Lessons Learned From a Randomized Controlled Trial of Short-Course Intravenous Antibiotic Therapy for Erysipelas and Cellulitis of the Lower Limb (Switch Trial)

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Background. The diagnosis of cellulitis is made clinically without a gold standard diagnostic test, and cellulitis has many disease mimics. There is currently no consensus for optimal antimicrobial treatment duration or method of antimicrobial delivery.

Methods. This was a randomized controlled open-label multicenter trial to determine the safety and efficacy of 24 hours of intravenous (IV) therapy compared with ≥72 hours of IV therapy, both followed by oral therapy to a maximum of 7–10 days' duration for the treatment of lower limb cellulitis.

Results. Over 40 months, 80 patients were recruited. Thirty-nine patients were assigned to 24 hours of IV antibiotics and 41 to ≥72 hours of IV antibiotics. The mean duration (range) of IV antibiotics in the 24-hour group was 25.5 (17–40) hours, and in the ≥72-hour group it was 78 (41.5–210) hours. Three patients in the 24-hour arm and 4 patients in the ≥72-hour arm were excluded from the analysis due to withdrawal from the trial. Analysis of the remaining patients revealed that 6 patients (4 in the intervention arm and 2 in the control arm) did not achieve an adequate response to therapy. Only 1 patient experienced self-limiting adverse effects of treatment.

Conclusions. The noninferiority of short-course IV therapy cannot be determined from this trial. Challenges included resource limitations for recruitment, misdiagnosis, participant withdrawal, and subjective responses to therapy based on visual assessment by treating clinicians. Further studies are needed to determine if short-course IV therapy is a suitable treatment option.

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Keywords. antibiotic therapy; cellulitis; erysipelas.

Cellulitis is an acute infection of the dermis and adjacent subcutaneous tissues characterized by swelling, pain, and erythema of the affected area [1]. It is a common global health problem in both inpatient and outpatient settings globally, with an incidence of 16.4–24.6/1000 person-years [1, 2]. The most common causative organism of cellulitis is *Streptococcus* spp., and the lower limb is the most commonly affected site [3]. Although the terms "cellulitis" and "erysipelas" are often used interchangeably, erysipelas is distinct from cellulitis in that it involves only the superficial dermis and lymphatics, whereas cellulitis involves deeper dermis and subcutaneous fat [4]. Predisposing factors that may contribute to the development of cellulitis include local trauma disrupting the skin barrier, edema, compromised lymphatic drainage, impaired host immune response, and other skin conditions such as tinea pedis [5]. For simplicity in this trial, the term cellulitis includes erysipelas.

The diagnosis of cellulitis is almost always based on clinical findings, as techniques to obtain specimens for microbial analysis such as needle aspiration are unnecessarily invasive, and of low yield, and blood cultures are also rarely positive [5, 6]. There is also no gold standard diagnostic test for cellulitis, and many conditions, including venous stasis dermatitis, lipodermatosclerosis, irritant dermatitis, erythema nodosum, acute gout, and other primary inflammatory skin conditions, may all present with features of erythema, warmth, edema, and pain [5, 7, 8].

Outcomes for patients with cellulitis are generally excellent with early recognition and appropriate antimicrobial therapy, and the condition carries a very low mortality [9]. However, there can still be significant morbidity associated with cellulitis, causing pain and disability in the acute phase.

Despite the frequency with which these conditions are encountered in practice, there is currently no consensus regarding

optimal treatment based on method of antimicrobial delivery or duration of treatment [10]. In addition, there is no validated tool to assist clinicians with assessment; thus there is significant variability in the clinical measurement of response to treatment [8, 11]. Effective and safe treatment that reduces time in hospital, intravenous access dwell time, and/or duration of antibiotic therapy has the potential to benefit not only patients' quality of life but the wider community as a result of economic savings and reduction of risk of emerging antibiotic resistance.

This prospective, multicenter randomized controlled trial was designed to compare outcomes of patients with cellulitis who received short-duration intravenous (IV) therapy with those of patients with cellulitis who received standard-duration IV antibiotic therapy followed by oral antibiotics. Contemporary local management of cases of lower limb cellulitis requiring parenteral antibiotics at University Hospital Geelong includes inpatient treatment or parenteral treatment at home via outpatient parenteral antimicrobial therapy services. The SWITCH pilot trial, conducted over 12 months beginning in November 2012, recruited patients presenting to University Hospital Geelong, a 450-bed teaching hospital in Geelong, Victoria, and the major hospital of Barwon Health, which services Southwestern Victoria [1, 2]. The trial was later extended to include 10 other hospitals in Victoria, New South Wales, Western Australia, and New Zealand.

METHODS

Patients were randomized to receive either 24 hours of IV antibiotics or ≥72 hours of IV antibiotics. After completing IV therapy, both groups continued oral antibiotics for a total duration of 7 to 10 days, which is consistent with contemporary Australian practice [12].

Primary Objective

The primary objective was to determine the safety and efficacy of 24 hours of IV antibiotic therapy followed by oral therapy compared with ≥72 hours of IV antibiotic therapy followed by oral therapy.

Study Design

We performed a randomized, open-label, noninferiority multicenter trial (SWITCH trial) comparing 24 hours of IV antibiotic therapy with ≥72 hours of IV therapy.

Patients were reviewed at 4 time points:

1) baseline (for recruitment, consent, and randomization);
2) 48–72 hours after randomization;
3) at the end of therapy (7–10 days after randomization);
4) by phone interview 30 days after randomization.

Inclusion Criteria

Participants were eligible for inclusion in the study if they met all of the following criteria:

1. spontaneous cellulitis or erysipelas of a lower limb with consistent clinical features, including erythema, pain, swelling of a lower extremity of acute onset with presence of or recent history of fevers and/or chills, rigors, and nausea;
2. age ≥18 years;
3. oral antibiotics effective against cellulitis <48 hours, IV antibiotics effective against cellulitis <24 hours;
4. planned for IV therapy as inpatient or via outpatient antimicrobial therapy services.

Exclusion Criteria

Potential participants were excluded from the study if they met any of the following criteria:

1. age <18 years;
2. pregnant female;
3. immunosuppression including any 1 of: active chemotherapy in the last 6 weeks, receipt of prednisolone >20 mg/d or neutropenia with neutrophil count <0.5 ×10^9/L, or alternative conditions significantly affecting the immune system;
4. alternative diagnosis, including but not limited to: venous eczema, diabetic foot infection, surgical site (wound) infection, or other open wound;
5. penetrating injury or bite;
6. suspected complication such as abscess or necrotizing infection;
7. septic shock or other reasons for intensive care unit admission;
8. antibiotics effective against cellulitis IV for >24 hours or oral for >48 hours (including receipt of flucloxacillin, dicloxacillin, cephalexin, cephazolin, clindamycin, and vancomycin)*;
9. patients unwilling to participate or who in the opinion of investigators would not be able to comply with the requirements of the study.

*Initially, patients were excluded if they had received antibiotics effective against cellulitis IV for >24 hours or oral for >48 hours (including receipt of flucloxacillin, dicloxacillin, cephalexin, cephazolin, clindamycin, and vancomycin); this was altered 5 months after trial commencement from >24 hours of IV or any oral antibiotics to >24 hours of IV antibiotics or >48 hours of oral antibiotics.

Screening

Potential trial participants were identified by referral from the emergency department, referral from the hospital-in-the-home service, referral from an in-patient ward, or twice-daily review of patients and their diagnoses in the emergency department. Potential participants were reviewed by either an infectious diseases registrar or physician to determine if they fulfilled inclusion criteria for the study and did not meet any exclusion criteria.

Randomization

Randomization for the study was performed before the initiation of participant recruitment via random block allocation. Allocation of participants to either the short-course or longer-course treatment arm occurred in ascending numeric order and was completed on enrollment into the study.

Primary Outcome Measure

The primary outcome measure was resolution of cellulitis, defined by all of the following 3 criteria: resolution of fever at visit 2 (day 2–3), absence of progression of skin and subcutaneous abnormalities at visit 3 (day 7–10), and absence of ongoing requirement for antibiotic therapy beyond the study period of 10 days.

Secondary Outcome Measures

Secondary outcome measures included the following information collected from study participants via a 10-day study diary [13], in-person visits, and 30-day telephone follow-up.

1. time to defervescence;
2. self-reported pain using the Wong-Baker Face Scale [14];
3. photographic assessment of the affected lower limb (photographs were taken at study visits by the study clinician and assessed retrospectively by a reviewer blinded to the study arm of the participants);
4. adverse events;
5. disease relapse or recurrence within 30 days.

Power Calculation and Data Analysis

Given the hypotheses of the primary analysis, the sample size was calculated based on the 1-sided hypothesis test for the difference of 2 proportions. Assuming an efficacy rate of 90% for both treatment arms, a 1-sided significance of 2.5% and 80% power to reject the null hypothesis of inferiority with a margin of 10% required a sample size of at least 284 participants (142 in each arm).

Patient demographics were compared using t tests and nonparametric tests of location for continuous and discrete data, respectively. The primary analysis was performed on the intent-to-treat population, with confidence intervals for the difference in proportions estimated using an exact binomial method. A per-protocol analysis, excluding patients who withdrew from the trial but including those who were withdrawn by investigators as failures, was also performed. A secondary analysis tested the hypothesis that the gradient in pain score was different by treatment arm over time. This was assessed by using the generalized estimating equations, with pain score as the dependent variable and day, treatment arm, and the interaction between day and arm as independent variables. This model accounts for repeated measures in the same patients, with standard errors calculated using the Huber White sandwich estimator. Analyses were performed using Stata 15.1 for Windows (College Station, TX).

This trial was registered with the Australia Council of Clinical Trials Registry (ACTRN12613001366741), was endorsed by the Australasian Society for Infectious Diseases, and was approved by the Barwon Health Human Research and Ethics Committee and the research and ethics committees at all trial sites.

RESULTS

The SWITCH study commenced enrolling patients in November 2012. Data from the pilot trial revealed that only 20% of potential participants screened were ultimately recruited to the SWITCH trial [13]. The majority of patients were excluded based on prior exposure to oral antibiotics for >48 hours and intravenous antibiotics for >24 hours before screening.

As the trial had not recruited to target and would likely not recruit to target within a reasonable time frame, the trial was expanded, with a total of 10 sites in Australia and New Zealand obtaining ethics approval to participate in patient enrollment. The results reported below, and summarized in Figure 1, combine results collected from both the pilot trial [13] and the multisite expansion of the study.

Over a 40-month period from November 2012 to March 2016, a total of 80 patients fulfilled the study criteria and were enrolled to participate in the SWITCH trial. The median age of participants was 58.5 years, all participants were Caucasian, approximately one-third were febrile at recruitment, and one-fifth had diabetes mellitus (Table 1). There were no other important coexisting medical conditions among study subjects. Of the 80 patients, 39 were recruited into the intervention arm and 41 into the control arm (Figure 1). Of the 80 patients administered intravenous antibiotics in the trial, the mean duration of IV antibiotics in the 24-hour group (range) was 25.5 (17–40) hours, and in the ≥72-hour group it was 78 (41.5–210) hours. The majority were administered cephazolin in both study arms (Table 2). Blood cultures were drawn on most patients in this study and were negative in all cases, and there was no other positive microbiology for any patients in this study.

Primary Outcome

Of the 39 participants allocated to the intervention (24-hour) group, 31 (79%) achieved the primary outcome of cellulitis resolution, compared with 35 of 41 (85%) in the control group. The difference in primary outcomes was –5.8% (95% confidence interval [CI], –22.5% to 10.7%). When excluding patients who withdrew consent, the proportions with success/cure were 31 of 38 patients (81.6%) in the intervention group and 35 of 39 patients (90%) in the control group (difference, –8.2%; 95% CI, –23.7% to 7.4%).

Secondary Outcomes

There were no significant differences in the duration of fever by intervention group (Mann-Whitney U test: $P = .34$). The decrease in pain score was 0.22 units per day in the 24-hour arm
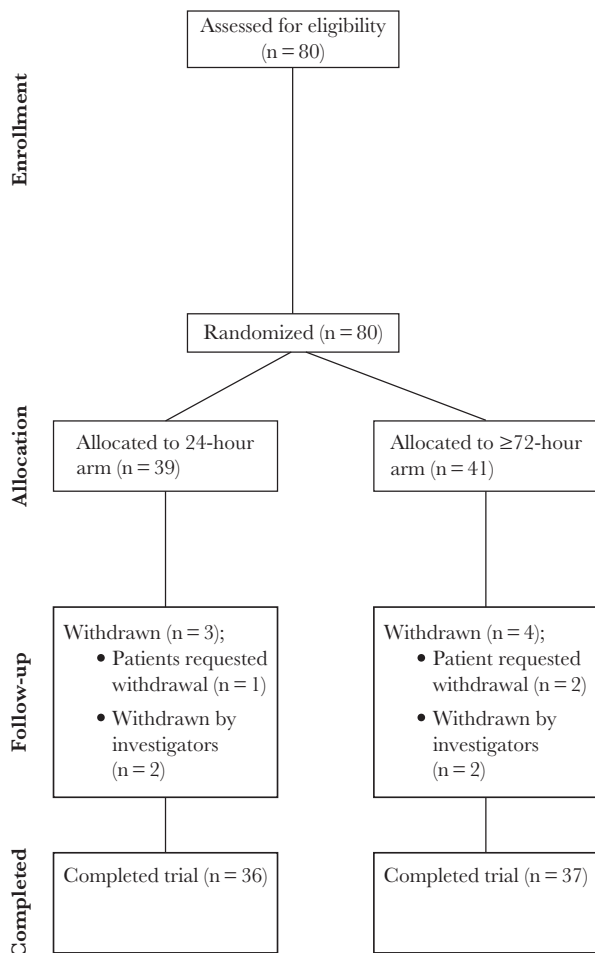
Figure 1. Flow diagram of patient randomization and follow-up.

and was similar in the ≥72-hour arm (–0.20 units per day, *P* for interaction arm × day = .55). There were no significant differences in overall pain scores in patients by intervention group (Figure 2).

Photography to allow for visual assessment of treatment response in the affected lower limb by a blinded reviewer was completed at baseline and in 59 patients (28 in the intervention arm and 31 in the control arm) at either or both visits 2 and 3. This assessment illustrated that the majority of participants had significant regression in their skin changes at visit 2 (48–72 hours) and visit 3 (7–10 days). Up to 14% of participants

Table 1. Baseline Characteristics of Trial Participants

Characteristic	24-Hour Arm	≥72-Hour Arm	Total
No. of patients	39	41	80
Male, No. (%)	29 (74.4)	31 (75.6)	60 (75)
Age, median (IQR), y	53 (33–74)	63 (45–70)	58.5 (40–70)
Fever (>38), No. (%)	13 (33.3)	16 (39.0)	29 (36.3)
Diabetes mellitus, No. (%)	7 (17.9)	10 (24.4)	17 (21.3)

Abbreviation: IQR, interquartile range.

Table 2. Intravenous Antimicrobial Prescribing for Cellulitis Based on Study Arm

| Antibiotic Administered	24-Hour Arm	≥72-Hour Arm	Total
Cephazolin	25	28	53
Flucloxacillin	8	4	12
Flucloxacillin/dicloxacillin then cephazolin	4	9	13
Teicoplanin then Cephazolin	1	0	1
Benzylpenicillin	1	0	1
Total	39	41	80

displayed extension of skin changes at visit 2, and it was not uncommon for skin appearances to be unchanged at visits 2 and 3. (Table 3). There were no statistical differences in rated skin changes between groups.

Participant Withdrawal

One patient randomized to the 24-hour arm and 2 patients randomized to the ≥72-hour arm chose to withdraw from the trial. Four patients were removed from the trial by the investigators. In the 24-hour arm, 1 patient developed hemodynamic instability within the 24-hour period, necessitating intensive care admission, and a second patient was withdrawn due to severe pain. In the ≥72-hour arm, 2 patients were withdrawn by investigators; 1 patient failed to respond to 6 days of IV therapy, and the second patient developed a soft tissue collection requiring surgical management.

Failures to Respond to Therapy and Relapses

Six patients were assessed by clinicians as not meeting the primary outcome measure for resolution of cellulitis, 4 from the 24-hour arm and 2 from the ≥72-hour arm. Among the 24-hour group, 1 patient relapsed and was administered an additional 5 days of oral antibiotics, a second patient relapsed 7 days after completing antibiotics and was administered further IV and oral antibiotics, a third patient received a prolonged course of oral
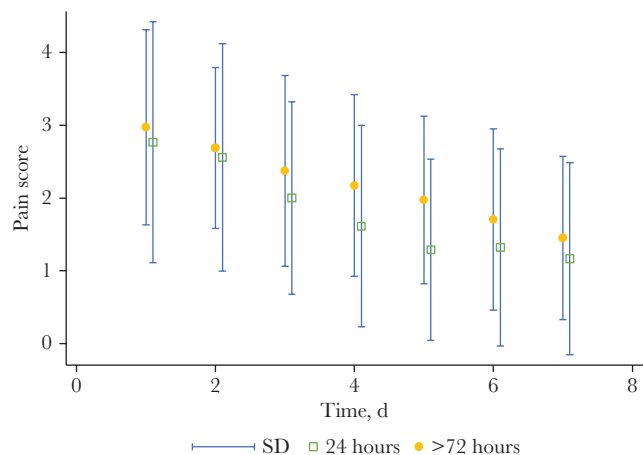
Figure 2. Wong-Baker Pain Scale scores by day and study arm.

Table 3. Photographic Assessment Results Based on Study Arm

Study Arm	Visit 2 (48–72 Hours)		Visit 3 (7–10 Days)	
	24 Hours	≥72 Hours	24 Hours	≥72 Hours
No. assessed	28	29	25	30
Significant regression, No. (%)	12 (43)	9 (31)	15 (60)	15 (50)
Minimal regression, No. (%)	9 (32)	9 (31)	8 (32)	12 (40)
Unchanged, No. (%)	3 (11)	7 (24)	2 (8)	2 (6)
Extension, No. (%)	4 (14)	4 (14)	0	1 (3)

antibiotics totaling 14 days, and a fourth patient recommenced IV antibiotics after starting oral antibiotics due to worsening cellulitis. Among the ≥72-hour group, 1 patient relapsed and was administered a further 6 weeks of oral antibiotics, and a second patient recommenced IV therapy for a further 7 days.

Adverse Events

Only 1 patient, randomized to the 24-hour arm, experienced an adverse event related to treatment. At day 8, the patient developed headaches and loose stools, which resolved after antibiotics were discontinued; tests for *Clostridium difficile* were negative.

DISCUSSION

Uncomplicated cellulitis is a common reason for referral to hospital, yet we experienced several challenges in conducting this trial. In this study, we found high rates of clinical cure in both arms, but because of the failure to recruit sufficient participants, there was not sufficient power to detect differences in the primary outcome. We have reported on the results from this study to provide pilot data for future studies and to disseminate some lessons learned.

Cellulitis is diagnosed solely on clinical grounds and may be confused with several mimicking conditions. Furthermore, the nomenclature in relation to skin and skin structure infections (SSSIs) may be used loosely due to overlapping signs, such that the distinction between cellulitis and an abscess may not always be clinically apparent [4]. There is also a lack of validated tools with which to assess a successful response to therapy [1, 7].

SSSIs are common reasons for patients presenting to primary care clinics and hospitals. In the United States, SSSIs account for 14 million outpatient visits and 650 000 hospital admissions annually. In the Australian context, it has been estimated that there are 26 000 cases of SSSIs per year requiring treatment [15]. Australian statistics have also reported potentially preventable hospitalizations in 2014–2015, with cellulitis accounting for 59 466 hospital separations in Australia [15]. Similarly, a study in Ireland revealed that one-third of patients with cellulitis were inappropriately admitted to hospital [16]. Moreover, misdiagnosis and the unnecessary use of antibiotics to treat noninfectious conditions [7] result in avoidable antibiotic exposure in half of all uncomplicated skin infections [17].

The rationale for shorter courses of antimicrobials is that cellulitis is characterized by a low bacterial burden, as evidenced by poor recovery of viable organisms from microbiological specimens and systemic symptoms, which respond rapidly to treatment [18].

Although antibiotic therapy is the accepted treatment for cellulitis, there is no consensus regarding the optimal treatment regimen [10, 11, 14, 19]. Intravenous therapy is said to be indicated in the presence of severe local symptoms and signs, significant systemic features, or lack of response to oral therapy after 48 hours [10]. In addition, hospital admission may be indicated in patients with systemic signs of infection, patients who previously failed oral antibiotic therapy, and those with unstable comorbidities [16]. However, several studies on the duration of IV therapy have not reached conclusive findings on an optimal duration, but have found that overuse of antibiotics is common and that the use of parenteral antibiotics may be unnecessary for some patients [11, 20, 21]. It has been demonstrated that it is not uncommon for IV therapy duration to be between 5 and 10 days [17, 22]. Australian studies that have focused on comparing home-based vs hospital treatment for cellulitis reported a mean duration of treatment of 6 days for an outcome of clinical cure [23, 24].

Treatment length can significantly affect the economic and social costs involved with cellulitis [19]. Shorter treatment involves medication cost savings and improves the quality of life of the patient by limiting the side effects of treatment and length of hospital stay. The studies by Grayson et al. and Donald et al. concluded that outcomes for treatment in the home were not significantly different than those in hospital and provided the benefit of freed-up hospital beds, improved quality of life for the patient, and reduced risk of nosocomial infection [23, 24].

The outcome of clinical cure in cases of cellulitis is ill-defined in the existing literature. In general terms, cure has been defined as the complete resolution of soft tissue infection, such that antibiotic therapy can be discontinued or changed to oral antibiotics [10]. In this trial, clinical assessment of cure was aided by the participant's diary to report fever, pain, analgesia intake, and mobility. Photographic assessment was also performed in this study, revealing that the majority of patients had visible regression in skin changes within 48–72 hours. However, a proportion of patients may have had either no visible changes or an extension to the affected area clinically despite appropriate therapy. This may explain why this trial could not overcome individual subjective clinician assessment of response to therapy and subsequent decisions to alter management.

This trial found that a shorter duration of IV therapy had similar results to a longer duration of IV therapy; however, the small size of the patient cohort in this study and the failure to recruit to target resulted in a failure of the noninferiority design. Therefore, it is not possible to conclude that short-course therapy is noninferior to longer therapy. The lessons learned

from performing this trial are several. First, conditions such as cellulitis, in which both diagnosis and response to therapy are clinically based and semisubjective, resist examination by traditional comparative trial methods. What is more, diagnostic ambiguity required the application of additional resources to ensure that strict inclusion and exclusion criteria were adhered to and that alternative diagnoses were excluded. The extent of this was unanticipated. Moreover, in relatively benign disease states such as SSTIs, where rapid recovery from systemic upset is the norm, there may be difficulty in retaining trial participants who perceive no personal benefit at completion of follow-up after recovery. Finally, in the case of common conditions such as cellulitis, for which there is a paucity of controlled treatment trial data, individual clinicians' practices tend to be deeply engrained. This led to protocol violations and subject withdrawal, as participating clinicians prioritized existing clinical practice over trial protocol.

Shorter-duration IV therapy for cellulitis, if proven to be safe and efficacious, would improve patients' quality of life, reduce risks of treatment, minimize avoidable antibiotic exposure, and deliver economic cost savings to health services. This question still needs to be answered by a clinical trial, with attention given to adequate resourcing for education and training of frontline investigators and surveillance and recruitment of eligible participants earlier in the course of infection before exclusion criteria are met. In addition, studying the treatment of cellulitis successfully will also require objective and validated outcome measures.

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