Prophylactic antibiotics for the prevention of cellulitis

UK Dermatology Clinical Trials Network's PATCH Study Group

Abstract

Background: Cellulitis of the lower leg accounts for 2–3% of hospital admissions (Cox et al, 1998), with an average length of in-patient stay of nine days. Studies have reported that up to half of these patients suffer further episodes (Cox et al, 1998; Dupuy et al, 1999). Reducing the recurrence of cellulitis could therefore have a significant impact on both patient morbidity and NHS costs. *Aims:* To assess whether prophylactic antibiotics prescribed after an episode of cellulitis of the leg results in fewer subsequent attacks and reduced health service costs. *Methods:* This article describes two related studies in which participants are randomised to receive either 12 months of prophylaxis (PATCH I) or six months of prophylaxis (PATCH II) (PATCH, prophylactic antibiotics for the treatment of cellulitis at home). The PATCH I study recruits only patients with recurrent disease defined as two or more episodes of cellulitis in the last three years. PATCH II has more open criteria and includes patients with a first episode of cellulitis and also participants with recurrent disease. It is expected that 260 patients will be recruited into PATCH I and 400 patients into PATCH II. *Conflict of interest:* The study is financed through grants from Action Medical Research (PATCH I) and the BUPA Foundation (PATCH II).

Key words

Lymphoedema
Cellulitis
Penicillin
Clinical trial

Cellulitis is a painful and potentially serious spreading infection of the dermis and associated subcutaneous tissues. Erysipelas is an infection of the skin which is more superficial than cellulitis. However, in practice, it is difficult to tell how 'deep' the infection is and so the term cellulitis is most frequently used.

Cellulitis of the lower leg is a common problem and currently accounts for 2–3% of hospital admissions in the UK and has significant morbidity and costs associated with it (Drugs and Therapeutics Bulletin, 2003). The average length of in-patient stay is nine days (Hospital Episode Statistics, Department of Health, 2002–2003), and 25–50% of treated patients suffer further episodes and other morbidity, such as oedema and ulceration (Cox et al, 1998; Dupuy et al, 1999).

Cellulitis often presents as an acute progressive onset of red, painful, hot, swollen and tender area of skin (*Figure 1*). The edge of the area may be well demarcated or more diffuse and can spread rapidly. A general malaise and/or constitutional upset are present in most cases and are often experienced before the localising signs. Cellulitis of the lower leg where ascending erythema and oedema are present, with associated general malaise and fever is usually due to streptococcal infection. Localised cellulitis when associated with a penetrating trauma more usually has *Staphylococcus aureus* as the main causative agent. The major complications of cellulitis include prolonged inpatient treatment, recurrent episodes, chronic oedema (thought to be due to damage to the lymphatic drainage system), ulceration of the leg, septicaemia and, rarely, invasive infection causing necrotising fasciitis and/or streptococcal toxic shock syndrome (Jorup-Ronstrom and Britton, 1987; Cox et al, 1998).

The most common causative organisms involved in cellulitis are *Streptococcus pyogenes* and *S. aureus*. Less common causative agents include *Streptococcus pneumoniae* and *Haemophilus influenzae*. The bacteria have often entered the body via a relatively subtle portal such as toe web fissures (Cox et al, 1998).

Penicillin is the most useful of the commonly used oral antibiotics against streptococci, although other agents such as flucloxacillin are often used when the suspected cause is a staphylococcal infection.

There are numerous risk factors associated with cellulitis of the lower leg, including previous episodes of cellulitis, leg oedema (especially lymphoedema), toe web maceration (often caused by tinea pedis), obesity and diabetes (Dupuy et al, 1999; Roujeau et al, 2004).

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A significant number of patients have recurrent episodes and other complications such as leg ulceration and chronic oedema that may lead to prolonged inpatient care. Recurrent disease is an important problem for people with cellulitis (Cox et al, 2006). The mechanisms of recurrent disease are uncertain and may be multifactorial, for example, a failure to fully eradicate streptococci (perhaps from damaged lymphatics) (Mortimer, 2003). The presence of lymphoedema (Dupuy et al, 1999) and venous insufficiency may be important.

The recently published CREST (Clinical Resource Efficiency Support Team) *Guidelines on the Management of Cellulitis in Adults* (CREST, 2005) recommend antibiotic prophylaxis for one to two years in patients with predisposing conditions, who have had at least two episodes of cellulitis at the same site. The CREST management of cellulitis sub-group aims to increase awareness of the need to improve the diagnosis and management of cellulitis within both primary and secondary care.

Reducing the frequency of recurrent episodes of cellulitis could have a dramatic impact on the treatment of this condition, with significant improvements on patient morbidity and subsequent financial benefits to the NHS (Jorup-Ronstrom and Britton, 1987; Cox et al, 1998; Dupuy et al, 1999). Nevertheless, existing evidence for the use of prophylactic antibiotics to prevent further episodes of cellulitis is limited and leads to inconsistency in treatment regimens. Two previously reported studies have highlighted the possible benefit of using prophylactic antibiotics to treat cellulitis (Kremer et al, 1991; Sjöblom et al, 1993), but the number of enrolled participants in these studies was small (16 and 40 respectively). The study described in this protocol will provide high quality evidence to support clinical decision-making for the first time.

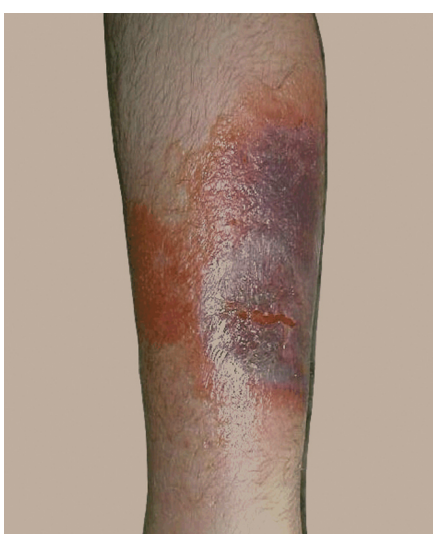

Figure 1. Typical cellulitis.

Rationale for the trial

The PATCH study consists of two related trials (PATCH I and PATCH II). These trials have been designed to assess the effectiveness of prophylactic antibiotics for the prevention of cellulitis.

The study aims to answer two key questions:

- Does penicillin (phenoxymethyl-penicillin, 250mg bd) given prophylactically after an episode of cellulitis of the leg prevent further attacks?
- Do the protective effects of prophylactic antibiotics continue to be seen once the prophylaxis is withdrawn?

The study is being coordinated through the UK Dermatology Clinical Trials Network (UK DCTN), which is a collaborative network of dermatologists, dermatology nurses, health service researchers and patients throughout the UK and Eire. The UK DCTN was set up to perform and support high-quality randomised controlled trials and to answer questions that are important to both clinicians and patients alike.

PATCH has been identified as a priority topic for the UK DCTN because:

- It answers an important question for patients and physicians
- It has significant cost implications for the NHS
- It is feasible within the structure of the network.

A recent survey of the UK DCTN membership revealed considerable variation in the use of prophylactic antibiotics among dermatologists for the treatment of cellulitis. Of these members, 21 (29%) never used prophylaxis and nine (12%) usually, or always, used prophylaxis. The majority (59%) used prophylaxis for recurrent cases, or if lymphoedema was present. This variation in practice reflects the poor evidence-base for the treatment of cellulitis and the need for good quality clinical data to support any changes in practice.

Results of an eight-month pilot study (Thomas et al, 2007), funded by the British Skin Foundation, have been used to inform the design of the PATCH trial by helping to identify appropriate recruitment strategies and areas of concern for patients, and to establish the most appropriate selection criteria and follow-up period. This pilot study also gave the principal investigators valuable training in the conduct and management of an independent clinical trial.

The investigation plan

The PATCH trials are two double-blind, randomised, controlled trials that compare penicillin with placebo for the prevention of further episodes of cellulitis. PATCH I compares a 12-month course of penicillin with placebo in patients with at least two previous episodes of cellulitis of the leg. PATCH II compares a six-month course of penicillin with placebo in patients who have received treatment for cellulitis of the leg (both first episode and recurrent cases).

The secondary objectives of both PATCH I and PATCH II are the same and look to determine whether the protective benefits of penicillin are observed only while treatment is maintained or if they continue in the longer term, which baseline factors best predict treatment success and whether prophylactic penicillin for cellulitis results in cost savings for the NHS.

Long-term follow-up will continue for up to 30 months after the treatment phase is maintained through daily diaries, telephone support and emergency appointments with the recruiting dermatologist. Participants are enrolled for a minimum of two years and up to three years in total, depending on

which study they are enrolled on and at what stage during the recruitment period they enrol. The study has been approved by Trent MREC (06/Q2404/22) and is being conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice and the European Union Clinical Trial Directive (ISRCTN: 34716921).

Setting

Recruitment onto the trials is taking place in up to 30 teaching and district general hospitals across the UK and EIRE, with an option to recruit in the community should recruitment in secondary care prove difficult.

Selection of participants

Patients will usually be identified by a participating UK DCTN clinician or dermatology nurse working at the recruiting site. However, other departments are increasingly involved in recruitment due to the nature of cellulitis, which may not primarily be seen in dermatology departments.

Patients are identified either at presentation or retrospectively via discharge coding. They are selected to enter the study on fulfilment of the following criteria:

- PATCH I: diagnosis of cellulitis of either leg (index episode) and history of at least one previous episode of cellulitis of either leg within the three years before the index episode
- PATCH II: diagnosis of cellulitis of either leg (index episode).

Exclusion criteria include (comprehensive list in the protocol on request):

- A period of greater than 12 weeks from the start of treatment for the index episode to the date of potential randomisation
- A known allergy to penicillin
- Preceding leg ulceration, surgery or penetrating trauma
- Patient unable to give informed consent.

The study is double blind — both investigator and participant are blind to the study medication, and both the penicillin and placebo tablets are identical in shape, size and colour.

Recruitment will take place over a period of 12–24 months with PATCH I completing recruitment at the end of December 2007 and PATCH II at the end of July 2008. The aim is to recruit 260 participants into PATCH I and 400 into PATCH II. This equates to a recruitment rate of one to two patients per centre per month if 30 centres are involved. Recruitment rates are reviewed regularly to assess the impact of the various recruitment strategies and the number of effective recruitment centres. Should recruitment be slower than expected, recruitment may continue for a further three to four months, or until adequate numbers have been achieved for the long-term follow-up study (depending on the availability of funds). The results from PATCH I will be ready for publication at the end of December 2009 and PATCH II by December 2010.

Primary outcome

The primary outcome is time to next episode (in either leg). The episode will be considered as starting on the first day of symptoms reported to a healthcare professional by the participant.

Secondary outcomes

Secondary outcomes include: the proportion of participants with repeat episodes of cellulitis, oedema and ulceration; the number of nights spent in hospital for the treatment of cellulitis of the leg; the number of adverse drug reactions; cost-effectiveness; and a predictor of response model.

Analysis

Analysis will be conducted on an intent-to-treat basis. Time to repeat episode of cellulitis will be assessed using survival analysis. Analyses will be two-sided ($p<0.05$) and 95% confidence intervals will be presented. Sub-group analyses are planned for patients with recurrent cellulitis compared to those with first episode cellulitis. A formal analysis plan will be developed before closure of the study database. Data will be analysed before breaking of the treatment allocation code.

Sample size

The sample size estimated in *Table 1* assumes an ability to detect a 50% reduction in relapse rate relative to placebo. It was felt that a 50% reduction relative to placebo was needed as a minimum clinically useful gain, given the lengthy duration and possible inconvenience of long-term prophylaxis.

Previous studies have suggested a range of possible recurrence rates for patients not receiving prophylaxis of between 20–50% (Jorup-Ronstrom and Britton, 1987; Cox et al, 1998), depending on the population being studied and the duration of follow-up. *Table 1* provides sample size estimates for various relapse rates, assuming 80% power and a significance level of 5%.

PATCH I

With a relapse rate in the placebo arm of 35% (relapse-free survival rate = 0.65), 260 participants will provide sufficient power to detect a 50% reduction in relapse rates compared to placebo (80% power, 20% loss to follow-up). A relapse-free survival rate in the placebo arm of 35% was chosen as a conservative estimate since having had a previous episode of cellulitis is an important risk factor for future episodes (Dupuy et al, 1999; Roujeau et al, 2004).

PATCH II

It is anticipated that the relapse rate in the placebo arm will be lower for PATCH II, as patients with first episode cellulitis will be included as well as those with recurrent disease. With a relapse rate of 25% (relapse-free survival rate = 0.75), 400 participants will provide sufficient power to detect a 50% reduction in relapse rate compared to placebo (80% power, 20% loss to follow-up). Results of the recent pilot study involving patients with a first episode of cellulitis, as well as those with recurrent disease, support these estimates: of the 70 cellulitis patients recruited, 32% had had a previous episode of cellulitis within the last three years, giving an estimated relapse-free survival rate for the placebo arm of 0.68.

A cost-effectiveness analysis will be conducted alongside the randomised controlled trial to determine the possible cost implications of the intervention for the NHS (Barber and Thompson, 2000). Six months of treatment with penicillin costs £20 and 12 months

costs £40; by contrast, a single hospital admission (average 9–10-day stay) costs approximately £2,000, indicating the magnitude of savings to the hospital for each case of cellulitis which could potentially be avoided.

Summary

These PATCH trials are addressing three key questions: Does antibiotic prophylaxis prevent further episodes of cellulitis? If so, which patients are most likely to benefit from prophylaxis and what potential cost savings may this bring to the NHS?

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Table I

Summary of sample size estimates

	PATCH I	PATCH II
Relapse-free survival rate at 2.5 years (placebo)	0.65	0.75
Relapse-free survival rate at 2.5 years (active)	0.825	0.875
N per arm	103	157
N per arm with 20% loss to follow-up	129	197
Total for study (both treatment arms)	**258**	**394**

Key Points

- Cellulitis commonly occurs in patients with lymphoedema.
- The current evidence base for the use of prophylactic antibiotics for the prevention of recurrent cellulitis is extremely limited.
- The UK Dermatology Clinical Trials Network (UK DCTN), is currently recruiting into two large-scale, multi-centre randomised controlled trials looking at the use of prophylactic antibiotics for patients with cellulitis.
- This article details the trial protocol for two trials in which 660 participants will be enrolled.

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