# Cefazolin-probenecid for the ambulatory management of skin and skin structure infection (SSSI)

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## Background

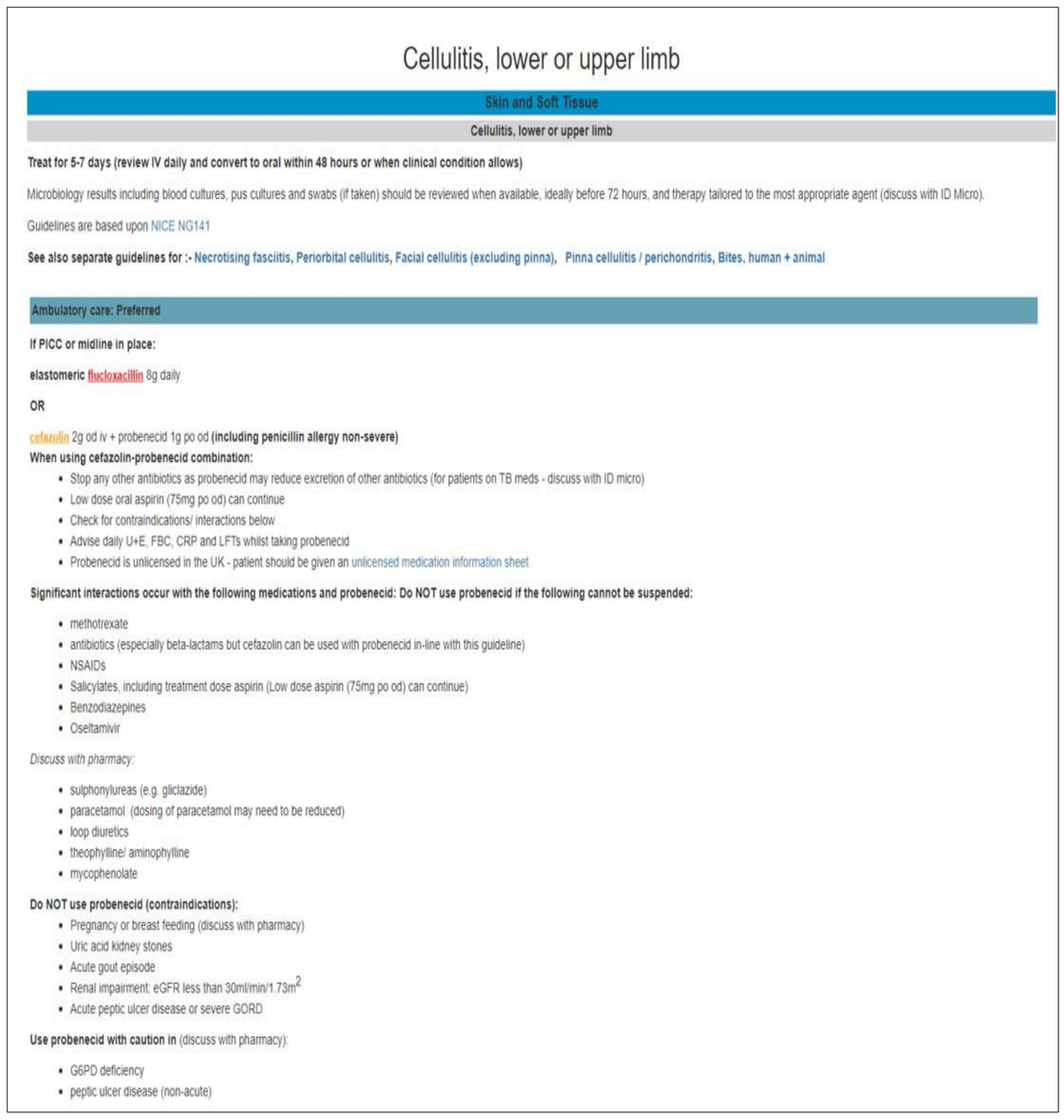
Cefazolin is a first-generation cephalosporin with excellent Gram-positive spectrum and is one of the most active anti-staphylococcal antibiotics (MSSA) [1]. It is normally prescribed every 6 to 8 hours, but when used in conjunction with probenecid it becomes a once daily antibiotic [2]. Cefazolin-probenecid is commonly used for ambulatory treatment of skin and skin structure infection (SSSI) in countries including USA, Canada, Australia and New Zealand [3].

The OUHFT had been using ceftriaxone in the ambulatory setting for the management of SSSI due to the convenience of once daily administration for this patient group. However, since the most common causative pathogens of SSSI are Gram-positive organisms such as *Streptococcus pyogenes* and *Staphylococcus aureus*, ceftriaxone has a broader antimicrobial spectrum than required [4]. Ceftriaxone is also known to be provocative of *Clostridioides difficile* infection [5]. To reduce use of ambulatory ceftriaxone, the Infection and Antimicrobial Stewardship (AMS) team developed a guideline for the use of cefazolin and probenecid for the management of SSSI in ambulatory patients. This guideline was published on the OUHFT MicroGuide® platform and promoted to key stakeholders (see Figure 1).

The AMS team conducted an audit to assess the safety and effectiveness of cefazolin-probenecid for the treatment of SSSI in OUHFT ambulatory care unit.

## Methods

The AMS team extracted a list of patients who had been treated with cefazolin-probenecid for audit using the pharmacy dispensing system between July 2021 to September 2022. Data were extracted from the electronic patients records and entered onto an excel spreadsheet for analysis.



Cellulitis, lower or upper limb

**Skin and Soft Tissue**

**Cellulitis, lower or upper limb**

**Treat for 5-7 days (review IV daily and convert to oral within 48 hours or when clinical condition allows)**

Microbiology results including blood cultures, pus cultures and swabs (if taken) should be reviewed when available, ideally before 72 hours, and therapy tailored to the most appropriate agent (discuss with ID Micro).

Guidelines are based upon NICE NG141

**See also separate guidelines for :-** Necrotising fasciitis, Periorbital cellulitis, Facial cellulitis (excluding pinna), Pinna cellulitis / perichondritis, Bites, human + animal

**Ambulatory care: Preferred**

**If PICC or midline in place:**

**elastomeric** flucloxacillin 8g daily

**OR**

cefazolin 2g od iv + probenecid 1g po od **(including penicillin allergy non-severe)**

**When using cefazolin-probenecid combination:**

- Stop any other antibiotics as probenecid may reduce excretion of other antibiotics (for patients on TB meds - discuss with ID micro)
- Low dose oral aspirin (75mg po od) can continue
- Check for contraindications/ interactions below
- Advise daily U+E, FBC, CRP and LFTs whilst taking probenecid
- Probenecid is unlicensed in the UK - patient should be given an unlicensed medication information sheet

**Significant interactions occur with the following medications and probenecid: Do NOT use probenecid if the following cannot be suspended:**

- methotrexate
- antibiotics (especially beta-lactams but cefazolin can be used with probenecid in-line with this guideline)
- NSAIDs
- Salicylates, including treatment dose aspirin (Low dose aspirin (75mg po od) can continue)
- Benzodiazepines
- Oseltamivir

*Discuss with pharmacy:*

- sulphonylureas (e.g. gliclazide)
- paracetamol (dosing of paracetamol may need to be reduced)
- loop diuretics
- theophylline/ aminophylline
- mycophenolate

**Do NOT use probenecid (contraindications):**

- Pregnancy or breast feeding (discuss with pharmacy)
- Uric acid kidney stones
- Acute gout episode
- Renal impairment: eGFR less than 30ml/min/1.73m$^2$
- Acute peptic ulcer disease or severe GORD

**Use probenecid with caution in** (discuss with pharmacy):

- G6PD deficiency
- peptic ulcer disease (non-acute)

Figure 1: Oxford University Hospital NHS Foundation Trust Antimicrobial Guideline for Cellulitis, lower or upper limb [6].

## Results and Discussion

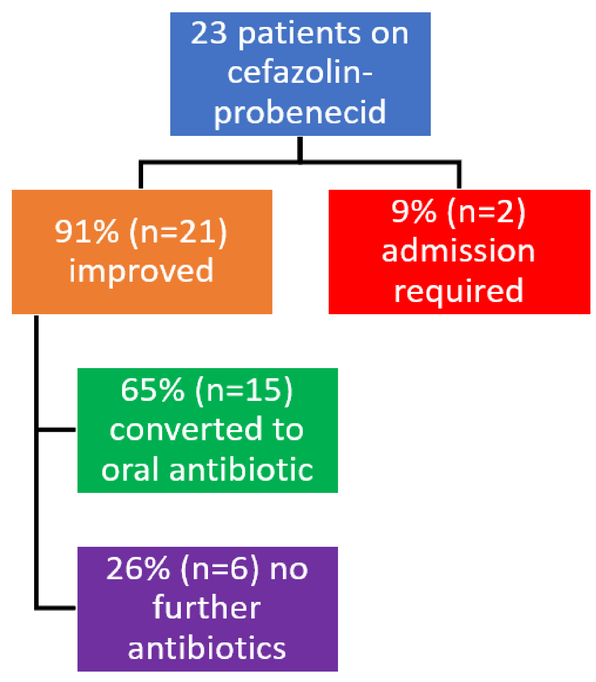
- Twenty-three patients who had received one or more doses of cefazolin-probenecid included in the audit.
- All patients were over 18 years of age (age range was 34-99 years with mean of 64)
- All patients had a diagnosis of SSSI (21 were lower limb cellulitis, 2 were upper limb cellulitis).
- Duration of cefazolin-probenecid treatment ranged from 1 to 10 days (mean 3.75, median 3).

Figure 2 shows that 91% (n=21) of the patients improved on cefazolin-probenecid and oral conversion was possible in 65% (n=15) of the cases. Most patients received follow-on oral flucloxacillin, a narrow spectrum penicillin based antibiotic.

In two cases, admission was required after attempted ambulation on cefazolin-probenecid. In one case this was due to severe necrotic lower limb cellulitis where ambulation with cefazolin-probenecid was attempted at the patients request, but admission was ultimately necessary. The second case was admitted due to social circumstances associated with functional decline rather than deteriorating cellulitis. In both cases, the failure of cefazolin-probenecid therapy was not considered the primary cause of admission.

Only one (4%) patient had a transient increase in serum creatinine which corrected during cefazolin-probenecid treatment. No other adverse effects were seen and there were no reports of occurrence of *Clostridioides difficile* infection.

Figure 2: The effectiveness of cefazolin-probenecid (CP) in SSSI treatment ambulatory care




## Conclusion

In this small pilot of ambulatory SSSI treatment, the regimen of cefazolin-probenecid was found to be safe and effective. This narrow spectrum, once daily regimen shows potential for the avoidance of broader spectrum agents like ceftriaxone. The adverse effects and clinical failure rates were low.

Further analysis of a larger number of SSSI cases receiving cefazolin-probenecid is required to understand which patient groups can best be targeted with cefazolin-probenecid treatment. In addition, dissemination of knowledge and feedback of this audit to prescribers is essential to raise the awareness and instil confidence in the use of this efficacious regimen for management of SSSI.

## References

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