

Oral versus parenteral antimicrobials for the treatment of cellulitis: a randomized non-inferiority trial

Craig A. Aboltins^{1,2*}, Anastasia F. Hutchinson^{3,4}, Rabindra N. Sinnappu⁵, Damian Cresp³, Chrissie Risteski³, Rajasutharsan Kathirgamanathan⁶, Mark A. Tacey^{3,7}, Herman Chiu⁶ and Kwang Lim^{2,8}

¹Department of Infectious Diseases, Northern Health, Epping, Melbourne, Victoria, Australia; ²Northwest Academic Centre, The University of Melbourne, Epping, Melbourne, Victoria, Australia; ³Northern Clinical Research Centre, Northern Health, Epping, Melbourne, Victoria, Australia; ⁴School of Nursing & Midwifery, Deakin University, Northern Health, Epping, Melbourne, Victoria, Australia; ⁵Hospital In The Home, Northern Health, Epping, Melbourne, Victoria, Australia; ⁶Emergency Department, Northern Health, Epping, Melbourne, Victoria, Australia; ⁷Department of Medicine, The University of Melbourne, Parkville, Melbourne, Victoria, Australia; ⁸Department of Medicine, Northern Health, Epping, Melbourne, Victoria, Australia

*Corresponding author. Tel: +61-3-84058000; E-mail: craig.aboltins@nh.org.au

Received 27 July 2014; returned 3 September 2014; revised 8 September 2014; accepted 13 September 2014

Objectives: To determine whether outcomes for patients with cellulitis treated with oral antimicrobials are as good as for those who are treated with parenteral antimicrobials.

Methods: A prospective randomized non-inferiority trial was conducted at a tertiary teaching hospital in Melbourne, Australia. Participants were patients referred by the emergency department for treatment of uncomplicated cellulitis with parenteral antimicrobials. Patients were randomized to receive either oral cefalexin or parenteral ceftazidime. Parenteral antimicrobials were changed to oral after the area of cellulitis ceased progressing. The primary outcome was days until no advancement of the area of cellulitis. A non-inferiority margin of 15% was set for the oral arm compared with the parenteral arm. Secondary outcomes were failure of treatment, pain, complications and satisfaction with care. This trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000685910).

Results: Twenty-four patients were randomized to oral antimicrobials and 23 to parenteral antimicrobials. Mean days to no advancement of cellulitis was 1.29 (SD 0.62) for the oral arm and 1.78 (SD 1.13) for the parenteral arm, with a mean difference of -0.49 (95% CI: -1.02 to +0.04). The upper limit of the 95% CI of the difference in means of +0.04 was below the 15% non-inferiority margin of +0.27 days, indicating non-inferiority. More patients failed treatment in the parenteral arm (5 of 23, 22%) compared with the oral arm (1 of 24, 4%), although this difference was not statistically significant ($P=0.10$). Pain, complications and satisfaction with care were similar for both groups.

Conclusions: Oral antimicrobials are as effective as parenteral antimicrobials for the treatment of uncomplicated cellulitis.

Keywords: drug therapy, antimicrobial agents, oral administration, parenteral infusions, randomized controlled trials

Introduction

Cellulitis is a potentially serious infection of the skin that is a common cause of presentation to emergency departments and admission to hospital. Patients presenting to hospital are often treated with parenteral antimicrobial therapy because of the severity of infection or because of progression after initial treatment with oral antimicrobials. Parenteral antimicrobials, whether administered in the inpatient setting or with outpatient parenteral antimicrobial therapy (OPAT), are associated with inherent costs, complications and discomfort. Oral antimicrobials with reliable

oral absorption and good activity against the bacteria that commonly cause cellulitis are readily available and are likely to be cheaper and associated with fewer complications than parenteral antimicrobials. Only limited evidence exists comparing oral with parenteral antimicrobials for this infection.^{1,2} A recent Cochrane review states the need for further evaluation of this issue given the potential benefits if oral antimicrobials were found to be equivalent in efficacy to parenteral antimicrobials.³ The aim of this study is to compare outcomes for patients with uncomplicated cellulitis who are treated with oral antimicrobials with those who are treated with parenteral antimicrobials. Our

hypothesis was that oral antimicrobials are at least as effective as parenteral antimicrobials.

Methods

A randomized, open-label, non-inferiority trial was performed at a single site, The Northern Hospital, a tertiary teaching hospital in metropolitan Melbourne serving a population of ~728000 people. Ethics approval for this study was from the Northern Health Research and Ethics Committee, approval number A43/10. Informed consent was given by all participants prior to taking part in this study. This trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000685910).

Protocol

Patients were eligible for inclusion in the study if they were referred by emergency department medical staff for treatment of cellulitis with parenteral antimicrobials because of severity of cellulitis or because of progression despite prior oral antimicrobial therapy. Cellulitis was defined by the presence of acute dermal/epidermal inflammation lasting <5 days and associated with pain, fever with a temperature of $\geq 37.8^{\circ}\text{C}$, tachycardia >90 beats/min, systemic symptoms or elevated inflammatory markers.

Patients were required to be aged ≥ 16 years and were eligible regardless of their referral being for treatment as an inpatient or with OPAT via the 'Hospital In The Home' (HITH) programme. The location of treatment was determined by treating clinicians as per standard hospital protocols. Criteria for exclusion were inability to give consent, being unavailable for follow-up, an alternative diagnosis to cellulitis, necrotizing fasciitis, complicated cellulitis (presence of severe sepsis, extensive bullous skin changes or abscess formation), mild cellulitis (limited area and no systemic symptoms), cellulitis complicating trauma, periorbital cellulitis, immunosuppressed patients, vomiting precluding oral antimicrobial therapy and prior treatment with oral antimicrobials for >48 h or with parenteral antimicrobials for >12 h. Screening and enrolment of patients was by trained members of the HITH department or the infectious diseases department.

Assessment of consenting patients in the emergency department consisted of collection of demographic data, clinical symptoms and signs, comorbidities and routine blood tests including white cell count and C-reactive protein. An indelible marker was used to draw an outline of the area of cellulitis on the patients skin for comparison on following assessments. The maximum diameter of the cellulitis was measured. Pain was assessed with a visual analogue scale with a range of 0–10.

Patients were randomized 1:1 with a 4 block schedule to either oral or parenteral antimicrobial treatment arms. Randomization was achieved with a password-protected online randomization tool, Sealed Envelope (Sealed Envelope, London, UK), by designated members of the study team (C. A. A., A. F. H. and R. N. S.). The protocol for patients assigned to the oral arm was to receive 1 g of cefalexin orally four-times daily for 10 days or, if they had immediate β -lactam hypersensitivity, 450 mg of clindamycin orally three-times daily for 10 days. Patients assigned to the parenteral antimicrobial arm were to receive 2 g of ceftazolin intravenously every 12 h or, if they had immediate penicillin hypersensitivity, 450 mg of clindamycin intravenously every 8 h. Parenteral antimicrobials were continued until the area of cellulitis was no longer progressing and the patient was afebrile, at which time treatment was continued with oral antibiotics, using doses as above, for a total antibiotic duration (parenteral plus oral) of 10 days. The antibiotics used were those recommended for treatment of cellulitis by the Australian Therapeutic Guidelines.⁴ Patients kept a medication diary for doses of oral antibiotics.

Patients had daily assessment initially. If the area of cellulitis had spread outside any part of the outline drawn on the patient's skin at the time of enrolment, a new outline was drawn and this was repeated daily

until the area of cellulitis stopped advancing. Further assessments were undertaken on days 7 and 28 post-enrolment. A satisfaction survey was administered on day 28. Assessments of both inpatients and outpatients were completed by study nurses who had undergone training and calibration.

Outcome measures

The primary outcome measure was time until no advancement of the area of cellulitis.⁵ Secondary outcomes were failure of treatment, pain, complications of treatment and satisfaction with care. Failure of treatment was defined by persistent/relapsed symptoms requiring a change or further course of antibiotics, readmission to hospital or a surgical procedure such as abscess drainage for subsequent management.

A safety and monitoring committee reviewed outcome data after 20 patients had been recruited and agreed that continuing the trial was safe.

Statistical analysis

The trial was designed to assess non-inferiority of the oral arm when compared with the parenteral arm. Based on clinician researcher opinion of acceptable clinical difference, a non-inferiority margin of 15% was used for the primary outcome. Specifically, the oral arm was considered non-inferior if the upper limit of the 95% CI for the difference in means was less than +15% of the mean value for the parenteral arm. Using an estimate of population variance of 0.15 days (SD) based on a previous study,⁵ a sample size of ≥ 18 patients in each arm was calculated to achieve 80% power, with a two-sided α error of 0.05. This sample size is a revised figure that was calculated 9 months after recruitment commenced, when the initial pre-recruitment calculation of 58 was found to be based on incorrect assumptions. The revised calculation was made prior to interim examination of results for the safety and monitoring committee and when recruitment was to schedule. After the required sample size was recruited, the trial management committee decided that enrolment was to continue for as long as study funding was available. Tests of superiority were used for secondary outcomes. The Mann-Whitney test was used to compare non-normally distributed continuous variables. The χ^2 test and Fisher's exact test were used for contingency tables. All tests were two-tailed and a *P* value of <0.05 was considered to indicate statistical significance. Statistical analysis was performed using Stata version 12.1 (StataCorp, TX, USA).

Results

The study recruited patients from February 2011 until April 2013. Figure 1 summarizes patient flow through the study. Forty-seven patients with one episode each of cellulitis were enrolled in the trial, with 23 patients in the parenteral arm and 24 patients in the oral arm. All enrolled patients were assessable for the primary outcome of non-progression of cellulitis. One patient, who experienced treatment failure on day 3, was lost to follow-up after day 7.

Baseline demographic and clinical features were similar between the two treatment groups (Table 1). Twenty (43%) patients had already received treatment with antibiotics for the current episode of cellulitis prior to enrolment. At enrolment, six patients (two patients in the oral arm and four in the parenteral arm) were admitted to hospital for the management of cellulitis or other comorbid conditions. The remaining 41 patients were managed at home.

Treatment was initially with either ceftazolin in the parenteral arm or cefalexin in the oral arm in all patients. No patients were

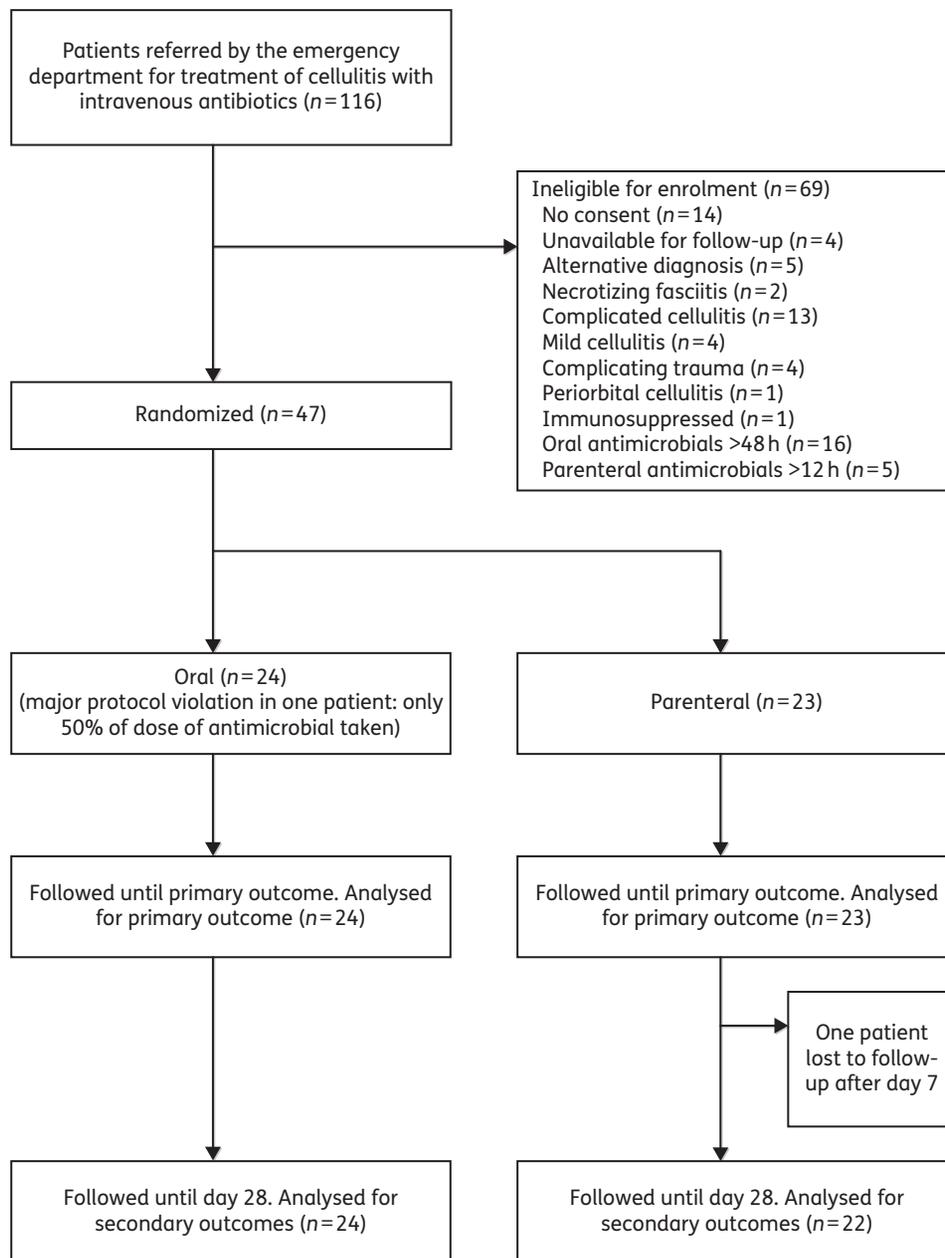


Figure 1. Patient enrolment, exclusion, randomization and follow-up.

initially treated with clindamycin. For one patient in the oral arm, treatment was changed to oral clindamycin after 5 days due to development of an allergic rash. A major protocol violation occurred in one patient in the oral arm who received 500 mg of cefalexin four-times daily instead of 1 g of cefalexin four-times daily.

On ITT analysis, the primary outcome of mean days to no advancement of cellulitis was 1.29 (SD 0.62) days for the oral arm and 1.78 (SD 1.13) days for the parenteral arm, with a mean difference of -0.49 (95% CI: -1.02 to $+0.04$). The upper limit of the 95% CI of the mean difference of $+0.04$ was below the specified $+15\%$ non-inferiority margin of $+0.27$ days, indicating that the oral treatment was non-inferior to parenteral

treatment (Figure 2). PP analysis of the primary outcome showed similar results after excluding the one patient with major protocol violation from the oral arm, with the difference between the oral and parenteral arms being -0.48 days (95% CI: -1.02 to $+0.07$), also satisfying non-inferiority criteria. All patients were afebrile at the time the cellulitis had stopped spreading.

The rate of failure of treatment was higher in the parenteral arm (5 of 23, 22%) when compared with the oral arm (1 of 24, 4%), although this difference was not statistically significant ($P=0.10$). The mean pain score on day 1 was significantly higher in the oral arm compared with the parenteral arm (4.8 versus 2.8; $P=0.03$); however, a higher baseline pain score in the oral arm meant the reduction in mean pain score at that time was similar

Table 1. Demographic and clinical features of patients at enrolment

Variable	Oral antimicrobials (n=24)	Parenteral antimicrobials (n=23)
Age (years), mean (SD)	48.4 (17.8)	44.5 (14.7)
Male, n (%)	16 (67)	15 (65)
Duration of symptoms (h), mean (SD)	67.1 (43.2)	56.1 (44.9)
Maximum diameter of erythema at enrolment (cm), mean (SD)	28.2 (18.7)	29.7 (15.2)
Site of cellulitis		
upper limb	3	3
lower limb	21	20
Mean pain score (/10)	5.3	3.8
Systemic symptoms ^a , n (%)	19 (79)	16 (70)
Temperature $\geq 37.8^{\circ}\text{C}$, n (%)	7 (29)	5 (22)
Heart rate >90 beats/min, n (%)	14 (58)	12 (52)
White blood cell count $\geq 12 \times 10^9$ cells/L, n (%)	13 (54)	9 (39)
C-reactive protein ≥ 100 mg/L, n (%)	14 (58)	8 (35)
Treatment of this episode prior to enrolment, n (%)		
parenteral	3	4
oral	8	5
Previous episodes of cellulitis, n (%)	5 (21)	2 (9)
Diabetes mellitus, n (%)	5 (21)	5 (22)

^aReported fever, rigors, nausea or malaise.

in the two groups (0.5 versus 0.5; $P=0.31$). Pain scores at days 7 and 28 were similar as were results from patient satisfaction surveys (Table 2). The overall rate of complications of treatment was similar across each group (29% in the oral group versus 32% in the parenteral group; $P=0.85$).

Discussion

The results of this study suggest that many patients with cellulitis referred for treatment with parenteral antimicrobial therapy improve just as quickly with oral antimicrobials as with parenteral antimicrobials, with oral antimicrobials shown to be non-inferior to parenteral antimicrobials in time to no advancement of cellulitis. Treating these patients with oral antimicrobials also appears to be effective and safe, with each group experiencing similar rates of failure of treatment, improvement in pain scores and side effects of treatment. Patients in either group were similarly satisfied with their treatment in this trial setting.

We have performed the only recent trial directly comparing oral and parenteral antimicrobials of similar class and spectrum of efficacy for the treatment of cellulitis. The antimicrobial regimens used are those recommended and commonly prescribed in Australia for this indication. The patients in our study had evidence of significant systemic illness and/or progression of cellulitis despite oral antimicrobials and so are representative of patients usually treated with parenteral antimicrobials, particularly with OPAT, which is increasingly being used for such patients.⁶ Our

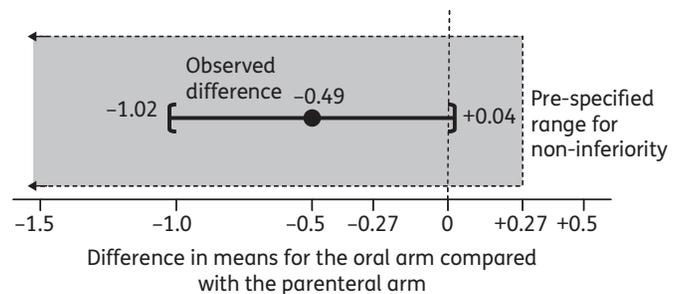


Figure 2. CI and non-inferiority margin for difference in means in days to no advancement of cellulitis.

study design did not include blinding of investigators, an important potential source of bias that we attempted to minimize by using the objective primary outcome of time until no advancement of the area of cellulitis. Cessation of spread of the area of cellulitis is a practical clinical outcome that has been suggested as a standard for studies investigating the treatment of skin and soft tissue infections.^{5,7} Most clinicians would, however, be primarily interested in failure of treatment in judging the efficacy of a treatment. Although our study was not powered to detect differences in failure of treatment, we did observe an unexpected trend to fewer failures in the oral arm compared with the parenteral arm. Twenty (43%) of the patients in our study had received antimicrobials for treatment of their cellulitis prior to enrolment, which may

Table 2. Secondary outcomes for each treatment group

Outcome/complication	Oral antimicrobials (n=24)	Parenteral antimicrobials (n=23)	P
Treatment failure, n (%)	1 (4)	5 (22)	0.10
Complications of treatment, n (%) ^a	7 (29)	7 (32)	0.85
pain, erythema at injection site	—	3 (14)	—
indigestion or nausea	4 (17)	2 (9)	0.45
allergic skin rashes	1 (4)	1 (4)	0.95
thrush	0	1 (4)	0.29
diarrhoea	3 (12)	1 (4)	0.34
Pain score, mean \pm SD			
baseline	5.3 \pm 2.7	3.8 \pm 3.8	0.13
day 1	4.8 \pm 2.4	2.8 \pm 2.9	0.03
day 7	1.9 \pm 1.7	1.9 \pm 2.7	0.33
day 28	0.3 \pm 0.6	0.4 \pm 1.7	0.19
Reduction in pain score, mean \pm SD			
baseline to day 1	0.5 \pm 1.9	1.0 \pm 2.5	0.31
baseline to day 7	3.4 \pm 3.3	1.9 \pm 3.0	0.64
baseline to day 28	5.0 \pm 2.8	3.4 \pm 3.5	0.22
Satisfaction ratings ^{b,c} , mean \pm SD			
convenience	3.5 \pm 0.9	3.2 \pm 1.5	0.90
effectiveness	3.7 \pm 0.5	3.4 \pm 0.7	0.10
overall satisfaction	3.9 \pm 0.3	3.7 \pm 0.6	0.27

^aData not obtained for one patient in parenteral arm for complications of treatment.

^bThree satisfaction surveys not returned.

^cScale 0–4: 0 = not satisfied; 4 = most satisfied.

have minimized any differences in treatment efficacy but does reflect real-world practice and is consistent with previous studies reporting outcomes with parenteral antimicrobials.^{5,8}

Only a limited number of studies have previously compared oral and parenteral antimicrobials for the treatment of cellulitis. In different trials in inpatients, roxithromycin was found to be equivalent to initial parenteral then oral penicillin⁹ and oral pristinamycin was shown to be superior to initial intravenous then oral penicillin in one other study.² In one older, quasi-randomized trial, oral penicillin was found to be equivalent to parenteral penicillin.¹ This is the only other study apart from ours to compare oral and parenteral antimicrobials of similar class and spectrum of activity. Recent studies in this area have mostly compared different parenteral treatments and have shown similar results to those achieved for primary and secondary outcomes in both groups in our study.^{5,10–12}

Current Australian and UK guidelines recommend parenteral antimicrobials for patients with significant systemic symptoms or progression of erythema despite oral therapy.^{4,13} Although parenteral antimicrobials are effective, they come with inherent costs, inconvenience of administration, discomfort and the rare although potentially serious complication of venous catheter-associated sepsis. Treating patients with oral antibiotics would obviate these issues.

This single-centre study is limited by its small size and its results need to be confirmed with larger multicentre trials. In particular, the unexpected trend seen of fewer treatment failures with oral antimicrobials needs to be further explored in studies

powered to compare this outcome. Importantly, findings from this study cannot be applied to patients with more severe cellulitis presenting with features of severe sepsis or extensive bullous changes that clearly need parenteral antimicrobials. There is also limited direct applicability to other skin and skin structure infections such as complicated skin abscesses and diabetic foot infections, particularly in areas such as the USA with high rates of community-acquired MRSA; however, comparisons of oral and parenteral treatments for these infections would be feasible and useful.

Acknowledgements

We thank Annie Bentley and the other staff of the HITH Department and Raquel Cowan, Karen Lim, Venkat Lavu and other staff of the Infectious Diseases Department for assistance with enrolment and management of patients.

Funding

Funding was provided internally by Northern Health, a Victorian public health service.

Transparency declarations

None to declare.

Author contributions

All authors except K. L. participated in study design. All authors except M. A. T. were involved in trial management and data acquisition. All authors had full access to the data. M. A. T., C. A. A., A. F. H. and K. L. performed the statistical analysis. C. A. A. wrote the initial draft. All authors were involved in critical revision of the manuscript. C. A. A. is the guarantor.

References

- 1 Jorup-Ronstrom C, Britton S, Gavlevik A *et al.* The course, costs and complications of oral versus intravenous penicillin therapy of erysipelas. *Infection* 1984; **12**: 390–4.
- 2 Bernard P, Chosidow O, Vaillant L. Oral pristinamycin versus standard penicillin regimen to treat erysipelas in adults: randomised, non-inferiority, open trial. *BMJ* 2002; **325**: 864.
- 3 Kilburn SA, Featherstone P, Higgins B *et al.* Interventions for cellulitis and erysipelas. *Cochrane Database Syst Rev* 2010; issue **6**: CD004299.
- 4 Antibiotic Expert Group. Cellulitis and Erysipelas. In: *Therapeutic Guidelines: Antibiotic. Version 14*. Melbourne: Therapeutic Guidelines Limited, 2010.
- 5 Corwin P, Toop L, McGeoch G *et al.* Randomised controlled trial of intravenous antibiotic treatment for cellulitis at home compared with hospital. *BMJ* 2005; **330**: 129.
- 6 Garrett T, Harbort Y, Trebble M *et al.* Once or twice-daily, algorithm-based intravenous cefazolin for home-based cellulitis treatment. *Emerg Med Australas* 2012; **24**: 383–92.
- 7 Talbot GH, Powers JH, Fleming TR *et al.* Progress on developing endpoints for registrational clinical trials of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections: update from the Biomarkers Consortium of the Foundation for the National Institutes of Health. *Clin Infect Dis* 2012; **55**: 1114–21.
- 8 Grayson ML, McDonald M, Gibson K *et al.* Once-daily intravenous cefazolin plus oral probenecid is equivalent to once-daily intravenous ceftriaxone plus oral placebo for the treatment of moderate-to-severe cellulitis in adults. *Clin Infect Dis* 2002; **34**: 1440–8.
- 9 Bernard P, Plantin P, Roger H *et al.* Roxithromycin versus penicillin in the treatment of erysipelas in adults: a comparative study. *Br J Dermatol* 1992; **127**: 155–9.
- 10 Pertel PE, Eisenstein BI, Link AS *et al.* The efficacy and safety of daptomycin vs. vancomycin for the treatment of cellulitis and erysipelas. *Int J Clin Pract* 2009; **63**: 368–75.
- 11 Leman P, Mukherjee D. Flucloxacillin alone or combined with benzylpenicillin to treat lower limb cellulitis: a randomised controlled trial. *Emerg Med J* 2005; **22**: 342–6.
- 12 Corey GR, Wilcox M, Talbot GH *et al.* Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. *Clin Infect Dis* 2010; **51**: 641–50.
- 13 National Institute for Health and Care Excellence. *Cellulitis—Acute—Clinical Knowledge Summary*. London: National Institute for Health and Care, 2012. <http://cks.nice.org.uk/cellulitis-acute>.