic kidney disease, liver cirrhosis, and chronic obstructive pulmonary disease). *P<0.001.
Abbreviations: BPG, benzathine penicillin G; HR, hazard ratio; CI, confidence interval; IM, intramuscular; CLD, clindamycin; IM CLD, intramuscular clindamycin.

participants (82.7%) had a recurrence. In addition to event rate, the incidence rate was estimated for the studied cohort, because participants were followed for different lengths of time in observational studies, and subjects at risk of developing index events remained eligible to contribute person-time as long as there was no occurrence of the index event under study. The incidence rates of recurrence were 0.36 (95% CI 0.25, 0.52) person-years in the antibiotic prophylaxis group (followed for 267.1 person-years) and were still lower compared with 1.86 (95% CI 1.18, 2.94) person-years in the observation group (followed for 43.5 person-years).

Within the antibiotic prophylaxis group, 62 out of 222 (27.9%) participants in the BPG prophylaxis and 34 out of 106 (32.1%) in the intramuscular clindamycin prophylaxis had a recurrence. This resulted in an incidence rate of recurrence of 0.31 (95% CI 0.21, 0.49) person-years in the BPG prophylaxis group (followed for 197 person-years) and 0.49 (95% CI 0.26, 0.90) person-years in the intramuscular clindamycin prophylaxis group (followed for 70.1 person-years).

The estimated median time to recurrence (Figure 1) was significantly longer in the antibiotic prophylaxis group than in the observation group (2.47 years [IQR, 1.62–3.32] vs 0.34 years [IQR, 0.16–0.52], P < 0.001). Moreover, the estimated median time to recurrence was 2.61 years (IQR, 1.37–3.86) in the BPG prophylaxis and 1.49 years (IQR, 0.89–

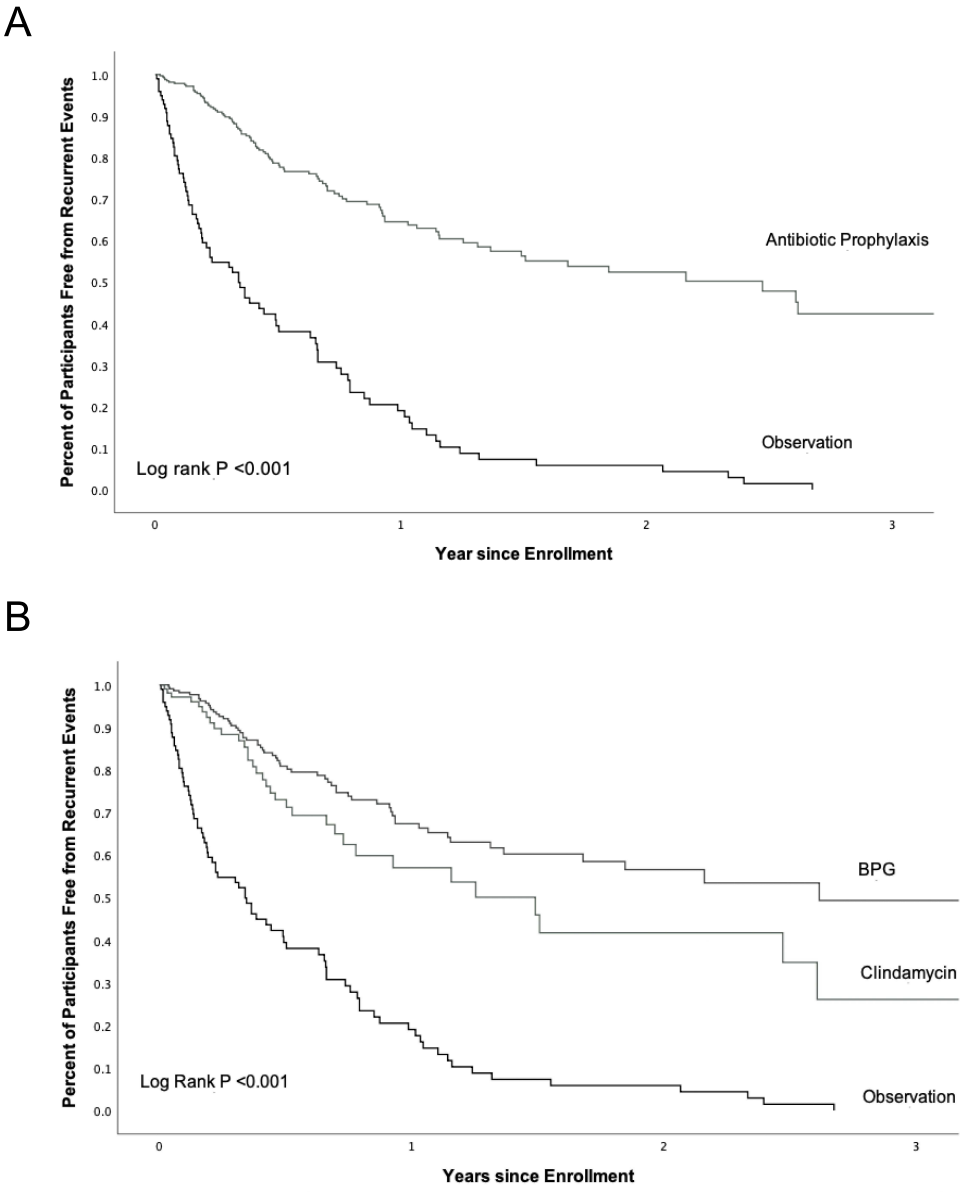

Figure 1 Kaplan-Meier survival curves to estimate recurrence-free time (**A**) recurrence-free time in participants receiving any antibiotic prophylaxis versus observation and (**B**) recurrence-free time in participants receiving antibiotic prophylaxis stratified by BPG and intramuscular clindamycin versus observation.

2.09) in the intramuscular clindamycin prophylaxis groups, both of which were significantly longer than that in the observation group (P < 0.001). Results from the Cox proportional hazards model are presented in Table 2. During the follow-up period, participants in the antibiotic prophylaxis group had a significant 82% reduction in the risk of cellulitis recurrence compared with those in the observation group (adjusted HR, 0.18; 95% CI, 0.13 to 0.26, P < 0.001).

Among the participants who received antibiotic prophylaxis, those in the BPG prophylaxis group had a significant 86% risk reduction in cellulitis recurrence (adjusted HR, 0.14; 95% CI, 0.09 to 0.20, P < 0.001), and those in the intramuscular clindamycin prophylaxis group had a significant 77% risk reduction in cellulitis recurrence (adjusted HR, 0.23; 95% CI, 0.14 to 0.38, P < 0.001), compared to those in the observation group. Therefore, the results indicate that both BPG and intramuscular clindamycin were effective prophylaxis for recurrent cellulitis. After adjusting for multiple covariates using a Cox proportional hazards model to compare BPG and intramuscular clindamycin, it was found that BPG was more effective than intramuscular clindamycin as a prophylactic antibiotic for recurrent cellulitis (adjusted HR, 0.47; 95% CI, 0.29 to 0.75, P = 0.002). This finding may be further supported by the amount of cumulative dose and the

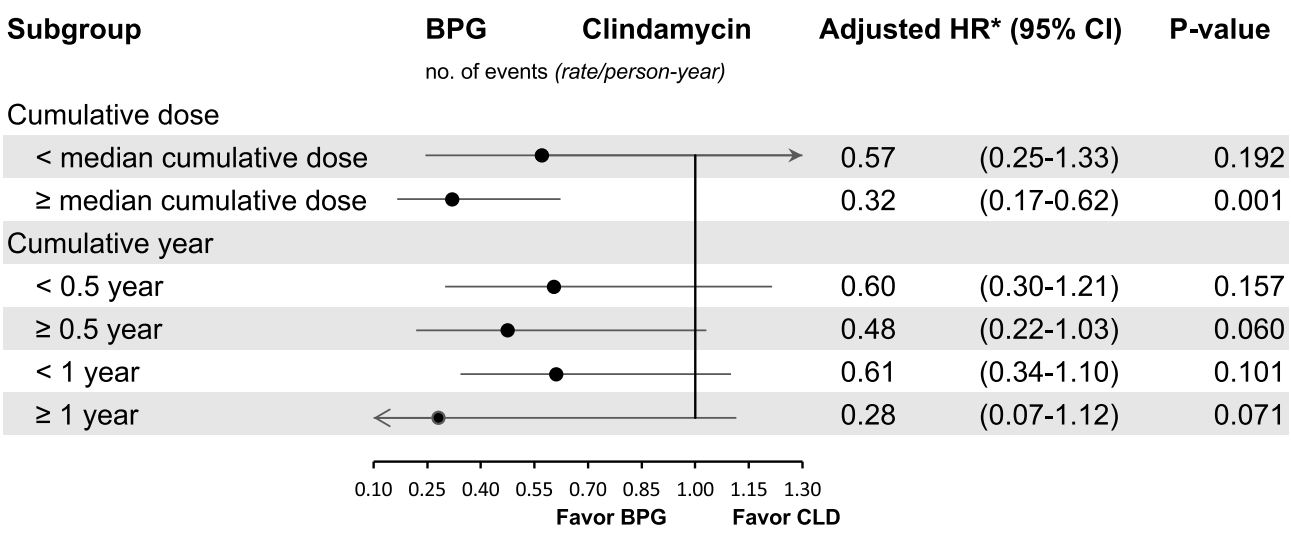

Figure 2 Comparison for cumulative dose and cumulative duration of prophylactic antibiotics administration between patients with benzathine penicillin G (BPG) and intramuscular clindamycin by logistic regression analyses. *Multiple models adjusted by age, gender, other skin conditions (including dermatitis, tinea pedis, skin break), lymphedema/venous insufficiency (including skin change with ulceration, deep vein thrombosis, skin change with dermatitis, skin change with hyperpigmentation, vein surgery), smoking, obesity, and other comorbidities (diabetes mellitus, hypertension, hyperlipidemia, stroke, cardiovascular disease, peripheral arterial occlusive disease, chronic kidney disease, liver cirrhosis and chronic obstructive pulmonary disease).
Abbreviations: BPG, benzathine penicillin G; HR, hazard ratio; CI, confidence interval; CLD, clindamycin.

duration of cumulative administration, according to the subgroup analysis. The subgroup analysis suggested that BPG was superior to intramuscular clindamycin in participants who received more than the median cumulative dose of the total antibiotic prophylaxis group (adjusted HR, 0.32; 95% CI, 0.17 to 0.62). Despite the limited sample size in each subgroup, a discernible trend favoring prolonged administration durations was apparent in the subgroup analysis of cumulative duration of administration (Figure 2).

Discussion

Recurrent cellulitis is a common infectious disease that can be challenging to manage due to its high risk of relapse. We investigated the impact of prophylactic antibiotics on the recurrence of cellulitis, and our findings highlight the potential benefits of using prophylactic antibiotics to prevent recurrent cellulitis. In the present study, the antibiotic prophylaxis group had a significantly lower estimated incidence rate of 0.36 (95% CI 0.25, 0.52) person-years compared to the observation group with an incidence rate of 1.86 (95% CI 1.18, 2.94) person-years. In addition, patients receiving antibiotic prophylaxis had a significantly longer estimated median time to recurrence of 2.47 years [IQR, 1.62–3.32] compared to those under observation with a median time to recurrence of 0.34 years [IQR, 0.16–0.52]. Even after adjusting for multiple risk factors, there was still a significant 82% reduction in the risk of developing recurrent cellulitis (adjusted HR, 0.18; 95% CI 0.13–0.26) in the antibiotic prophylaxis group compared to the observation group. Previous studies have reported recurrence rates in patients who did not receive prophylaxis ranging from 40% (with a mean follow-up of 14.5 months) to 50% (with 18 months of follow-up).[14,15] Prophylactic antibiotics, such as daily oral erythromycin, daily oral phenoxy-methylpenicillin, and monthly intramuscular BPG, were found to be effective in preventing cellulitis recurrence in these studies. However, prior to the two large randomized controlled trials (PATCH I and PATCH II), the results of earlier small studies were limited by small sample sizes, with each prevention arm consisting of only 16 to 34 patients. The PATCH 1 trial,[16] which included patients with recurrent cellulitis of more than two episodes within the previous three years, showed a significantly lower recurrence rate of 22% in patients receiving 12 months of prophylactic oral low-dose penicillin compared to 37% in those receiving placebo ($P < 0.001$), with a hazard ratio of 0.55 (95% CI 0.35–0.86, $P = 0.01$). The PATCH 2 trial,[17] which more aggressively included patients with one or more episodes of cellulitis and treated them with 6 months of prophylactic oral low-dose penicillin compared to placebo, showed a lower recurrence rate of 20% in patients receiving prophylaxis compared to 33% in those receiving placebo,

but the difference was not statistically significant (HR, 0.53; 95% CI 0.26–1.07). Meta-analyses by Oh et al[12] and Dalal et al[18] demonstrated the results of these studies and still showed a significant benefit for the prevention of cellulitis recurrence with prophylactic antibiotics compared to placebo or no prophylaxis. In Taiwan, Chen et al[19] investigated the effect of monthly administration of 1.2–2.4 MIU BPG for recurrent cellulitis and demonstrated a significant protective effect compared to no prophylaxis (IRR, 0.53 [95% CI, 0.39–0.72, $p < 0.001$]). The incidence rates reported in their study were 1.25 episodes/patient-year (a total of 180 episodes followed up for 144.5 years) in patients not receiving prophylaxis compared to 0.73 episodes/patient-year in patients with monthly intramuscular BPG (a total of 52 episodes followed up for 71.7 years). Although heterogeneity existed between previous studies, all studies had a consistent direction of positive impact for use of prophylactic antibiotics.

Additionally, in certain clinical scenarios, the use of penicillin-based regimens may be limited that triggers the important need to consider alternative prophylactic antibiotics other than the commonly used BPG regimen. Accordingly, we investigated the efficacy of monthly intramuscular clindamycin as an alternative option to BPG. Our analysis demonstrated that patients who received monthly intramuscular antibiotic prophylaxis, either with BPG or intramuscular clindamycin alone, experienced significantly lower incidence rates and longer median time to recurrence compared to those who did not receive prophylaxis. Following adjustment for multiple risk factors, both BPG and intramuscular clindamycin prophylaxis demonstrated a significant reduction in the risk of cellulitis recurrence compared to observation alone. While both antibiotics showed a significant risk reduction in cellulitis recurrence compared to observation alone, the results indicate some notable differences. The incidence rate of recurrence was lower in the BPG group (0.31 person-years; 95% CI, 0.21–0.49) compared to the intramuscular clindamycin group (0.49 person-years; 95%, 0.26–0.90). In addition, the median time to recurrence was significantly longer in the BPG group (2.61 years; IQR 1.37, 3.86) than in the intramuscular clindamycin group (1.49 years; IQR 0.82, 2.09). The adjusted hazard ratio also showed a greater risk reduction with BPG prophylaxis compared to intramuscular clindamycin prophylaxis (adjusted HR, 0.47; 95% CI, 0.29–0.75). In order to study the different dose–response relationship and time–response relationship between BPG and intramuscular clindamycin, the result of our further analysis showed that as the cumulative dose increased, BPG exhibited superiority over intramuscular clindamycin and demonstrated a tendency towards a longer duration of cumulative administration. These findings suggest that BPG may have some advantages over intramuscular clindamycin as a prophylactic antibiotic for recurrent cellulitis, a potentially longer duration of efficacy of BPG over intramuscular clindamycin, but further studies are needed to confirm these results.

Although prophylactic antibiotics have been shown to be effective in preventing recurrent cellulitis, the use of antibiotics may have some concerns about the risk of adverse effects, including the development of Clostridium difficile colitis. Clostridium difficile colitis is a well-known adverse effect associated with the use of clindamycin. Both the dose and duration of antibiotic therapy are contributing factors to the development of Clostridium difficile–associated diarrhea.[20] Short-term administration of antibiotics is typically associated with low risks.[20,21] In addition, the risk of adverse effects may be further mitigated by prolonging the interval between clindamycin doses in patients with stable control. It is important to note that while a reference showed a single dose of surgical antibiotic prophylaxis may increase the risk of C. difficile colonization and symptomatic disease, but this study did not specifically investigate clindamycin.[22] Therefore, the exact risk of C. difficile colitis following single-dose clindamycin remains unclear, and further research is needed to assess this specific scenario. In our study, no adverse events were reported following our low-dose prophylactic antibiotics, suggesting that the risk of C. difficile colitis associated with this type of prophylaxis may be low. The pooling results on adverse reactions also reported no significant difference between prophylaxis groups and placebo group, with an overall pooled estimate of RR 0.87 (95% CI 0.58 to 1.30; P = 0.48; I2 = 19%) in a Cochrane systemic review and meta-analysis, indicating that prophylaxis with low-dose antibiotics is relatively safe.[18]

Overall, these studies suggest that prophylactic antibiotics may be an effective strategy for reducing the risk of recurrent cellulitis in patients with a history of multiple episodes. However, it is crucial to consider both the potential benefits and risks of using antibiotics, as well as individual patient factors, when developing a treatment plan. Although several studies have demonstrated the prophylactic effect of intramuscular BPG, it has faced significant drug shortages in the clinical setting, and some patients have developed allergic reactions to penicillin, limiting its administration for those with recurrent cellulitis. These clinical challenges have yet to be fully resolved, resulting in the need for alternative options to monthly intramuscular antibiotics

other than intramuscular BPG. Therefore, the present study aimed to identify a suitable alternative option to monthly intramuscular antibiotics, and found that monthly intramuscular clindamycin was effective in preventing recurrent cellulitis when compared to observation alone. As such, it could be considered as a reasonable alternative option, particularly for patients who are allergic to penicillin or in cases of benzathine penicillin shortage.

The study has several limitations. As an observational study, the follow-up times for each group varied, and the use of prophylactic antibiotics was left to the discretion of the ID specialists' and patients' willing, which may have introduced selection bias and residual confounding. To minimize these limitations, we used Cox regression with multivariable adjustment to control for known potential factors, such as age, gender, vulnerable factors for recurrent cellulitis, and other comorbidities. Furthermore, we excluded patients who received broad-spectrum systemic antibiotics for other infections during the prophylactic periods to avoid interference from other antibiotic and disease conditions. We also conducted subgroup analyses to examine the dose-response and time–response relationship, which helped enhance the association between the use of prophylaxis and recurrent cellulitis. Electronic healthcare databases can mitigate certain types of recall bias compared to traditional self-report data, albeit not entirely but to a lesser extent. Acknowledging the inherent limitations of electronic healthcare databases, including the potential missing information and minor adverse events, may have been overlooked, and the use of electronic healthcare databases can still provide valuable insights into real-world clinical practice and outcomes.

Finally, larger and more diverse patient populations are needed to assess the potential risks associated with antibiotic prophylaxis, including the risk of C. difficile colitis.

Conclusion

Antibiotic prophylaxis has demonstrated potential benefits in preventing recurrent cellulitis. Additionally, both the BPG and intramuscular clindamycin regimens showed a significant reduction in the risk of cellulitis recurrence compared to observation alone, suggesting that intramuscular clindamycin may serve as a reasonable alternative to BPG. However, as the cumulative dose and duration of prophylactic antibiotics increase, BPG may still have a superior impact in preventing cellulitis recurrence. Further studies are needed to explore the optimal dose and duration of both BPG and intramuscular clindamycin for prophylaxis in recurrent cellulitis.

Data Sharing Statement

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The present study was conducted after the approval of the institutional review board of the Chi Mei Medical Center (CMMC) and adhered to the guidelines outlined in the Declaration of Helsinki. All patient data were anonymized. Patient informed consent was waived due to the retrospective and observational nature of the study, and patient welfare was not affected by the waiver.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ong BS, Dotel R, Ngian VJJ. Recurrent cellulitis: who is at risk and how effective is antibiotic prophylaxis? *Int J Gen Med*. 2022;15:6561–6572. doi:10.2147/IJGM.S326459
2. Cranendonk DR, Lavrijsen APM, Prins JM, Wiersinga WJ. Cellulitis: current insights into pathophysiology and clinical management. *Neth J Med*. 2017;75(9):366–378.
3. Soo JK, Bicanic TA, Heenan S, Mortimer PS. Lymphatic abnormalities demonstrated by lymphoscintigraphy after lower limb cellulitis. *Br J Dermatol*. 2008;158(6):1350–1353. doi:10.1111/j.1365-2133.2007.08423.x
4. Raff AB, Kroshinsky D. Cellulitis: a review. *JAMA*. 2016;316(3):325–337. doi:10.1001/jama.2016.8825

5. Pavlotsky F, Amrani S, Trau H. Recurrent erysipelas: risk factors. *J Dtsch Dermatol Ges*. 2004;2(2):89–95. doi:10.1046/j.1439-0353.2004.03028.x
6. Collazos J, De La Fuente B, Garcia A, et al. Cellulitis in adult patients: a large, multicenter, observational, prospective study of 606 episodes and analysis of the factors related to the response to treatment. *PLoS One*. 2018;13(9):e0204036. doi:10.1371/journal.pone.0204036
7. Brindle R, Williams OM, Barton E, Featherstone P. Assessment of antibiotic treatment of cellulitis and erysipelas: a systematic review and meta-analysis. *JAMA Dermatol*. 2019;155(9):1033–1040. doi:10.1001/jamadermatol.2019.0884
8. Inghammar M, Rasmussen M, Linder A. Recurrent erysipelas – risk factors and clinical presentation. *BMC Infect Dis*. 2014;14:270. doi:10.1186/1471-2334-14-270
9. Cannon J, Dyer J, Carapetis J, Manning L. Epidemiology and risk factors for recurrent severe lower limb cellulitis: a longitudinal cohort study. *Clin Microbiol Infect*. 2018;24(10):1084–1088. doi:10.1016/j.cmi.2018.01.023
10. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis*. 2014;59(2):147–159. doi:10.1093/cid/ciu444
11. Vignes S, Dupuy A. Recurrence of lymphoedema-associated cellulitis (erysipelas) under prophylactic antibiotherapy: a retrospective cohort study. *J Eur Acad Dermatol Venereol*. 2006;20:818–822. doi:10.1111/j.1468-3083.2006.01648.x
12. Oh CC, Ko HC, Lee HY, Safdar N, Maki DG, Chlebicki MP. Antibiotic prophylaxis for preventing recurrent cellulitis: a systematic review and meta-analysis. *J Infect*. 2014;69(1):26–34. doi:10.1016/j.jinf.2014.02.011
13. Mason JM, Thomas KS, Crook AM, et al. Prophylactic antibiotics to prevent cellulitis of the leg: economic analysis of the PATCH I & II trials. *PLoS One*. 2014;9(2):e82694. doi:10.1371/journal.pone.0082694
14. Sjoblom AC, Eriksson B, Jorup-Ronstrom C, Karkkonen K, Lindqvist M. Antibiotic prophylaxis in recurrent erysipelas. *Infection*. 1993;21(6):390–393. doi:10.1007/BF01728920
15. Chakroun M, Ben Romdhane F, Battikh R, Souki A, Bouzouaia N. Interet De La Benzathine Penicilline Dans La Prevention Des Recidives D'erysipele [Benzathine penicillin prophylaxis in recurrent erysipelas]. *Med Mal Infect*. 1994;24(10):894–897. French. doi:10.1016/S0399-077X(05)80579-7
16. Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med*. 2013;368(18):1695–1703. doi:10.1056/NEJMoa1206300
17. Thomas K, Crook A, Foster K, et al.; UK Dermatology Clinical Trials Network's PATCH Trial Team. Prophylactic antibiotics for the prevention of cellulitis (erysipelas) of the leg: results of the UK Dermatology Clinical Trials Network's PATCH II trial. *Br J Dermatol*. 2012;166(1):169–178.
18. Dalal A, Eskin-Schwartz M, Mimouni D, et al. Interventions for the prevention of recurrent erysipelas and cellulitis. *Cochrane Database Syst Rev*. 2017;6(6):CD009758. doi:10.1002/14651858.CD009758.pub2
19. 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(5):613–618. doi:10.1016/j.jmii.2015.08.008
20. Pépin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis*. 2005;41(9):1254–1260. doi:10.1086/496986
21. Stevens V, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of Clostridium difficile infection. *Clin Infect Dis*. 2011;53(1):42–48. doi:10.1093/cid/cir301
22. Privitera G, Scarpellini P, Ortisi G, Nicastro G, Nicolin R, de Lalla F. Prospective study of Clostridium difficile intestinal colonization and disease following single-dose antibiotic prophylaxis in surgery. *Antimicrob Agents Chemother*. 1991;35(1):208–210. doi:10.1128/AAC.35.1.208