Consensus Document on the Management of Cellulitis in Lymphoedema

Cellulitis is an acute spreading inflammation of the skin and subcutaneous tissues characterised by pain, warmth, swelling and erythema. In lymphoedema, attacks are variable in presentation and, because of differences from classical cellulitis, are often called acute inflammatory episodes. Cellulitis will be the term used here (related terms: erysipelas, lymphangitis). Most episodes are believed to be caused by *Group A Streptococci* (Mortimer 2000, Cox 2009). However, microbiologists consider *Staph aureus* to be the cause in some patients (e.g. Chira and Miller, 2010).

Some episodes are accompanied by severe systemic upset, with high fever and rigors; others are milder, with minimal or no fever. Increased swelling of the affected area may occur. Inflammatory markers (CRP, ESR) may be raised. It is difficult to predict response to treatment. Cellulitis can be difficult to diagnose and to distinguish from other causes of inflammation particularly in the legs e.g. lipodermatosclerosis. Cellulitis most commonly affects one leg only whereas lipodermatosclerosis more commonly affects both legs.

A recent Cochrane review concluded that it was not possible to define the best treatment for cellulitis in general based upon existing evidence (Kilburn et al 2010). Furthermore, the treatment of cellulitis in lymphoedema may differ from conventional cellulitis.

With this background, this consensus document makes recommendations about the use of antibiotics for cellulitis in patients with lymphoedema, and advises when admission to hospital is indicated. Prompt treatment is essential to avoid further damage to the lymphatics of the affected part which in turn may predispose to repeated attacks.

1. ACUTE ATTACK OF CELLULITIS

1.1. A decision whether hospital admission is indicated should be based on the level of systemic upset i.e. if:

- signs of septicaemia (hypotension, tachycardia, severe pyrexia, confusion, tachypnoea or vomiting) are an absolute indication for admission;
- continuing or deteriorating systemic signs, with or without deteriorating local signs, after 48hrs of antibiotic treatment;
- unresolving or deteriorating local signs, with or without systemic signs, despite trials of first and second line antibiotics.

1.2. Management at home

1.2.1. It is essential that the patient is closely monitored, ideally by the GP. To establish a baseline to monitor progress, record:

- extent and severity of rash – if possible, mark and date the edge of the erythema (may be difficult in lymphoedema as the rash is often blotchy);
- level of systemic upset;

- CRP/ESR/white cell count may be helpful in diagnosis and monitoring of treatment.

- Microbiology of any cuts or breaks in the skin should be considered before antibiotics are started.

1.2.2. Oral amoxicillin 500mg 8-hourly is the treatment of choice. If there is any evidence of *Staph aureus* infection e.g. folliculitis, pus formation or crusted dermatitis, then flucloxacillin 500mg 6-hourly should be prescribed in addition or as an alternative.
Microbiologists suggest that the use of single agent Flucloxacillin for all cellulitis covers both *Strep*. and *Staph*. infections. This is, therefore, an acceptable alternative. (See www.thebls.co.uk or www.lymphoedema.org for more detailed discussion of the relative merits of Amoxicillin and Flucloxacillin).

1.2.3. Patients who are allergic to penicillin should be prescribed erythromycin 500mg 6-hourly or clarithromycin 500mg 12-hourly (see also 3.1-3.3).

1.2.4. If there is no or a poor response (unresolving inflammation or development of systemic symptoms) to oral amoxicillin after 48 hours, then clindamycin 300mg 6-hourly should be substituted as second line oral treatment.

1.2.5. Antibiotics should be continued until all signs of acute inflammation have resolved; this may mean taking antibiotics for 1-2 months and the course of antibiotics should be for **no less** than 14 days from the time a definite clinical response is observed.
Skin changes e.g. discolouration / staining may persist for months or longer following severe cellulitis and do not necessarily require ongoing antibiotics.

1.2.6. Bed rest and elevation of the affected part is essential. Avoid compression garments during the acute attack. However, they should be replaced as soon as the affected area is comfortable enough to tolerate them.

1.2.7. Appropriate analgesia, e.g. paracetamol, as necessary. It is probably advisable to avoid NSAIDS e.g. ibuprofen during the acute attack. On occasions these medications may be associated with rare complications such as necrotizing fasciitis.

1.2.8. When the inflammation is sufficiently reduced, wearing of compression garments and normal levels of exercise may resume. A return to work depends on the patient's occupation, and there being no deterioration when normal levels of exercise are established.

1.2.9. Unusual circumstances, e.g. animal bite or lick preceding an attack, or a failure of infection to respond to the recommendations above, should prompt discussions with a local microbiologist.

1.3. Management in hospital

1.3.1. Choice of antibiotics in hospital is usually made according to local guidelines. Hospital guidelines commonly recommend single agent iv Flucloxacillin 2g 6hly, as this is felt to cover both *Staph.* and *Strep.* infections (Leman and Mukherjee, 2005)

1.3.2. If there is no or a poor response to this regimen after 48 hours, clindamycin 600mg 6-hourly iv should be substituted.

1.3.3. Penicillin allergic patients should receive clindamycin as in 1.3.2.

1.3.4. For the treatment of ano-genital cellulitis the recommended first line treatment is amoxicillin 2g 8-hourly iv plus gentamicin 5mg/kg iv daily; dose to be adjusted according to renal function and assay. NB: Local hospital guidelines may differ from this.

1.3.5. Monitoring of CRP / ESR / WCC / temperature is recommended and microbiology of any cuts or breaks in the skin before antibiotics started. Blood cultures may be appropriate.

1.3.6. Extent and severity of rash – if possible, mark and date the edge of the erythema (may be difficult in lymphoedema as the rash is often blotchy).

1.3.7. A switch to oral treatment with amoxicillin 500mg 8-hourly, or clindamycin 300mg 6-hourly should not be made before:

• Temperature down for 48 hours;

• Inflammation much resolved;

• CRP falling.

then continue as in 1.2.5 to 1.2.9.

1.4. Antibiotics "in case"

1.4.1. The risk of further attacks of cellulitis in lymphoedema is high. It is recommended that patients who have had an attack of cellulitis should carry a two week supply of antibiotics with them particularly when away from home for any length of time, e.g. on holiday. Amoxicillin 500mg tds is recommended or, for those allergic to penicillin, erythromycin 500mg qds or clarithromycin 500mg bd. Antibiotics should be started **immediately** familiar symptoms of cellulitis develop but a medical opinion should be sought as soon as possible.

1.5. Preventing or reducing recurrent episodes of cellulitis

1.5.1. There is evidence that decongestive lymphatic therapy (DLT) reduces the frequency of attacks (Ko et al 1998). Control of the swelling is therefore important. Patients undergoing intensive DLT and known to have suffered cellulitis in the past during DLT may benefit from antibiotic cover in case cellulitis is provoked.

- Patients who have not experienced previous episodes of cellulitis do not require antibiotics during intensive treatments.

- It is recommended that patients with a history of previous episode(s) of cellulitis during DLT are prescribed a therapeutic course of antibiotics for the duration of the intensive treatment (as per points 1.2.2 or 1.2.3).

1.5.2. Patients undergoing surgical procedures such as knee replacement or carpal tunnel surgery on the lymphoedematous region should receive a therapeutic course of antibiotics commenced before surgery (oral or iv as appropriate) as described previously (see points 1.2.2 or 1.2.3) or as indicated by the procedure.

1.5.3. There is evidence that specialist lymphoedema surgery in combination with optimised conservative treatment in carefully selected patients may reduce the frequency of cellulitis.

2. RECURRENT CELLULITIS

2.1. Antibiotic prophylaxis should be considered in patients who have two or more attacks of cellulitis per year. Penicillin V 250mg bd (500mg bd if BMI ≥ 33, refer to end for guide) should be the first choice. Prophylaxis may need to be life-long if relapse occurs when antibiotics are discontinued after a two year period of successful prophylaxis. For those allergic to penicillin, erythromycin 250mg bd is recommended; if this is not tolerated then clarithromycin 250mg daily is an alternative (see also 3.1-3.3). It is recommended that patients requiring antibiotic prophylaxis for ano-genital cellulitis should receive trimethoprim 100mg daily taken at night.

2.2. Apart from the swelling, other risk factors for recurrent cellulitis including cracked, macerated, inter-digital skin, dermatitis, open wounds including leg ulcers, and weeping lymphangiectasia (leaking lymph blisters on the skin surface) should be treated. Treatment of inter-digital fungus should be with application of terbinafine cream daily for two weeks. This may be followed by maintenance treatment, providing the skin is unbroken, with alcohol wipes daily.

2.3. It may not be possible to fully prevent further episodes of cellulitis even with prophylactic antibiotics. However, there may be a reduction in the frequency of cellulitis and / or the severity of episodes. If the response to first line prophylactic antibiotics is inadequate then alternative strategies including trials of other prophylactic antibiotics e.g. clindamycin 150mg daily or cefalexin 125mg daily or doxycycline 50mg daily may need to be considered. In these circumstances, review by local specialist lymphoedema services and advice from microbiologists is recommended. There is a need to balance the use of certain antibiotics (e.g. clindamycin, cefalexin) as prophylaxis against the risk of predisposing to C.difficile infections.

2.4. The Health Protection Agency's 2008 annual report on antimicrobial resistance and prescribing reported that no resistance to penicillin has been observed in the UK or elsewhere when prescribed for the treatment of group A Streptococci.

3. DRUG INTERACTIONS

3.1. It is recommended that the prescriber checks individual drug interactions particularly when prescribing macrolides e.g. erythromycin, and clarithromycin. The most common interactions are outlined below (3.3-3.4).

3.2. Patients who have experienced an anaphylactic reaction to penicillin should not be given antibiotics from the cephalosporin family e.g. cefuroxime, cefotaxime, ceftazadime and cefalexin.

3.3. For patients receiving a statin e.g. simvastatin or atorvastatin who are penicillin allergic (not anaphylaxis) the recommended first line antibiotics are cefalexin 500mg taken 8-hourly or doxycycline 200mg taken for the first day and then 100mg daily (please refer to 1.2.5 for details of the length of antibiotic course). Patients requiring prophylactic antibiotics should be offered cefalexin 125mg taken at night or doxycycline 50mg daily.

3.4. It is known that many of the different groups of antibiotics alter the anti coagulant effect of coumarins e.g. warfarin. It is advised that the interactions are checked before prescribing antibiotics for patients receiving coumarins.

4. RECOMMENDATIONS FOR THE TREATMENT OF CELLULITIS IN CHILDREN WITH LYMPHOEDEMA

4.1. As in adults, cellulitis in children may present with local symptoms of pain, discomfort, redness or swelling with or without general ill health and malaise. It is important to treat early and recognise that those children who present with systemic symptoms of infection or have deteriorating local signs should be seen in hospital and treated aggressively with intravenous antibiotics.

4.2. The management of cellulitis in children with lymphoedema should follow the previous sections (1-3) with reference to appropriate documents (e.g. BNF) to determine the required antibiotic dose(s).

4.3. It has been suggested that children requiring hospital admission should receive amoxicillin plus flucloxacillin. If there is any suspicion of toxic shock syndrome clindamycin should be prescribed in addition to amoxicillin and flucloxacillin.

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BMI approximate calculations (to be used if unable to obtain height and weight)

At 5 foot 2 inches (1.58m) an individual would have a BMI of >33 if they weighed more than 12 stone 13lbs (82kg).

At 5 foot 4 inches (1.62m) an individual would have a BMI of >33 if they weighed more than 13 stone 8lbs (86kg).

At 5 foot 7 inches (1.7m) an individual would have a BMI of >33 if they weighed more than 15 stone (95kg).

At 5 foot 10 inches (1.78m) an individual would have a BMI of >33 if they weighed more than 16 stone 10lbs (106kg).

At 6 foot 1 inches (1.86m) an individual would have a BMI of >33 if they weighed more than 17 stone 13lbs (114kg).

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We welcome any comments from users (to be directed to vaughan.keeley@derbyhospitals.nhs.uk).

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The LSN has produced a fact sheet based on the Consensus Document, 'Management of Cellulitis in Lymphoedema'.

Order forms are available on the LSN website or from the LSN office.
Website: www.lymphoedema.org
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Consensus Document on the Management of Cellulitis in Lymphoedema: Flucloxacillin versus Amoxicillin.

Flucloxacillin is commonly recommended as the drug of choice for the treatment of cellulitis (CREST 2005, Eron et al. 2003). The rationale for choosing flucloxacillin is that it has an effect on streptococcal bacteria as well as staphylococcal. However, the general view amongst lymphoedema specialists in the UK is that streptococci are the major cause of cellulitis in lymphoedema and therefore anti-streptococcal antibiotics are preferred (Mortimer 2000, Cox et al 1998).

The decision by the consensus group to recommend amoxicillin as the first line oral antibiotic is based on a combination of the experience of the group and from the available literature.

The main factors considered were:

1. The effectiveness of both antibiotics against streptococcal infections.
2. Tissue penetration.
3. The side effect profile.
4. The reported drug resistance.

1. Although both antibiotics are effective against Group A beta haemolytic streptococci, the minimum inhibitory concentration for amoxicillin is lower than that for flucloxacillin (≤0.03μg/ml for amoxicillin versus and 0.1 μg/ml for flucloxacillin) (Istre el at 1981, Medsafe, accessed 19.02.2010).

2. The penetration of different antibiotics into lymphoedematous tissue is not established but evidence would suggest that it is likely to be better for amoxicillin than flucloxacillin. Wise et al (1980) studied the penetration of six antibiotics, including amoxicillin (low protein binding) and flucloxacillin (highly protein bound), into tissue fluid obtained from blisters. The study applied the theory that only the protein-free fraction of an antibiotic can act against bacteria and therefore if other factors are equal, a drug with low protein binding should be superior to one with higher binding. This study concluded that the penetration of antibiotic into the blister fluid was not affected by serum protein binding unless that binding is very high and this difference was demonstrated when amoxicillin was compared to flucloxacillin. The more highly bound flucloxacillin achieved blister fluid levels of about one third of those of amoxicillin.
A contrasting study by Bergan et al (1986) studied the passage of intravenous administration of flucloxacillin into peripheral lymph and skin blisters. This study identified that this highly protein bound antibiotic demonstrated good tissue penetration. It did, however, demonstrate slightly delayed passage into extravascular sites with slightly later peak concentrations and persistently lower levels in extravascular fluid than in serum, as might be expected when compared with an antibiotic that is not protein bound.

3. Anecdotally, patients seem to tolerate amoxicillin better than flucloxacillin. However, the side effect profile, taken from the electronic Medicines Compendium, for both drugs is similar with common side effects (incidence between 1/100-1/10) including gastrointestinal disorders. Skin rashes have been recognised as a common side effect of oral amoxicillin and an uncommon side effect (1/1000-1/100) of

flucloxacillin. The reported side effects were taken from data collected 6000 patients taking amoxicillin and 929 taking flucloxacillin.

4. The Health Protection Agency's 2008 annual report on antimicrobial resistance and prescribing reported resistance to clindamycin, erythromycin and tetracycline in group A streptococci. However, no resistance to penicillin has been observed in the UK or elsewhere so there is no particular advantage of either amoxicillin or flucloxacillin in this regard.

Conclusion:
Although the consensus group favours amoxicillin as the first line oral antibiotic for treating cellulitis in lymphoedema, flucloxacillin is considered to be an acceptable alternative.

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