BRITISH JOURNAL OF HOSPITAL MEDICINE

CORE TRAINING FOR DOCTORS

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Diagnosis and management of cellulitis and erysipelas

Cellulitis and erysipelas result from bacteria infection and present as a spreading, tender and erythematous rash. Most frequently they are caused by Gram-positive bacteria which are able to penetrate into soft tissue through a breach in the skin. They make up approximately 3% of all acute hospital admissions in the UK, accounting for significant morbidity and considerable financial burden to the NHS.

Diagnosis is primarily based on the clinical syndrome with adjunctive laboratory-based blood testing. Depending upon the site of infection other diagnoses may need exclusion through specific investigations. Treatment is with empirical antimicrobials in most circumstances.

Large-scale controlled trial evidence for specific antimicrobial choices in the treatment of cellulitis and erysipelas is lacking, with national and local guidelines being based on a combination of best evidence, local epidemiology data and expert opinion. Outpatient parenteral antimicrobial therapy and long-term chemoprophylaxis are emerging methodologies for the management of these conditions.

This article reviews the current evidence and guidelines for the diagnosis, management and prevention of cellulitis.

Cellulitis and erysipelas are bacterial infections resulting in inflammation of the skin and underlying soft tissue. Clinically there is evidence of an acute onset, tender, spreading erythematous rash with or without systemic upset (Stevens, 2010). Both conditions are widely considered part of the same pathological process (Kilburn et al, 2010).

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Cellulitis is an infection primarily affecting the deep epidermis and dermis. The most common causative organisms are *Staphylococcus aureus* and beta-haemolytic streptococci (Bannister et al, 2006). These bacteria are common commensals on human skin but cause pathology when they breach its surface. *Table 1* highlights some other notable pathogens (Eron et al, 2003; Stevens, 2010).

Erysipelas is a more superficial infection affecting the upper epidermis and superficial lymphatics. The vast majority of cases are caused by exotoxins released by *Streptococcus pyogenes* (Bannister et al, 2006).

Epidemiology

Cellulitis most commonly affects the lower limbs. Toe web intertrigo, fungal infections, wounds or ulceration allow bacterial entry into soft tissues. Iatrogenic cellulitis may develop as a result of medical procedures such as venous cannulation or around surgical wounds. Inflammatory skin diseases such as eczema are at risk of secondary infection (Stevens, 2010).

Cellulitis most commonly affects adults and the elderly while erysipelas is often a disease of young children and the elderly. Patients who are immunocompromised, have peripheral vascular disease, and those with venous stasis of the lower limbs are at an increased risk of infection (Bannister et al, 2006).

There are approximately 200 cases of cellulitis per 100 000 patients each year in the UK with 82 113 hospital admissions in 2008/9. Of these the mean length of hospital stay was 7.2 days. The cost to the NHS for bed stays as a result of cellulitis has been estimated as £133 million per annum (Phoenix et al, 2012).

Clinical presentation

Cellulitis presents acutely as an erythematous, hot and tender, pink rash with poorly defined margins. Erysipelas causes a vivid red rash that is raised from the surrounding skin and has a clearly demarcated border

(Stevens, 2010). Involvement of the pinna (Milian's sign) is specific to erysipelas (Madke and Nayak, 2012).

In addition to the rash there may be associated ulceration, blister development, purulent discharge, soft tissue oedema, abscess formation and lymphadenopathy. Cellulitis is also often associated with features of systemic upset (Bannister et al, 2006).

Necrotizing fasciitis is a severe potential complication of cellulitis, which is characterized by rapidly spreading destruction of soft tissues and fascia and has a mortality rate of approximately 30%. Management is principally surgical with adjunctive antimicrobial therapy (Huang et al, 2011).

Several classification systems for the severity of cellulitis and erysipelas have been put forward although none have an objectively validated evidence base (Marwick et al, 2011). The most widely used divides patients into four classes based on the clinical presentation and comorbidities and is summarized in *Table 2* (Eron et al, 2003).

Diagnosis

The diagnosis of cellulitis and erysipelas is principally a clinical one based on the appearance of the rash and associated clinical features (*Figures 1–3*). Differential diagnoses include deep vein thrombosis, varicose eczema and peripheral oedema (Clinical Resource Efficiency Support Team, 2005).

Laboratory blood testing may show a raised white cell count with a predominant neutrophilia and a raised C-reactive protein level. Normal biochemical markers do not exclude disease (Phoenix et al, 2012).

Swabs of intact skin sent for culture are of no benefit, but open wounds swabs are useful for determining antimicrobial sensitivities. Blood cultures are positive in just 5% of cases and are recommended only where there are features of systemic upset

Table 1. Likely causative organism of cellulitis in specific settings or with given risk factors

Setting or risk factor	Likely causative organism
Buccal cellulitis	*Haemophilus influenzae*
Cellulitis in neonates	Group B beta-haemolytic streptococci
Crepitus cellulitis	*Clostridium* spp
Diabetes mellitus, peripheral vascular disease	*Staphylococcus aureus*, group B streptococci, *Streptococcus agalactiae*
Dog and cat bites	*Pasteurella multocida, Capnocytophaga canimorsus*
Exposure to a hot tub	*Pseudomonas aeruginosa*
Handling raw fish, erysipeloid	*Erysipelothrix rhusiopathiae*
Human bite	*Eikenella corrodens, Fusobacterium* spp., *Strep. pyogenes*
Immunocompromised host	*P. aeruginosa*
Laceration in fresh water	*Aeromonas hydrophila*
Laceration in sea water	*Vibrio vulnificus*
Liver cirrhosis	*Campylobacter fetus, Klebsiella pneumoniae*
Orbital and periorbital cellulitis	*S. aureus, Strep. pneumoniae, H. influenzae*
Reptile contact	*Salmonella* spp.
Venous stasis, saphenous venectomy	Group A, C or G beta-haemolytic streptococci

From Eron et al (2003), Stevens (2010)

Table 2. Classification of the severity of cellulitis and erysipelas based on clinical presentation

Class	Clinical
1	The patient is systemically well with no evidence of sepsis and no relevant comorbidities (e.g. diabetes mellitus, peripheral vascular disease)
2	The patient is systemically ill with fever but has no relevant comorbidities or the patient is systemically well but has one or more relevant comorbidity
3	The patient is systemically ill and has one or more relevant comorbidity or there is limb-threatening infection
4	The patient is septic (tachycardia, tachypnoea, hypotension and fever) or there is evidence of life-threatening infection (e.g. necrotizing fasciitis)

From Eron et al (2003)

Figure 1. Reddening as a result of erysipelas on a man's face.

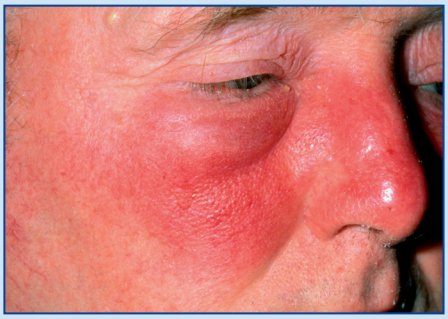

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Figure 2. Cellulitis of the foot.

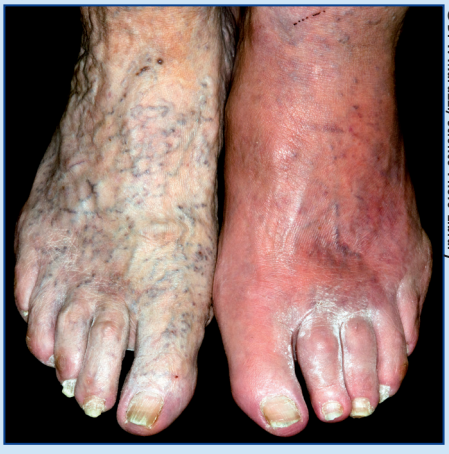

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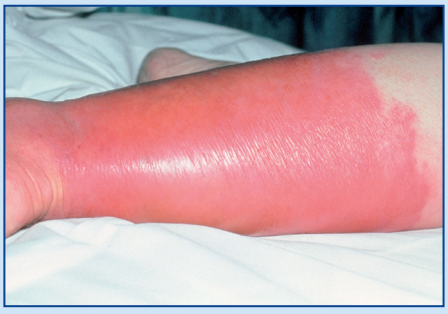
Figure 3. Inflammation as a result of cellulitis on the lower leg.



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(Clinical Resource Efficiency Support Team, 2005). Cultures of pus or bullae fluid are more likely to yield positive results and should be performed if possible. Imaging may be useful in excluding potential differential diagnosis or complications (Phoenix et al, 2012).

Management

Clinical assessment

The specific management of cellulitis and erysipelas depends upon the location and severity of the infection and patient comorbidities. Simple measures include analgesia, elevation and rest (Phoenix et al, 2012). Management of fever may be achieved with antipyretics and adequate hydration is essential (Clinical Resource Efficiency Support Team, 2005). The rash should be delineated and reviewed regularly so that response to treatment may be assessed.

If there is clinical evidence of sepsis (*Figure 4*) then particular care needs to be taken when deciding where and how to manage a patient. The Survive Sepsis campaign and the UK Sepsis Trust (Daniels et al, 2011) advise that completing the 'sepsis six' investigations and treatments reduces overall sepsis mortality by 50%. This includes:

1. High flow oxygen therapy
2. Blood cultures
3. Treatment with broad spectrum antimicrobials
4. Give an intravenous fluid challenge
5. Measure serum lactate
6. Accurate hourly urine output (a urinary catheter may be necessary).

Figure 4. Clinical definition of systemic inflammatory response syndrome and sepsis. From Nystrom (1998).

Systemic inflammatory response syndrome is defined as the presence of two or more of the following parameters:

- Core body temperature <36°C or >38°C
- Heart rate >100 beats per minute
- Respiratory rate >20 breaths per minute or $PaCO_2$ <4.3 kPa
- Total white cell count <$4x10^9$ cells/litre or >$12x10^9$ cells/litre (or >10% left shift, i.e. neutrophilia)

When there is concurrent evidence of infection a clinical diagnosis of sepsis can be made

Antimicrobial treatment

Despite the significant burden of cellulitis and erysipelas, the evidence base for antimicrobial choices is lacking. A Cochrane review (Kilburn et al, 2010) assessed 25 studies of cellulitis but was unable to draw definitive conclusions for antimicrobial choices. The Clinical Resource Efficiency Support Team (2005) published recommendations for antimicrobial choices in cellulitis, summarized in *Table 3*.

While the Clinical Resource Efficiency Support Team (2005) offers general recommendations, local guidelines should be followed where they are available. These are based on regional patterns of bacterial resistance and are more frequently updated to take account of changing pathogenicity and novel evidence. Narrow spectrum antimicrobials, targeting the most probable causative organisms, are generally preferred in the first instance for the treatment of cellulitis and erysipelas. Emerging antimicrobial resistance must also be considered and where there is any uncertainty as to antimicrobial choices, specialist advice should be sought from clinical microbiologists.

Response to treatment should be assessed based on clinical features, patient observations and biochemical markers. The Clinical Resource Efficiency Support Team (2005) notes that the appearance of the rash may worsen in the first 48 hours. However, patients who fail to respond to 48 hours of treatment should be promptly discussed with clinical microbiologists and the diagnosis should be reviewed. In particular, resistant organisms should be considered.

There is little evidence for continuation of intravenous therapy beyond 3 or 4 days. Clinical Resource Efficiency Support Team (2005) advise that switching to oral antimicrobials should be considered when a patient has been afebrile (<37.8°C) for 48 hours, biochemical markers of infection are reducing, there is clinically apparent improvement and relevant comorbidities have been stabilized. However, there are few data from research studies and clinical judgement should be used on an individual basis. A total of 1–2 weeks of antimicrobial treatment is usually sufficient for cellulitis and erysipelas, but clinical judgement should again be used when deciding on treatment cessation (Clinical Resource Efficiency Support Team, 2005).

Antimicrobial treatment of cellulitis caused by meticillin-resistant *Staphylococcus aureus*

Cellulitis caused by meticillin-resistant *Staphylococcus aureus* (MRSA) presents a specific therapeutic challenge, as most commonly used antimicrobials are ineffectual. The British Society for Antimicrobial Chemotherapy (Gemmell et al, 2006) recommends the use of glycopeptides (e.g. teicoplanin) or linezolid for the treatment of cellulitis caused by MRSA where there is a high risk of bacteraemia. They suggest tetracyclines should be used more widely for less severe infections and combination treatment of rifampicin/glycopeptide with fusidic acid should be considered where single agent therapy has failed. In addition they advise the use of clindamycin in MRSA infections susceptible to erythromycin.

Outpatient parenteral antimicrobial therapy

Outpatient parenteral antimicrobial therapy is an increasingly common method for

Table 3. Recommended antimicrobial choices for the treatment of cellulitis

Cellulitis	Empirical antimicrobial	Penicillin allergy
Class 1	Flucloxacillin 500 mg four times daily (oral)	Clarithromycin or clindamycin
Class 2 and 3	Flucloxacillin 2 g four times daily (intravenous)	Clarithromycin or clindamycin
Class 4 (necrotizing fasciitis)	Benzylpenicillin 2.4 g 4-hourly (intravenous) + clindamycin 900 mg three times daily (intravenous)	Clarithromycin or clindamycin
Human bite	Co-amoxiclav	Clarithromycin
Dog/cat bite	Co-amoxiclav	Doxycycline + metronidazole
Fresh water exposure	Flucloxacillin + ciprofloxacin	Clarithromycin + ciprofloxacin

From Clinical Resource Efficiency Support Team (2005)

treating patients who are deemed to required intravenous antimicrobials but not admission to an acute hospital bed. For practical reasons different antimicrobial agents are often used, commonly ceftriaxone and teicoplanin, which are given once daily or less frequently, therefore limiting the disruption to the life of the patient (Chapman et al, 2009).

Patients may be eligible for outpatient parenteral antimicrobial therapy if it is their first presentation with cellulitis or erysipelas, there is no evidence of sepsis, they have no unstable comorbidities and their home situation permits. The final decision regarding this may be subjective and should be made by a senior clinician. Corwin et al (2005) found that approximately 30% of patients presenting to an acute hospital with cellulitis were suitable for outpatient parenteral antimicrobial therapy.

The cost of outpatient parenteral antimicrobial therapy is less than 50% of a hospital admission for the same patient and patient satisfaction has been shown to be higher. Of 344 patients with cellulitis managed by a Sheffield-based outpatient parenteral antimicrobial therapy service, 87% were cured at the end of their treatment as defined by the study, and only 6.3% required later admission to hospital (Chapman et al, 2009). Outpatient parenteral antimicrobial therapy is therefore advised for use where possible and clinically appropriate (Phoenix et al, 2012).

Prophylaxis

Cellulitis and erysipelas have a high recurrence rate post treatment – estimations suggest approximately 30% of cases will recur within 3 years of treatment. Venous stasis and lymphoedema are the most common predisposing factors for recurrence. A systematic review and meta-analysis by Oh et al (2014) showed that antimicrobial prophylaxis significantly reduced the number of patients developing recurrent cellulitis with a risk ratio of 0.46 (95% confidence interval 0.26–0.79). Currently, 1–2 years of penicillin V or erythromycin is recommended for prophylaxis in patients who have had more than one previous episode of cellulitis by the Clinical Resource Efficiency Support Team (2005).

Conclusions

Cellulitis and erysipelas are a common cause of morbidity and hospital admission in the UK, accounting for a significant cost to the NHS. However, as yet there have been no large clinical trials comparing the available antimicrobials or analysis of how they should be used. Current national guidelines by the Clinical Resource Efficiency Support Team are based on a combination of best evidence and expert opinion.

While this generic UK-wide guidance exists, many hospitals have developed their own antimicrobial usage policies based on local antimicrobial resistance patterns in consultation with clinical microbiologists. Clinical judgement plays an important role in diagnosis and risk stratification and final decisions regarding patient management should therefore be made by a senior clinician experienced in managing the disease.

Large scale controlled trials are still required to provide definitive evidence for specific antimicrobial choices when treating cellulitis and erysipelas and to provide further evidence for the use of outpatient parenteral antimicrobial therapy and chemoprophylaxis. BJHM

Conflict of interest: none.

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KEY POINTS

- Cellulitis and erysipelas are commonly caused by Gram-positive bacteria and present as acute onset, spreading and tender erythematous rashes with or without associated systemic upset.
- They are common and lead to significant morbidity as well as a considerable financial burden on the NHS.
- Diagnosis is primarily clinical but may be aided by laboratory-based blood tests and radiological imaging.
- Empirical antimicrobial therapy in association with supportive measures and symptom management form the mainstay of treatment for cellulitis and erysipelas.
- There is a paucity of high quality trial data for appropriate antimicrobial choices and therefore current treatment guidelines are based on best evidence and expert opinion.
- Outpatient parenteral antimicrobial therapy and long-term chemoprophylaxis are emerging methodologies for the improved management of patients with cellulitis and erysipelas.