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REVIEW

Recurrent Cellulitis: Who is at Risk and How Effective is Antibiotic Prophylaxis?

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Abstract: Recurrent cellulitis following successful treatment is common and prevention should be a major component in the management of cellulitis. Conditions that increase the risk of recurrence include chronic edema, venous disease, dermatomycosis and obesity. These risk factors should be actively managed as further episodes of cellulitis increases the risk of recurrence. The role of non-antibiotic measures is important and should be first-line in prevention. Antibiotic prophylaxis is effective, but its role is limited to non-purulent cellulitis where risk factors are appropriately managed.

Keywords: cellulitis, recurrence, risk factors, edema, venous insufficiency, antibiotic prophylaxis

Introduction

Cellulitis is a bacterial infection of the skin and subcutaneous tissues where recurrent episodes are common following successful treatment. Recurrent cellulitis is associated with short term and potentially long-term morbidity as well as significant health care costs.[1,2] Reducing the risk of recurrence involves the identification and management of risk factors and instituting preventative measures, which may include antibiotic prophylaxis.

Cellulitis refers to an infection involving the deep dermal tissues.[3] Erysipelas, an infection involving the superficial dermal structures is often included in the broad definition of cellulitis,[4] in research studies and health administration coding systems.[5] In this review, cellulitis refers to the broad definition encompassing both conditions, also referred to as non-purulent cellulitis. Cellulitis presents with local signs of inflammation (pain, swelling, erythema and warmth) and may be associated with a systemic inflammatory response.[6] Purulent infections and abscesses can coexist with cellulitis[6] but are primarily separate conditions, and therefore excluded from this review.

We will review studies on the risk factors for recurrent cellulitis, including those that examine their pathophysiology, clinical aspects and management. The indication and role of prophylactic antibiotics, as well as non-antibiotics measures to prevent recurrence of cellulitis will be presented.

Epidemiology

Precise descriptions of the incidence of cellulitis are hampered by varying definitions in clinical and epidemiological studies. The reported incidence ranges from 1.5 to 24.6 per 1000 patient years[7,8] with around a quarter of patients requiring hospital treatment.[7] Recurrent cellulitis is reported to occur with an incidence rate ranging from 16% to 53% within three years.[8–14] Recurrence rates are generally higher in studies which are hospital based[10,12,15–17] than in studies on community or mixed community and hospital patients.[8,11] There is also an increasing risk for recurrence with subsequent episodes, occurring at shorter time intervals than the previous.[12,13] Recurrent cellulitis episodes that require hospitalisation are usually more severe and associated with a longer length of stay.[13,18] There is increasing incidence of cellulitis with increasing age[11,19,20] partly due to concurrent comorbid disease and lymphatic changes[21] that are predisposing factors.

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Pathophysiology

Cellulitis originates when pathogenic bacteria enters the subcutaneous tissues through the dermal barrier. The risk is accentuated by dermal pathology, such as fungal foot infections and ulcers. Skin surface pathogenic organisms in immunocompetent individuals, when identified through aspirate, blood cultures or serology are predominantly beta-hemolytic streptococci[3,9,22,23] or staphylococci (*S. aureus*),[24] the latter believed to predominate in purulent cellulitis.[6] In the immunocompromised host, cellulitis can be associated with gram negative or fungal organisms.[25]

Lymphatic dysfunction is likely to be the main pathology associated with recurrent cellulitis.[26] Lymphatic abnormalities have been found in 77% to 87% of patients with lower limb cellulitis in lymphoscintigraphy scans four weeks after recovery from cellulitis.[27,28] Any other condition that impairs lymphatic drainage and function can also predispose to recurrent cellulitis. Systemic pathology such as immunodeficiency and cancer can additionally increase the risk of cellulitis. These further increases when systemic diseases like diabetes is associated with skin pathology.[29]

Risk Factors for Recurrent Cellulitis

Few studies specifically examine risk factors for recurrent cellulitis. The majority of studies are retrospective examining hospital or community patients. Current knowledge on recurrent cellulitis pathophysiology will therefore need to be derived from studies on cellulitis which examined single and recurrent episodes together. Risk factors for single episodes are associated with trauma, wounds or environmental exposure that are unlikely to recur.[18,30] Risk factors which are not modifiable or managed appropriately are more frequently associated with recurrent cellulitis.

The main risk factors that are more likely to be associated with recurrent episodes of cellulitis are local conditions such as diseases of the skin particularly chronic edema,[11,13,16,17,31] dermatomycosis[8,11,15,17] and venous insufficiency.[8,11,13,16,17,31] Obesity was a common factor in many studies.[8,20,31] Some studies found an association with diabetes, cancer and peripheral vascular disease. The criteria used to diagnose these conditions in the studies are not standardized but do provide an estimate of risk of recurrence. Those which are more commonly associated with recurrent cellulitis as opposed to single episodes, and where available, their respective proportion and odds ratio, are outlined in Table 1.

By definition, a prior episode of cellulitis is a risk factor for recurrence. Around 35 to 47% of patients who present to hospital with cellulitis have a prior episode.[10,32] A small study found that a prior episode was the only significant factor predictive of further recurrences.[12] The inflammation in cellulitis can lead to tissue damage and fibrosis, subsequently affecting interstitial flow, systemic response to infection and bacterial and toxin clearance.[33] Where interstitial flow is reduced in severe and repeated infections, it will result in lymphatic insufficiency further impairing immune function.[34] This inflammatory response in cellulitis is suspected to be driven by inflammatory modulators and bacterial toxins rather than bacterial load.[6] Reducing the duration and severity of cellulitis is likely to reduce the risk of future recurrence.

Chronic Edema and Lymphedema

Chronic edema is a major risk factor for cellulitis.[10] It is now defined as edema from any cause, present for over three months.[35] Chronic edema impairs cell nutrition and oxygenation, compromising tissue viability.[36] It can also lead to chronic inflammation and accumulation of cellular debris resulting in fibrosis and lymphatic dysfunction,[37] increasing risk of ulceration and infection. The main causes of chronic edema are lymphedema, venous insufficiency, obesity and immobility and is often multifactorial.[38] Edema is common and can be present in 38% of hospitalised patients.[39] It is estimated that over one third of patients with chronic edema will develop recurrent cellulitis, with risk increasing with severity of edema.[33] A meta-analysis on risk factors for cellulitis assessed chronic edema to be an independent risk factor for cellulitis with an odds ratio of 6.8.[40] Many of the risk factors for recurrent cellulitis are directly or indirectly related to chronic edema.[13]

Lymphedema has been recognised as a risk factor for cellulitis and refers to failure of development of lymphatics as in primary lymphedema, or lymphatic damage in secondary lymphedema. The majority of secondary lymphedema cases were thought to be due to cancer or its associated treatment, or filariasis in endemic countries.[34] Recently it has become increasingly recognised that there is evidence of lymphatic failure in chronic edema from any cause.[38] The lymphatics play

Table 1 Recurrent Cellulitis Risk Factor

Risk Factor		Proportion of Recurrent Cellulitis Cases	Odds Ratio (Univariate)	Odds Ratio (Multivariate)
Local Risk Factors	Chronic edema/ Lymphedema	13.4%[16] 26.5%[17] 26.1%[31]	6.8 (2.9–15.9)[16] 8.50 (3.13–23.0)[17] 5.7 (2.7–11.4)[31]	4.3 (1.3–14.0)[16] 9.18 (3.22–26.16)[17]
	Ulcer/chronic wounds		4.88 (1.22–19.45)[8] ≥65 years old	
	Venous insufficiency/ varicose veins/phlebitis	11.3%[16] 49.0%[17] 23.2%[31]	3.62 (1.19–10.96)[8] ≥65 years old 2.7 (1.3–5.6)[16] 3.97 (2.20–7.16)[17] 5.1 (2.5–10.7)[31]	2.3 (1.0–5.2)[16] 3.45 (1.79–6.66)[17]
	Dermatomycosis/Tinea Pedis	31.4%[17]	1.89 (1.02–3.48)[17] 4.24 (1.21–14.91)[8] 45–64 years old	
Systemic Risk Factors	Obesity	40.6%[31]	5.85 (1.28–26.79)[8] 45–64 years old 3.3 (1.9–5.7)[31]	
	Cancer	25.4%[16] 13.0%[31]	2.0 (1.2–3.7)[16] 2.5 (1.1–5.8)[31]	
	Diabetes Mellitus	23.2%[31]	2.0 (1.0–3.8)[31]	
Cellulitis specific Risk Factors	Lower limb/Tibial site location	78.2%[16] 83.0%[11] Tibial site location		
	Previous local surgery/ saphenectomy	32.4%[16]	2.0 (1.3–3.0)[16]	

Notes: Reported statistically significant results comparing risk factors of recurrent and single episodes of cellulitis. Case control or cross-sectional studies where odds ratios are reported.[8,16,17,31]

a major role in removing excess interstitial fluid and macromolecules, and can be overloaded and dysfunctional in chronic edema.[38] Uncontrolled lymphedema will lead to progressive fat deposition and fibrosis which can be difficult to treat.[41] Lymphedema is usually diagnosed when the edema is non-pitting and does not resolve with elevation, but the absence of these signs does not exclude the presence of lymphedema.[34,36] For patients who develop cellulitis, the presence of lymphedema may be associated with a longer duration of cellulitis and fever.[42]

Venous Insufficiency and Venous Dermatitis

Chronic venous disease with venous stasis dermatitis can mimic cellulitis,[43] particularly when there is bilateral involvement. It can also predispose to bacterial cellulitis. Venous insufficiency results in sustained venous hypertension and chronic inflammatory changes in the dermal tissues, which can lead to lipodermatosclerosis, skin ulceration and chronic edema.[44] Cellulitis can also occur in patients with venous insufficiency in the absence of obvious dermatitis or ulcers.[45] Previous deep venous thrombosis is a risk factor for recurrent cellulitis[17] likely due the complication of venous insufficiency.

Chronic Wounds and Ulcers

Chronic wounds and ulcers act as a portal of entry for pathogenic bacteria. Chronic ulcers are commonly colonised by bacteria, with higher microbiological diversity in wounds of larger size and longer duration with streptococcus species, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* most implicated.[46] The development of a bacterial biofilm in chronic wounds also delay wound healing and increases risk of infection.[46] Tissue samples may be required in deeper wounds in certain conditions to effectively treat infected ulcers.[47] Ulcers are more commonly associated as a risk factor for recurrent cellulitis in the older age groups.[8]

Dermatological Conditions

Chronic and recurrent dermatomycosis including tinea pedis and onychomycosis are frequently associated with an increased risk of recurrent cellulitis,[48] particularly in the younger age groups.[8] The link to cellulitis with tinea pedis is supported by bacterial cultures of interdigital space of patients which grew potentially pathogenic bacteria with the majority group A (beta-hemolytic) streptococcus.[49] Dermatomycosis can recur up to a rate of 25% despite successful treatment, particularly in patients with diabetes, inappropriate footwear, and a family history.[20,50] Other skin conditions associated with recurrence include psoriasis[20] and operations involving lower leg veins.[13,32]

Obesity

Obesity has been associated with multiple comorbidities and is a risk factor for cellulitis by several mechanisms. Skin infections are common in obesity and can occur in up to 50% of patients.[51] Chronic edema is identified in up to 80% of obese patients.[37] Obesity negatively affects lymphatic transport and lymph node architecture[52,53] predisposing to skin infections. Cellulitis in obese patients is also associated with adverse outcomes and treatment failure.[54]

Cancer and Immunodeficiency

Patients with cancer can have a fourfold risk of recurrence of cellulitis.[11] The main risk factor would be edema due of tumour invasion, lymph node resection and radiation. Over one in four patients with breast cancer have lymphedema.[27,55,56] Cellulitis in cancer can also occur in atypical sites such as periorbital and septal cellulitis.[57] Neutropenia also predisposes to infections from atypical fungal organisms, and more severe and invasive bacterial skin infections.[58,59]

Diabetes

Diabetes is a systemic illness that is associated with multisystem pathology and common infections. It is also associated with other conditions which predispose to recurrent cellulitis such as obesity and tinea pedis.[29] Complications of diabetes such as peripheral neuropathy and microvascular disease leading to ulcers also increases the risk of infection.[60] Poor glycemic control has been associated with an increased risk of cellulitis.[61]

Other Risk Factors

Cellulitis located in the lower limbs has the highest risk of recurrence given much of the pathology related to cellulitis occurs at this anatomical site.[11,16] One study found a higher recurrence of cellulitis in the tibial region as compared to the femoral region or the foot.[11] Other risk factors that were identified include peripheral vascular disease,[13,17] chronic kidney disease,[17] chronic obstructive pulmonary disease,[13,30] and liver disease.[13] Social factors associated with the other established risk factors are also important, particularly homelessness which can be linked to poor skin and general health care.[62] Recurrent cellulitis has also been associated with foreign bodies in case reports.[63,64]

Previous tonsillectomy was found to be a risk factor for recurrent cellulitis.[20,65] The nature of this association warrants further research to explore relationships with potential pathophysiology and location of cellulitis episodes. Recurrent episodes of cellulitis requiring hospital admission is reported to be associated with hypertension, hypoalbuminemia, and hyperlipidemia.[66] These are likely comorbidities linked to main risk factors.

A predictive model on risk factors derived from a population-based retrospective cohort study for recurrent cellulitis based on the presence of tibial area involvement, prior malignancy and dermatitis estimated a risk of recurrence from 17.3%, 50.6% and 92.8% depending on the number of risk factors.[11] Known established risk factors may not be present

in all cases of recurrent cellulitis. It is likely that subclinical pathology related to tissue damage from cellulitis accounts for many cases where an established risk factor is not apparent. There may be potentially other risk factors which are yet to be identified. A potential risk factor requiring further study is genetic predisposition to recurrent cellulitis.[67]

Non-Antibiotic Measures

Initial management in the prevention of recurrent cellulitis involves the identification and management of risk factors. Published guidelines also recommend addressing these factors, either locally or systemically, in addition to antibiotic prophylaxis.[68–70]

Local Factors

Chronic edema has been identified as a major risk factor for single-episode and recurrent cellulitis.[10] Conditions leading to chronic edema include lymphedema, chronic venous hypertension, congestive heart failure and obesity.[16,18] Graduated compression stockings (GCS) are commonly used in the management of chronic edema due to chronic venous disease and lymphedema. These stockings exert their greatest pressure at the ankle, and the level of compression gradually decreases in a proximal fashion. Compression is classified according to the approximate pressure the stocking applies; Class 1 refers to pressure of less than 20mmHg; Class 2, pressure of 20–30mmHg; Class 3, pressure of 30mmHg or greater. GCS are contraindicated in patients with peripheral vascular disease, peripheral neuropathy, or allergy to the stocking material.[71] Thrombo-Embolus Deterrent (TED) stockings, in contrast, are not suitable as they offer a different level of compression. Compliance with GCS can be an issue with non-compliance rates of up to 63%. Factors for non-compliance includes discomfort, cosmetic appearance, contact dermatitis or pruritis.[72]

In a randomized, non-blinded single-center study of 84 patients, 41 patients were assigned to compression therapy and 43 to education. The degree of compression and stocking type were determined by the severity of the edema, shape of the limb, skin integrity and ease of application and removal by the patient or their caregivers. In the GCS group, a high proportion (88%) of patients reported wearing these ≥ 4 days per week. GCS therapy compared to education alone was shown to reduce recurrence with hazard ratio of 0.23 (95% CI 0.09 to 0.59, P=0.002).[73]

The use of pneumatic compression devices in patients with edema due to chronic venous insufficiency or lymphedema is associated with reduction in recurrence.[74] Surgical intervention with lymphatic venous anastomosis in carefully selected patients with chronic lymphedema may reduce recurrent episodes.[75–77] In cases associated with chronic venous insufficiency where other measures have been unsuccessful, examination with intravascular ultrasound to identify possible iliac vein outflow obstruction and venous stenting may reduce future recurrence.[45]

Individuals with associated tinea pedis should be educated on foot hygiene with attention to the interdigital webbings of the toes.[62] The use of topical or systemic antifungal agents may be needed to control recurrent tinea pedis despite adequate foot hygiene.[78]

Systemic Factors

In patients with diabetes mellitus, fungal skin infections are common. Chronic hyperglycemia affects cellular immunity and phagocytic function. Effective glycemic control may decrease recurrence of cellulitis.[79]

Weight reduction and maintenance of a healthy weight in the obese individual may reduce recurrence[62,78,80] and improve the success of antibiotic prophylaxis.[14]

The use of systemic steroids in the management of cellulitis is controversial and there is currently no evidence that steroids prevent recurrent cellulitis.[70,81]

Decolonization strategies in cases due to methicillin-sensitive *Staphylococcus aureus* or methicillin-resistant *Staphylococcus aureus* have shown mixed results. In some cases, periodic decolonization can be considered and potential decolonization of other household members, where colonization of the bacteria is documented.[82]

Vaccine development against group A streptococcus (GAS) presents many challenges as it possesses several pathogenic factors leading to infection of the host. In addition, there is extensive strain diversity, and this varies in different geographical locations.[83] In a non-randomized trial of 100 patients, the use of streptococcal vaccine produced from heat-inactivated mixture of 12 different streptococci types, was shown to reduce the frequency or avoided further episodes of cellulitis.[84] Currently, the J8-DT/HD-MAP vaccine appears promising as it has been demonstrated to significantly reduce the number of *Streptococcus*

pyogenes colony forming units in animal studies.[85] There are no established GAS clinical trials in humans at the time of this review.[86]

Antibiotic Prophylaxis

Currently antibiotic prophylaxis is only indicated for non-purulent infection and directed against beta-hemolytic streptococci, particularly *Streptococcus pyogenes*.[87] Besides recurrent cellulitis, prolonged antimicrobial therapy to prevent infection has been used successfully in other conditions including rheumatic fever and asplenia.[88]

Prophylactic antibiotics have been used in recurrent cellulitis for over 40 years.[89] However, only a total of 513 participants are enrolled across five randomized controlled trials (RCT) for this common entity - one benzathine penicillin trial (n=58),[90]

Table 2 Randomized Controlled Trials: Antimicrobial Prophylaxis for Recurrent Cellulitis

Trial	Definition	Interventions	Result	Note
Penicillin to Prevent Recurrent Leg Cellulitis.[14]	Two or more episodes of cellulitis in the previous three years.	Active: 12 months of 250mg twice daily penicillin V (n = 136). Control: Placebo (n = 138).	22% vs 37% had recurrence (HR 0.55; 95% CI 0.35–0.86; *p*-value 0.01), NNT 7. Not effective in patients with chronic oedema, three or more episodes of cellulitis and BMI ≥ 33.	Followed for up to three years. Participants with history of leg ulcers were excluded.
Prophylactic antibiotics for the prevention of cellulitis (erysipelas) of the leg.[92]	The study assessed the role of prophylaxis after treatment of acute episode of cellulitis. 79% had a prior history of cellulitis.	Active: 6 months of penicillin V 250mg twice daily (n=60). Control: Placebo (n=63).	20% vs 33% had recurrence (HR = 0.53; 95% CI 0.26–1.07; *p*-value 0.08).	Followed for up to two years. Those with leg ulcers were excluded. Higher BMI in treatment arm (34 vs 31). This study failed to reach the target of 400 participants.
Benzathine penicillin prophylaxis in recurrent erysipelas.[90]	Enrolment after treatment of an acute episode of cellulitis. Unknown if participants had prior cellulitis.	Active: (n=24) Benzathine penicillin 1.2 million units IMI every 15 days, unclear duration. Control: Open label (n=34).	0% vs 26% had recurrence (*p*-value <0.007).	Followed for up to one year. Obesity, lymphedema and tinea pedis were noted in 40–60% of patients. Non-English publication (French).
Antibiotic prophylaxis in recurrent erysipelas.[93]	Two or more episodes in the last three years.	Active: (n=20) Penicillin V 1 g twice daily if body weight was < 90 kg, 1 g + 2 g if 90–120 kg and 2 g twice daily if > 120 kg. If penicillin allergic, erythromycin 250mg twice daily; 250mg +500mg and 500mg twice daily for the corresponding weight groups. Control: Open label (n=20).	10% vs 20% had recurrence (*p*-value 0.06).	Follow up for up to three years. Duration of prophylaxis unclear. Local skin care and compression for leg edema allowed. 5/20 participants received erythromycin. Median follow up for 14 ½ months. Presence or absence of leg ulcers not defined.
Long-term antimicrobial therapy in the prevention of recurrent soft-tissue infections.[91]	Two or more episodes during the previous year.	Active: 18 months of 250mg twice daily erythromycin (n=16). Control: Open label (n=16).	0% vs 50% had recurrence during the study (*p*-value <0.002).	3/16 participants on erythromycin changed to penicillin V 250mg twice daily due to gastrointestinal side effects. The presence or absence of ulcers is not defined.

one erythromycin trial (n=32)[91] and three phenoxymethylpenicillin trials (n = 423)[14,92,93] (Table 2). In a Cochrane analysis[4] of these five trials, prophylactic antibiotic reduced recurrence by 69% (risk ratio 0.31, 95% confidence interval 0.13 to 0.72), with an estimated number needed to treat (NNT) of six. Its role in patients with leg ulcers is unclear as this group was excluded in recurrent cellulitis RCTs.[14,92]

Antibiotic prophylaxis for recurrent cellulitis can be considered when there are two or more episodes of cellulitis in the previous 12 months. Current guidelines on antimicrobial prophylaxis are outlined in Table 3.

Table 3 Guidelines and Recommendations

Resource	Definition of Recurrent Infection	Recommendations
Infectious Diseases Society of America (2014).[97]	3–4 episodes of cellulitis per year despite attempts to treat or control predisposing factors.	Identify and treat predisposing conditions. Consider penicillin or erythromycin twice daily for 4–52 weeks, or IMI benzathine penicillin every 2–4 weeks until predisposing factor is corrected. Antibiotic dose was not provided.
British Lymphology Society (2016).[68]	Two or more episodes per year.	Decongestive lymphatic therapy, skin care with emollients, daily alcohol wipes to web-space (if skin is intact) and treatment of tinea. Recommended antibiotic is penicillin V 250mg twice daily (500mg twice daily if BMI ≥ 33). If penicillin allergic, use erythromycin 250mg twice daily. If this is not tolerated use clarithromycin 250mg daily. Consider ceasing prophylaxis after two years of successful therapy. If it recurs, continue lifelong or until risk factors are corrected. Consider clindamycin 150mg daily or cefalexin 125mg daily or doxycycline 50mg daily if the first line antibiotic fails.
Australian Lymphology Association (2015).[104]	Two or more episodes in a 12-month period despite diligent skin care and treating all contributing factors.	Penicillin V 500mg daily or 250mg twice daily. If penicillin allergic, use erythromycin 250mg daily. Double the dose of these antibiotics if weight >100kg. Reduce dose after 1 year of successful therapy to 250mg daily and can be discontinued after 2 years of successful prophylaxis. Treat lifelong if recurs on ceasing prophylaxis. Trial of clindamycin 150mg daily if the first line antibiotic fails. May need to increase dose during summer months if recurrence occurs in summer. Manage underlying condition and provide good skin care.
South Korean Guideline for SSTI (2017).[69]	3–4 episodes per year.	Check for and modify correctable factors. Oral amoxicillin or intramuscular (IM) benzathine penicillin G recommended as first line agent (dose was not defined).
The diagnosis and treatment of peripheral lymphedema: Consensus Document of the International Society of Lymphology (2020).[105]	Lymphedema patients with repeated episodes despite optimal compression therapy.	Prophylactic penicillin (dose not defined). Duration guided by medical risk/benefit assessment.
Therapeutic Guidelines, Australia (2021).[103]	Not defined (“frequent infections”).	Phenoxymethylpenicillin 250mg twice daily for up to 6 months initially, then review regularly

Antibiotics

Phenoxymethylpenicillin

Oral phenoxymethylpenicillin (also known as penicillin V) is the preferred antibiotic for recurrent cellulitis prevention. The PATCH I trial by the British Dermatology Association[14] was a placebo controlled, double-blind RCT that examined 274 patients with two or more episodes of cellulitis in the previous three years demonstrated that oral penicillin V (250mg twice daily) prophylaxis for 12 months reduced the risk of a repeat episode of cellulitis by 45% (HR 0.55; CI: 0.35–0.86). Participants with chronic edema, BMI ≥ 33 kg/m2 or history of three or more episodes of cellulitis, had no significant response to this prophylactic regimen.

The reason for the lack of significant response to patients with three or more episodes was unclear and requires further study. Unmanaged risk factors may be contributory and patients with frequent recurrence should be thoroughly evaluated for risk factor modifications. The limited efficacy of prophylactic antibiotics in chronic lymphedema has also been noted previously.[94] Patients with chronic leg edema should be offered compression stockings.[73] Obese patients may require a higher dose of penicillin V, such as 500mg twice daily for patients with BMI ≥ 33kg/m2.[68] A higher dose has also been used (as high as 2g twice daily).[93] Low dose penicillin is usually well tolerated whereas higher doses increase the risk of gastrointestinal side effects.

Streptococcus species has remained exquisitely sensitive to penicillin over the years,[95,96] though with recent reports of beta lactam resistance,[97] emphasizing the need for judicious evidence-based use of antibiotic prophylaxis.

Benzathine Penicillin

Benzathine penicillin is a long-acting penicillin given by intramuscular injection (IMI) and used when a patient is unable to take oral antibiotics due to gastrointestinal intolerance, malabsorption, patient's preference, or non-compliance with oral antibiotics. Dose and frequency of IMI administration include 1.2–2.4 million units every 2–4 weeks. It is generally started at four weekly intervals but reduced to 3 or 2 weekly intervals if it fails to prevent recurrence. Benzathine penicillin is most effective if there are no predisposing or unmodified factors for recurrence.[98] Long term benzathine penicillin IMI is usually well tolerated and measures to reduce pain and discomfort is discussed elsewhere.[99] It is commonly used for other indications such as secondary prophylaxis for rheumatic fever.

An RCT comparing 1.2 million units of benzathine penicillin every 2 weeks to no prophylaxis[90] revealed at one year follow-up, 9 of 34 (26%) controls had cellulitis compared to none (0/24) in those who received prophylaxis. The finding is supported in observational studies. Prophylactic benzathine penicillin 2.4 million units IMI every 3 weeks (for four months) was given to 12 patients after a first attack of erysipelas.[89] Five patients who were allergic to penicillin received no prophylaxis and were used as control. During prophylaxis none of the 12 patients developed cellulitis compared to 1 in 5 control (20%) developed the infection. Similarly, a single center retrospective study reported a significantly less frequent recurrence in patients receiving monthly IMI benzathine penicillin (among 72 cases, with prophylaxis the incidence rate of cellulitis was 0.73 episode/patient-year versus 1.25 episodes/patient-year without prophylaxis ($p<0.001$)).[100] These results cannot be generalized due to the small sample size, single center study or non-randomized design. Also, others have failed to replicate this finding.[20]

Erythromycin

Erythromycin is used if a patient is allergic to penicillin. The usual dose of erythromycin for preventing recurrent cellulitis is 250mg twice daily. In an open-label RCT involving 32 patients with two or more episodes of cellulitis in the previous year, there was no relapse in erythromycin recipients (250mg twice daily for 18 months), in 0/16 participants, compared with 50% relapse (8/16) without prophylaxis, $p <0.001$.[91] Erythromycin was well tolerated except in 3/16 (20%) patients who for gastrointestinal side effects were switched to penicillin V 250mg twice daily. Small sample size and open-label design were the limiting factors of this study.

Key considerations when using erythromycin are potential drug resistance and drug-drug interactions. There are reports of increasing resistance to erythromycin in group A streptococcus. Erythromycin resistance is more common in groups B, C and G streptococcus (30–45%).[101,102]

Penicillin Allergy

For patients with non-severe hypersensitivity to penicillin, cefadroxil or cefalexin can be considered. In the presence of severe hypersensitivity to penicillin, options include erythromycin, clindamycin, doxycycline, or trimethoprim-sulfamethoxazole (Table 3). These antibiotics have a variable anti-*Staphylococcus aureus* coverage and are generally reserved for prevention of purulent cellulitis or after failure of penicillin V. Underlying risk factors should be reassessed after a breakthrough infection. Those with recurrent *S. aureus* infection may benefit from staphylococcus decolonisation.[82]

Duration of Prophylaxis

Duration of prophylaxis is not clearly defined but is generally continued for 6–12 months. The protective effect of antibiotics in preventing cellulitis is lost after cessation (RR 0.88, 95% CI 0.59 to 1.31).[4] Hence, antibiotics may be extended if recurrence occurs on discontinuation or until predisposing factor is corrected. Long term low dose prophylactic antibiotic is generally well tolerated.[4] Drawbacks include risk of allergic drug-reactions, development of drug-resistance, *C. difficile* infection, and prescription costs.

Conclusion

Recurrent episodes can occur after successful treatment of cellulitis. Conditions that commonly increase the risk of cellulitis include chronic edema, venous disease, dermatomycosis and obesity. A rigorous approach to the management of risk factors is important as the risk of recurrence increases with repeated episodes. Both local and systemic factors if present, need to be targeted, especially if antibiotic prophylaxis is considered. Phenoxymethylpenicillin is the preferred antibiotic. Other antibiotics can be considered in cases of penicillin allergy, intolerance, or failure.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of

the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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