

Diagnosis and management of cellulitis

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Cellulitis is an acute, spreading, pyogenic inflammation of the lower dermis and associated subcutaneous tissue. It is a skin and soft tissue infection that results in high morbidity and severe financial costs to healthcare providers worldwide. Cellulitis is managed by several clinical specialists including primary care physicians, surgeons, general medics, and dermatologists. We assess the most recent evidence in the diagnosis and management of cellulitis.

What is the extent of the problem?

In 2008-9 there were 82 113 hospital admissions in England and Wales lasting a mean length of 7.2 days¹; an estimated £133m (€170m; \$209m) was spent on bed stay alone.² Cellulitis accounted for 1.6% of emergency hospital admissions during 2008-9.³

In Australia, hospital admissions for cellulitis have risen to 11.5 people per 10 000 (2001-2) with the average admission lasting 5.9 days.⁴ In the US more than 600 000 hospitalisations were recorded in 2010,⁵ representing 3.7% of all emergency admissions.⁶ In all, 14.2 million Americans visited primary care physicians, hospital outpatient departments, and emergency services with skin and soft tissue infections in 2005, an increase from 321 to 481 visits per 100 000 (50% increase; P=0.003) since 1997. Over 95% of this change was attributed to

SOURCES AND SELECTION CRITERIA

We searched PubMed and the Cochrane library for recent and clinically relevant cohort studies and randomised controlled trials on cellulitis, using the search terms “cellulitis”, “erysipelas”, “diagnosis”, “investigation”, “recurrence”, “complications” and “management”. For position statements and guidelines we consulted the British Lymphology Society (BLS), National Health Service Clinical Knowledge Summaries (CKS), Clinical Resource Efficiency Support Team (CREST), and Infectious Disease Society of America (IDSA).

abscesses and cellulitis. Hospital visits for abscesses and cellulitis have increased from 173 to 325 per 1000 population (88% increase; P<0.001).⁷

What causes cellulitis?

Cellulitis is caused by a wide range of organisms (see table 1). The majority of cases are caused by *Streptococcus pyogenes* or *Staphylococcus aureus*. A review of prospective and retrospective laboratory studies found that *S aureus* accounted for 51% of all aspiration and punch biopsy cultures positive for cellulitis, and *Streptococcus* accounted for 27%.⁸

A prospective study demonstrated that the majority of *S aureus* infections in the US are now methicillin resistant; among 389 blood culture isolates of *S aureus*, 63% (244) were CA-MRSA.¹⁴

A multicentre study of 11 US hospitals reported a prevalence of MRSA ranging from 15% to 74% (59% overall).¹⁵ A recent review reports an increase in CA-MRSA rates in Europe.¹⁶

Who is at risk of cellulitis?

No link with age or gender has been established. However, a recent prospective case controlled study comprising 150 patients with cellulitis and 300 controls found white people to be at higher risk.¹⁷ Alcohol intake and smoking have been disproved as risk factors in case-control studies.¹⁸

Commonly identified risk factors are listed in the box. General systemic risk factors include venous insufficiency, regarded to be the most frequent¹⁹; lymphoedema, both a predisposing factor and a complication of cellulitis²⁰; peripheral vascular disease; diabetes mellitus; and obesity.⁹ Local factors include tinea pedis, ulcers, trauma, and insect bites.⁹

Can cellulitis be prevented in those at risk?

Besides the management of lymphoedema, there is no evidence to support the active management of other risk factors including diabetes mellitus, peripheral vascular disease, and tinea pedis.

In lymphoedema, decongestive lymphatic therapy, con-

Table 1 | Treatment recommendations for cellulitis based on organisms⁹⁻¹³

| Clinical presentation | Organism | Antibiotic |
|--|--------------------------------|--|
| Typical cellulitis | <i>Streptococcus pyogenes</i> | Amoxicillin or flucloxacillin |
| Typical cellulitis—pus forming | <i>Staphylococcus aureus</i> | Flucloxacillin |
| Typical cellulitis in the US—pus forming | CA-MRSA, HA-MRSA | Doxycycline or minocycline or clindamycin or vancomycin |
| Penicillin allergy | NA | Erythromycin or clarithromycin or clindamycin |
| Cat or dog bite | <i>Pasteurella multocida</i> | Co-amoxiclav; if allergic to penicillin: doxycycline and metronidazole |
| Freshwater exposure | <i>Aeromonas hydrophila</i> | Ciprofloxacin |
| Saltwater exposure | <i>Vibrio vulnificus</i> | Doxycycline |
| Necrotising fasciitis | <i>Clostridium perfringens</i> | Benzylpenicillin, ciprofloxacin, and clindamycin |
| Butchers and fish handlers | <i>Erysipelothrix</i> | Ciprofloxacin |

SUMMARY POINTS

Cellulitis episodes in the United States, the United Kingdom, and Australia have risen over the past decade, with an increase in community acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA) cases of cellulitis in the US, and to a lesser extent the UK and Australia. Antibiotic resistant strains of CA-MRSA are already emerging
Diagnosis is based on clinical findings with investigations lending weight to confirm or refute diagnosis

Existing guidelines need revision, taking into consideration CA-MRSA and other emerging strains as well as using new clinical classification systems such as the Dundee criteria

Use outpatient parenteral antibiotic therapy if available

More randomised control trials assessing the management of predisposing factors and long term therapy for recurrent cellulitis are required

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Previous articles in this series

- ▶ Management of osteoarthritis of the knee (*BMJ* 2012;345:e4934)
- ▶ Management of difficult and severe eczema in childhood (*BMJ* 2012;345:e4770)
- ▶ Management of chronic epilepsy (*BMJ* 2012;345:e4576)
- ▶ The diagnosis and management of tinea (*BMJ* 2012;345:e4380)
- ▶ Perioperative management of patients taking treatment for chronic pain (*BMJ* 2012;345:e4148)

Predisposing risk factors for lower limb cellulitis^{9 17}

General

Non-modifiable—pregnant; white race
Modifiable—venous insufficiency; lymphoedema; peripheral arterial disease; immunosuppression; diabetes

Local

Non-modifiable—trauma; animal and insect bites; tattoos
Modifiable—ulcers; eczema; athlete's foot (tinea pedis); burns

sisting of manipulation of the lymphatic system through massage, has been associated with reduced recurrence of cellulitis. In a prospective study of 299 people who underwent decongestive lymphatic therapy the incidence of cellulitis infections decreased from 1.10 to 0.65 infections per person per year.²¹

How is the diagnosis of cellulitis made?

Clinical diagnosis

Cellulitis most commonly affects the lower extremities, and often presents as an acute, tender, erythematous, and swollen area of skin. In severe cases blisters, ulcers, oedema, associated lymphangitis, and lymphadenopathy may be present. Constitutional features include fever and malaise. In the late stages widespread features of sepsis including hypotension and tachycardia may also be present.

Other conditions can masquerade as cellulitis. Several differential diagnoses (see table 2), especially in the lower limbs, can present with similar signs and symptoms. In a recent prospective study of 145 patients, 28% of patients were incorrectly diagnosed with lower limb cellulitis. The diagnosis most commonly mistaken as cellulitis was (venous) stasis dermatitis (37%).²²

In view of the potential for misdiagnosis on clinical observation alone, investigations are sometimes recommended to help confirm or refute the diagnosis.

Blood investigations

In a prospective study of 150 people admitted to the emergency department that examined the feasibility of using C reactive protein level and white cell count as indicators of bacterial infections including cellulitis, white cell counts had a specificity of 84.5% and a sensitivity of 43.0% and C reactive protein had a sensitivity of 67.1%, specificity of 94.8% (positive predictive value 94.6% and negative predictive value 67.9%).²³ An elevated level of C reactive protein is a better indicator of bacterial infection than an elevated white cell count but a normal level of C reactive protein cannot rule out an infection. Blood investigations do not appear to be clinically useful for diagnosis.

Microbiology

Prospective studies have shown true positive rates from blood cultures in those with suspected cellulitis are between 2-4%.^{24 25} In a retrospective study of 757 people admitted to a medical centre with cellulitis, blood cultures were performed for 553 people (73%)—only 11 (2%) were positive. Eight of 11 patients with positive blood cultures were changed from empirical treatment with cefazolin to penicillin. Furthermore, all those in the study, including those with systemic toxicity, recovered, whether a blood culture was taken or not. The cost of negative blood cultures was \$34 950 (£22 255; €28 560) and the cost for the 11 positive cultures was \$1100, amounting to an excess cost of \$36 050. The authors concluded blood cultures were neither clinically effective or cost effective.²⁰ National guidelines, including the Northern Ireland Clinical Resource Efficiency Support Team (CREST) 2005 guidelines on the management of cellulitis in adults, recommend taking blood cultures only in patients that have significant systemic upset including pyrexia (>38°C).¹⁰

In a prospective study of 50 patients with cellulitis, cultures from skin biopsies and aspirations that showed true positives were found to be 20% and 10% respectively.²⁵ CREST guidelines suggest the use of skin biopsies and aspirations in only selected patients, where the diagnosis of cellulitis is in doubt.¹⁰

In regard to wound swabs, a multicentre prospective study from France that analysed wound swab samples from 214 patients with lower limb cellulitis identified 183 (85.5%) positive cultures; *S aureus* and *Streptococcus* being the most frequently isolated micro-organisms (56% and 21% respectively). Sensitivities from the swabs showed resistance to the empirical antibiotics that had initially been used, prompting a change in antibiotics.²⁶ CREST guidelines suggest the use of swabs on open cellulitis wounds.¹⁰

Imaging

Imaging techniques are useful when there is a suspicion of an underlying abscess associated with cellulitis, necrotising fasciitis, or when the diagnosis of cellulitis is uncertain. In a retrospective study of 542 emergency department patients for whom the clinical diagnosis of cellulitis was in doubt, 109 (17%) were found to have a deep vein thrombosis on Doppler ultrasound.²⁷

In a prospective observational study of 216 adult emergency department patients with a clinical diagnosis of lower limb cellulitis, an ultrasonography scan changed the management in 71 patients (56%) in regard to the need for drainage of underlying abscesses. In the pre-test group that were believed not to need drainage of any underlying abscess, ultrasonography resulted in a change in management in 32 of 44 patients (73%), including 16 in whom drainage was eliminated. In the pre-test group that was believed to not need further drainage, ultrasonography changed the management in 39 of 82 (48%), with 33 receiving drainage and six receiving further diagnostic imaging. Ultrasound may therefore guide management of cellulitis by detection of occult abscess, prevention of invasive procedures,

Table 2 | Common differential diagnoses for cellulitis with defining characteristics¹⁰

| Differential | Defining characteristics |
|--------------------------------|--|
| Stasis dermatitis | Absence of pain or fever; circumferential; bilateral |
| Acute arthritis | Involvement of joint; pain on movement |
| Pyoderma gangrenosum | Ulcerations on the legs; history of inflammatory bowel disease |
| Hypersensitivity/drug reaction | Exposure to allergen or drug; pruritus; absence of fever; absence of fever or pain |
| Deep vein thrombosis | Absence of skin changes or fever |
| Necrotising fasciitis | Severe pain, swelling and fever; rapid progression; pain out of proportion; systemic toxicity; skin crepitus; necrosis; ecchymosis |

Table 3 | Eron clinical classification system³⁴

| Class | Systemic toxicity | Comorbidities | Oral v intravenous antibiotics | Outpatient v hospital admission |
|-------|---|--|--|---|
| I | No sign | None | Oral | Outpatient |
| II | May or may not have systemic illness | Peripheral vascular disease, obesity, venous insufficiency | Intravenous | Hospital admission for 48 hours then outpatient parenteral antibiotic therapy |
| III | Significant systemic toxicity—confusion, tachycardia, tachypnoea, hypotension | Unstable | Intravenous | Hospital |
| IV | Sepsis syndrome/necrotising fasciitis | Unstable | Intravenous with or without surgical debridement | Hospital |

and providing guidance for further imaging or consultation.²⁸

Other imaging studies, such as MRI (magnetic resonance imaging) may be useful in those with an equivocal diagnosis of cellulitis or with suspicion of necrotising fasciitis. According to CREST guidelines, the physician should be alert to the possibility of necrotising fasciitis upon presentation of tense oedema, skin necrosis, crepitus, paraesthesia with an elevated white cell count greater than $14 \times 10^9/L$, and in the haemodynamically stable patient an MRI scan is warranted.¹⁰ In a prospective study of 36 patients with a clinical diagnosis of acute infectious cellulitis, MRI demonstrated necrotising fasciitis in 16 people, all of whom underwent surgical debridement. Distinct MRI features were found in people with necrotising soft tissue infections, including hyper-attenuating signals on T2 weighted images at the deep fasciae and poorly defined areas of hyper-intense signal on T2 weighted images within muscles. In cellulitis, signal intensity abnormalities are only within the subcutaneous fat.²⁹

What is the treatment of cellulitis?

General measures include rest, elevation of any affected limbs, and analgesia. The area of cellulitis should be clearly marked and reviewed daily for progression or regression to assess the efficacy of the antibiotic regimen.¹⁰

However, there is still uncertainty regarding the optimal antibiotic choice, duration, and route of antibiotic therapy, and the use of corticosteroids. A recent Cochrane review could not draw any definitive conclusions on the optimal antibiotics, duration, or route of administration from an analysis of 25 randomised controlled trials, as no two trials had compared the same antibiotics.³⁰ A summary of the main antibiotics that are currently recommended in US and UK national guidelines, as well as in large prospective studies, are provided in table 1.

CREST guidelines still recommend amoxicillin or flucloxacillin for the majority of cases of cellulitis caused by

S aureus, *Streptococcus*, or when the organism has not been identified,¹⁰ but clinicians should take into account the rise in CA-MRSA rates. The 2011 Infectious Diseases Society of America national guidelines have now recommended patients with pus forming cellulitis to be treated with antibiotics that target CA-MRSA.¹¹

The efficacy of other agents that target CA-MRSA has been studied. One retrospective cohort study has shown doxycycline or minocycline to be effective in 95% of patients (n=276) with CA-MRSA.¹² Clindamycin is also therapeutic, with susceptibility in isolates as high as 93%. However, the development of resistance is not uncommon and as it associated with cases of *Clostridium difficile*, it should be discontinued on the development of diarrhoea.³¹ In those with severe cellulitis requiring admission to hospital, linezolid and vancomycin were found to have good efficacy.³²

When should a person be admitted to hospital for intravenous antibiotics?

The Cochrane review from 2010 also states the need for further evaluation of oral versus intravenous antibiotics as well as the efficacy of outpatient parenteral antibiotic therapy (OPAT).³⁰

In a prospective study of 205 consecutive adults admitted to a Scottish hospital for cellulitis, 43% were found to be overtreated based on CREST guidelines. The study suggests they possibly could have been managed as outpatients on oral antibiotics.³³ The CREST guidelines determine route of administration based on the Eron clinical classification system, taking into consideration the presence of systemic toxicity and comorbidities.

Eron classification v Dundee classification

The Eron classification is based on expert opinions, and is among the most widely used classification systems for diagnosis and treatment of cellulitis.³⁴ The Eron classification is summarised in table 3.

However, new criteria such as the 2011 Dundee clas-

Table 4 | Eron classification v Dundee classification^{15 33}

| Parameter | Eron (2003) | Dundee (2010) |
|-------------------------------|--|--|
| Strength of evidence | Expert opinion | Retrospective study of 205 consecutive patients |
| Incorporated into guidelines? | CREST and NHS acute trusts | NA |
| Validated? | Yes | Yes |
| Criteria | Comorbidities including obesity and peripheral vascular disease | The importance of comorbidities |
| | Systemic toxicity: pyrexia ($>38^\circ C$), hypotension, tachypnoea, and tachycardia | Obesity and peripheral vascular disease not counted towards hospital admission |
| | | Up to date definition of systemic inflammatory response syndrome (SIRS) |
| | | Standardised and validated early warning scores |

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database Syst Rev* 2010;6:CD004299—the most recent review of randomised controlled trials on various antimicrobial options for cellulitis, with evidence for the most commonly used antibiotics

Thomas K, Crook A, Foster K, Mason J, Chalmers J, et al; for the 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;166:169-78—a recent randomised controlled trial that assessed the efficacy of long term prophylactic penicillin V for recurrent cellulitis. No statistical significance was seen in the reduction in rates of recurrence with penicillin V

Chronic oedema and lymphoedema *BMJ* learning module. <http://learning.bmj.com/learning/module-intro/lymphoedema.html?moduleId=10029385>—*BMJ* module on the diagnosis, investigation, and treatment of lymphoedema associated with cellulitis

Information resources for patients

Cellulitis Support Group. www.mdjunction.com/cellulitis—forums for cellulitis sufferers to discuss various treatment options (free registration required)

ONGOING RESEARCH

UK Dermatology Clinical Trials Network. Prophylactic antibiotics for the treatment of cellulitis at home (PATCH) I study—a multicentre randomised control trial in the UK assessing the efficacy of a one year course of penicillin V prophylaxis versus placebo in patients with recurrent cellulitis

sification are also available³³—a comparison between the two is provided in table 4. Seventy per cent of people that, based on Eron recommendations, would be treated with inpatient stay and intravenous antibiotics meet the criteria for outpatient management based on the Dundee criteria.³³ Further validation of the Dundee criteria is required.

Outpatient parenteral antibiotic therapy (OPAT)

A prospective study on 344 episodes of treatment administered by a UK OPAT service showed that 87% of patients were cured, readmission rate was 6.3%, and patient satisfaction was high. OPAT costs 41% of inpatient costs when calculated using conservative cost measurements. The authors of the study concluded that clinicians should use OPAT where available³⁵; this is supported by CREST guidelines.¹⁰

When should a switch to oral antibiotics be made?

CREST guidelines suggest indications for a switch to oral therapy are apyrexia (<37.8°C) for 48 hours, regression of cellulitis from a clearly marked area (on daily review), and a falling C reactive protein level.¹⁰

When to seek further advice?

CREST and NHS Clinical Knowledge Summaries guidelines suggest that if there is doubt in the diagnosis, atypical presentations, or no improvement in clinical symptoms and signs after 48 hours, then advice from a dermatologist or microbiologist or both should be sought.²⁹

Can recurrence be prevented?

Several prospective and retrospective studies suggest a high proportion of cellulitis sufferers develop recurrent episodes, especially in those with untreated predisposing factors.⁹⁻²⁰ One retrospective study reported 47% recurrence in a cohort of 171 people who had suffered one prior episode.²⁰

Antibiotic prophylaxis

The Dermatology Clinical Trials Networks PATCH II trial (prophylactic antibiotics for the treatment of cellulitis at home II) was a large, multicentre, randomised trial in the UK that assessed the efficacy of 6 months of penicillin V prophylaxis in reducing recurrence. A total of 123 participants were randomised into those treated with penicillin (n=60) versus placebo (n=63); recurrence rates were 20% and 33% respectively (hazard ratio 0.53, 95% confidence interval 0.26 to 1.07, P=0.08) with no difference in the number of adverse effects between both groups.¹³ The authors of this study conclude that there is no statistical significance seen in the reduction of cellulitis rates for penicillin V for prophylaxis, but there are promising results and longer term prophylaxis (for one year) may be required. The PATCH I trial, which assesses one year penicillin V prophylaxis, is under way.¹³ CREST guidelines advise antibiotic prophylaxis with penicillin V or erythromycin for 1 to 2 years in patients with two or more previous episodes of cellulitis.¹⁰

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ANSWERS TO ENDGAMES, p 48 For long answers go to the Education channel on bmj.com

PICTURE QUIZ

A South African man with renal failure and pulmonary shadowing

- 1 The posteroanterior radiograph of the chest shows ground glass shadowing in both lung fields, consolidation in the right middle and lower lobes, and no evidence of cavitation.
- 2 Differential diagnoses include bacterial, viral, or atypical infection; pulmonary oedema; and pulmonary renal syndromes, such as vasculitides and Goodpasture's syndrome.
- 3 Send blood and sputum for culture to look for bacterial infection. Test for viruses in blood and combined nose and throat swab samples. Look for legionella antigen in urine and HIV antibodies in blood. Bronchoalveolar lavage is indicated for the diagnosis of pneumocystis pneumonia. A full immunological screen is also needed to test for vasculitides and Goodpasture's disease.
- 4 Perform renal ultrasound to determine whether the kidneys are of normal size, whether there is evidence of chronic renal disease, and to exclude obstruction. Perform a renal biopsy to look for rapidly progressive glomerulonephritis, acute tubular necrosis, and HIV associated nephropathy.
- 5 Treat pneumocystis pneumonia with co-trimoxazole, and then start antiretroviral therapy for primary HIV infection and HIV associated nephropathy. Treat secondary hypertension associated with renal disease with antihypertensives, such as angiotensin converting enzyme inhibitors. Lastly, haemodialysis is indicated in an HIV positive patient while awaiting consideration of suitability for renal transplantation.

ANATOMY QUIZ

Magnetic resonance imaging of the lumbar spine

- A: Conus medullaris
- B: Root of cauda equina
- C: Annulus fibrosus of L2/3 intervertebral disc
- D: Posterior longitudinal ligament
- E: Nucleus pulposus of L3/4 intervertebral disc
- F: Interspinous ligament
- G: Spinal dura
- H: Rectum

STATISTICAL QUESTION

Statistical tests for independent groups: time to event data

The log rank test (answer c) would have been used to compare treatment groups in the time until healing of the reference leg ulcer.