Management of infected lymphoedema in adults admitted to secondary care

University Hospitals of Leicester NHS
NHS Trust

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1. Introduction

This guideline aims to provide UHL staff caring for adult inpatients with advice on the diagnosis and management of acute cellulitis in lymphoedema and advice on preventing further episodes.

Lymphoedema is the swelling of one or several parts of the body owing to lymph accumulation in the extracellular space. It is often chronic, worsens if untreated, predisposes to infections and causes an important reduction in quality of life.[1]

Cellulitis is an acute spreading inflammation of the skin and subcutaneous tissues characterised by pain, warmth, swelling and erythema. Attacks of cellulitis in lymphoedema may differ in presentation from cellulitis without lymphoedema, and can be difficult to distinguish from other causes of inflammation (see 'diagnosis' section below).[2]

Cellulitis is a frequent problem for patients with lymphoedema, and recurrence is common. It is important that episodes are promptly diagnosed and treated, as they can lead to sepsis, or cause further damage to the lymphatics with increased risk of repeat infection.

Cellulitis in lymphoedema is predominantly caused by beta-haemolytic *Streptococci* (particularly Group A *Streptococcus*) and *Staphylococcus aureus*.

Beta-haemolytic *Streptococci* are universally sensitive to beta-lactam antibiotics (penicillins). Staphylococcus aureus is often resistant to penicillin and amoxicillin, but is sensitive to flucloxacillin. Methicillin Resistant Staphylococcus aureus (MRSA) is resistant to all beta lactams.

Resistance to other classes of antibiotics is common in both *Streptococci* and *Staphylococci*. Therefore any penicillin allergy history should be thoroughly explored, and the exact nature documented (e.g. rash vs anaphylaxis). It is also important to note that side effects with one antibiotic (e.g. GI upset with flucloxacillin) should not be recorded as an allergy to the entire class.

2. Scope

This policy applies to all staff in UHL caring for patients with lymphoedema.

3. Recommendations, Standards and Procedural Statements

3.1 Diagnosis of cellulitis in lymphedema

Cellulitis in lymphoedema can be accompanied by severe systemic upset, with high fever and rigors. However the patient may also be afebrile; one study of cellulitis in lymphoedema [3] found fever was present in less than half of cases, whilst increased swelling of the affected limb was almost always seen. The erythema may be more diffuse and blotchy compared to cellulitis without lymphoedema.

There are many causes for limb inflammation in lymphoedema. See appendix 1 for a flowchart produced by the British Lymphology Society to help assess causes of erythema in lymphoedema.

3.2 Assessment

As with any other infection, assessment of severity should include reviewing for signs of sepsis. Cases of red flag sepsis should be managed as per the trust sepsis guidelines.

Patients should also be reviewed for evidence of necrotising fasciitis. Symptoms of necrotising fasciitis include: pain out of keeping with clinical findings, crepitus, rapidly spreading cellulitis, and systemic toxicity. Cases of suspected necrotising fasciitis should be immediately discussed with the on call surgical team and the on call microbiologist.

Other key features of patient assessment include:

Risk factors for resistant organisms:

- Previous microbiology results e.g. MRSA colonisation, previous wound swab results
- Previous antibiotic use, and clinical response
- Any preceding injury e.g. animal bite, penetrating injury – need to consider tetanus prophylaxis
- Location of cellulitis e.g. anogenital

Risk factors for recurrence:

- Dermatological conditions e.g. eczema
- Fungal infections, e.g. ‘athletes foot’ or onychomycosis
- Immunosuppression e.g. diabetes
- BMI >30

Assessment of severity:

- Where possible, the area of cellulitis should be marked to allow objective comparison over time. This may not always be possible in lymphoedema, as the cellulitis may be blotchy
- Presence of systemic symptoms (e.g. fever, malaise, rigors)

3.3 Investigations

- Swabs from edge of ulcers, any weeping or blistered skin, or macerated/fissured areas between toes should be sent for culture and sensitivity testing
- Blood cultures should be sent from patients with history of fever
- Inflammatory markers (WCC/CRP) may be helpful to monitor treatment response

- If evidence of fungal nail infection – nail clippings or skin scrapes to be sent for microscopy and fungal culture

3.4 Treatment of acute episodes

3.4.1 General principles:

- Patients report rest and elevation provides symptomatic relief during an acute attack of cellulitis. However a return to normal levels of activity should be encouraged as soon as the patient is feeling better.
- Analgesia should also be prescribed as appropriate
- Compression garments should be removed if the limb has become too swollen for them to fit comfortably. However, they should be replaced as soon as possible to prevent worsening of lymphoedema. This may require a change in the size of the compression garment to accommodate the increased swelling after cellulitis.

3.4.2 Empirical antibiotic treatment

Empirical antibiotic treatment options are listed below. These may need to be altered if the patient has a history of antibiotic resistance. See section 3.4.3 for actions to take if patients fail to respond to initial empirical therapy.

Antibiotic prophylaxis should be suspended whilst the patient is on treatment dose antibiotics.

Intravenous antibiotics should be switched to oral when safe to do so, in line with the trust's IV to PO switch policy (trust reference B2/2023). Metronidazole has excellent oral bioavailability, so the oral route is listed as first line. If the oral route is unavailable, then IV metronidazole can be substituted, but should be converted to PO as soon as possible.

The total duration of treatment refers to combined PO and IV e.g. if 2 days IV antibiotics are given then 12 days PO would follow. 14 days treatment is longer than recommended in NICE guidelines, however these guidelines are not specifically for infection in lymphoedema. The 2022 British Society of Lymphoedema guidelines recommend 14 days treatment, and advise that shorter courses are associated with a significantly higher risk of relapse. If recurrence/deterioration occurs soon after completion of a 14-day course, advice should be sought from microbiology, as longer courses are occasionally needed.

Skin changes e.g. discolouration/staining may persist for months or longer following severe cellulitis and do not require ongoing antibiotics.

Limb cellulitis

	1st line	Penicillin allergy	MRSA positive	2nd line agent (if poor response to first line)	Duration
Mild disease with no systemic upset	Flucloxacillin 1g QDS PO	Doxycycline 200mg OD PO (Discuss with microbiology if known to be colonised with a tetracycline-resistant organism)		Linezolid 600mg BD PO (See section 3.4.3)	14 days
Systemic upset or severe disease	Flucloxacillin 2g QDS IV	Vancomycin IV dose as per vancomycin prescription chart		Discuss with microbiologist	14 days

Anogenital cellulitis

	1st line	Mild penicillin allergy	Moderate-severe Penicillin allergy / known cephalosporin allergy	MRSA positive	2nd line agent (if poor response to first line)	Duration
Mild disease with no systemic upset	Flucloxacillin 1g QDS PO	Doxycycline 200mg OD PO	Doxycycline 200mg OD PO	Doxycycline 200mg OD PO	Co-amoxiclav 625mg TDS PO + Amoxicillin 500mg TDS PO <u>Penicillin allergy</u>: Co-trimoxazole 960mg BD PO + Metronidazole 400mg TDS PO	14 days
		(Discuss with microbiology if known to be colonised with a tetracycline-resistant organism)			See section 3.4.3	
Systemic upset or severe disease	Co-amoxiclav 1.2g TDS IV	Ceftriaxone 2g BD IV + Metronidazole 400mg TDS PO	Vancomycin IV + Ciprofloxacin 500mg BD PO + Metronidazole 400mg TDS PO	Add IV vancomycin if not already part of regime	Discuss with microbiologist	14 days

Infected Animal bites

	1st Line	Mild Penicillin allergy	Moderate - Severe Penicillin allergy / known cephalosporin allergy	MRSA colonised	Duration
No systemic upset	Co-amoxiclav 625mg TDS PO	Doxycycline 200mg OD + Metronidazole 400mg TDS PO (Discuss with microbiology if known to be colonised with a tetracycline-resistant organism)			14 days
Systemic upset	Co-amoxiclav 1.2g TDS IV	Ceftriaxone 2g BD IV + Metronidazole 400mg TDS PO	Discuss with microbiology	Add IV Vancomycin	14 days
See NICE website for further details on the management of animal bites, including antibiotic prophylaxis for non-infected bites, indications for tetanus prophylaxis, and rabies risk assessment. https://cks.nice.org.uk/topics/bites-human-animal/					

3.4.3 Ongoing therapy:

If patients fail to improve after 48 hours of first line PO therapy, but remain systemically well:

- Review diagnosis – see appendix 1 for alternative causes of erythema in lymphoedema
- Review any microbiology results
- Consider if the patient has any GI absorption issues e.g. gastroparesis, and consider a switch to IV therapy

If cellulitis remains the most likely diagnosis, there are no microbiology results to guide therapy, and oral therapy is still felt to be appropriate, see sections below for ongoing management.

3.4.3.1 Limb cellulitis with mild disease/no systemic upset, poor response to first line therapy

- Consider a switch to PO linezolid 600mg BD for 14 days.
    - Linezolid has a number of useful attributes for the treatment of soft tissue infection. It has extremely high oral bioavailability, a large volume of distribution and is reliably active against *Streptococci* and *Staphylococcus aureus* (including MRSA).
    - However linezolid has a number of important interactions including; monoamine oxidase inhibitors , serotonergic medicines such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and opiates (including tramadol). See the prescribing information for full details (https://www.medicines.org.uk/emc/product/5119/smpc#gref). It should generally not be co-prescribed with any of these medications. It can also enhance the hypoglycaemic effect of glucose lowering agents so should be used in caution to patients prescribed these.

- Linezolid can also cause peripheral neuropathy, optic neuritis, and bone marrow suppression, though the risk is mainly with prolonged (>2 weeks) use. Patients should be warned to report these side effects promptly as they may not be reversible.
- Linezolid should also be avoided in patients with a history of seizures.

- If patients fail to improve despite linezolid, or if linezolid is contra-indicated, discuss with microbiology

3.4.3.2 Limb cellulitis with systemic upset, poor response to first line therapy

- Patients with systemic upset who fail to improve despite IV therapy should be discussed with a microbiologist.

3.4.3.3 Anogenital cellulitis with no systemic upset, poor response to first line therapy

- If there is a poor response after 48 hours of first line PO therapy, then the infection may be due to gram negative organisms or anaerobes.
- Patients should be switched to 14 days of PO co-amoxiclav 625mg TDS + amoxicillin 500mg TDS. Penicillin allergic patients, or patients known to be colonised with MRSA should be switched to co-trimoxazole 960mg BD + metronidazole 400mg TDS PO for 14 days.
- Co-trimoxazole is contra-indicated in patients with acute porphyria, and should be used in caution in patients with severe asthma, or with G6PD deficiency. It can also cause hyperkalaemia, so should be used in caution if patients are co-prescribed agents such as ACE inhibitors , angiotension II receptor antagonists or spironolactone.
- Discuss with a microbiologist if co-trimoxazole is contra-indicated , or if the patient is known to be colonised with co-trimoxazole resistant organisms.

3.5 Preventing recurrence

- Underlying skin conditions such as dermatitis, or ulcers, should be optimised as far as possible

- Fungal infections of the skin or nails of the feet should be treated in line with NICE guidance (https://cks.nice.org.uk/topics/fungal-nail-infection/ and https://cks.nice.org.uk/topics/fungal-skin-infection-foot/)

- Obesity is also a risk factor for recurrent infection, and can worsen oedema, so weight loss should be encouraged.

- Patients who have had an episode of cellulitis, and who are likely to be unable to access healthcare promptly (e.g. going on holiday) should be offered a 14-day ‘rescue pack’ of antibiotics to take if symptoms occur.

3.5.1 Antibiotic prophylaxis

Antibiotic prophylaxis can be considered in patients who have had 2 or more episodes of cellulitis in one year, or patients who are undergoing surgery on an area of lymphoedema.

However, before starting antibiotic prophylaxis, a thorough review should be undertaken to assess the following:

- Were all the episodes definitely cellulitis, and not a mimic? (see appendix 1)

- Were these separate episodes, or one episode of cellulitis which was incompletely treated e.g. by multiple short (5-7days) courses of antibiotics?

    - In this situation the symptoms of cellulitis may resolve in a few days but recur after 2-3 weeks. This may reflect an incompletely treated single episode of cellulitis which should be treated with a longer course of antibiotics (at least 2 weeks) and counted as one episode

- Was there a clear, easily reversible cause e.g. fungal skin infection. In which case, this should be treated before using continuous prophylactic antibiotics.
- Did the patient have any positive culture results, and did these yield any organisms resistant to the empirical prophylaxis regimes? In which case, microbiology discussion is advised.

3.5.2 Antibiotic prophylaxis regimes:

Indication	**1st line**	**Penicillin allergy/ MRSA colonised**	**Alternative**
Recurrent Limb cellulitis	Penicillin V 250mg BD PO For patients with BMI >33 or weight >100kg dose should be increased to 500mg BD	Doxycycline 100mg OD PO	Clarithromycin 250mg OD PO
Recurrent Anogenital cellulitis	Penicillin V 250mg BD PO For patients with BMI >33 or weight >100kg dose should be increased to 500mg BD	Trimethoprim 100mg ON	
Surgery on a lymphoedematous region Or **Undergoing decongestive lymphatic drainage (DLT) with a history of cellulitis triggered by DLT**	Flucloxacillin 1g QDS for 5 days	Doxycycline 200mg OD for 5 days	

3.5.3: Ongoing management of antibiotic prophylaxis

The need and effectiveness of antibiotic prophylaxis should be reviewed at least annually.

- Patients with recurrent limb cellulitis despite prophylaxis should be discussed with a microbiologist.
- Patients with anogenital cellulitis who have cellulitis despite penicillin V should be switched to trimethoprim prophylaxis in the first instance. If further episodes occur, they should be discussed with a microbiologist.

If patients have had no further episodes of cellulitis for one year, and any modifiable risk factors have been addressed, consider stopping antibiotic prophylaxis. If the patient has had no episodes after 2 years then antibiotic prophylaxis should be stopped.

Prophylaxis may need to be life-long if relapse occurs after prophylactic antibiotics have been discontinued and there are persistent risk factors. However, ongoing regular review (at least annually) is still recommended for those on long term prophylaxis. Discontinuation should be reconsidered if risk factors have improved at any stage.

4. Education and Training

None required

5. Monitoring and Audit Criteria

All guidelines should include key performance indicators or audit criteria for auditing compliance,

if this template is being used for associated documents (such as procedures or processes) that support a Policy then this section is not required as all audit and monitoring arrangements will be documented in section 8 of the Policy.

Key Performance Indicator	Method of Assessment	Frequency	Lead
Cases of infected lymphoedema failing to respond to empirical therapy	Microbiology electronic referrals	ongoing	Microbiology

6. Supporting Documents and Key References

1. Brouillard, Pascal, et al. "Primary lymphoedema." Nature Reviews Disease Primers 7.1 (2021): 77.

2. British Lymphology Society , Guidelines on the Management of Cellulitis in Lymphoedema, Oct 2022

3. Krasagakis K., Valachis A., Maniatakis P., Kruger-Krasagakis S., Samonis G., Tosca A.D. Analysis of epidemiology, clinical features and management of erysipelas. Int. J. Dermatol. 2010;49(9):1012-1017. doi:10.1111/j.1365-4632.2010.04464.x

7. Key Words

List of words, phrases that may be used by staff searching for the Policy on SharePoint

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This table is used to track the development and approval and dissemination of the document and any changes made on revised / reviewed versions

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Appendix 1: