Efficacy and safety of intravenous ceftriaxone at home versus intravenous flucloxacillin in hospital for children with cellulitis (CHOICE): a single-centre, open-label, randomised, controlled, non-inferiority trial

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Summary

Background Outpatient parenteral antimicrobial therapy in children is common despite no evidence of its efficacy or safety from clinical trials. We aimed to compare the efficacy and safety of intravenous antibiotic therapy at home with that of standard treatment in hospital for children with moderate to severe cellulitis.

Methods The Cellulitis at Home or Inpatient in Children from the Emergency Department (CHOICE) trial was a randomised, controlled, non-inferiority trial in children aged 6 months to 18 years who presented to the emergency department at The Royal Children's Hospital (Melbourne, VIC, Australia) with uncomplicated moderate to severe cellulitis. Participants were randomly assigned to receive either intravenous ceftriaxone (50 mg/kg once daily) at home or intravenous flucloxacillin (50 mg/kg every 6 h) in hospital with web-based randomisation, stratified by age and periorbital cellulitis. The primary outcome was treatment failure, which was defined as no clinical improvement or occurrence of an adverse event, resulting in a change in empiric antibiotics within 48 h of the first dose. Secondary outcomes included adverse events and acquisition of antibiotic-resistant bacteria. Outcomes were assessed in all randomised participants with outcome data (intention-to-treat population) and in all individuals who received treatment as allocated and did not have any major protocol violations (per-protocol population). For home treatment to be non-inferior to hospital treatment, the difference between groups in the proportion of children with treatment failure in the intention-to-treat population had to be less than 15%. This trial is registered with ClinicalTrials.gov, number NCT02334124.

Findings Between Jan 9, 2015, and June 15, 2017, we screened 1135 children for eligibility, of whom 190 were randomly assigned to receive ceftriaxone at home (n=95) or flucloxacillin in hospital (n=95). The intention-to-treat analysis comprised 188 children (93 in the home group and 95 in the hospital group) because two children in the home group were found to be ineligible after randomisation and were excluded. Treatment failure occurred in two (2%) children in the home group and in seven (7%) children in the hospital group (risk difference –5·2%, 95% CI –11·3 to 0·8, p=0·088). In the per-protocol analysis, treatment failure occurred in one (1%) of 89 children in the home group and in seven (8%) of 91 children in the hospital group (–6·5%, –12·4 to –0·7). Fewer children treated at home than in hospital had an adverse event (two [2%] *vs* ten [11%]; p=0·048). There was no difference between groups in rates of nasal acquisition of meticillin-resistant *Staphylococcus aureus* or gastrointestinal acquisition of extended-spectrum β-lactamase-producing bacteria or *Clostridium difficile* after 3 months.

Interpretation Home treatment with intravenous ceftriaxone is not inferior to treatment in hospital with intravenous flucloxacillin for children with cellulitis. The standard of care for the intravenous treatment of uncomplicated cellulitis in children should be home or outpatient care when feasible.

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Introduction

Use of intravenous antibiotics in non-inpatient settings, known as outpatient parenteral antimicrobial therapy (OPAT), has increased in children.[1,2] This change in practice is due to increased awareness among clinicians that admission to hospital can negatively affect quality of life in children, can lead to hospital-acquired infections, and is associated with greater costs than OPAT.[3–5]

Given the choice, children and caregivers will often choose treatment at home, an important factor as health care becomes more patient-centred.[6,7] As a result of this acceptance, OPAT has shifted rapidly from being a novel concept to an accepted model of care. However, published evidence for its use in children has not kept pace. A systematic review[8] of studies published between Jan 1, 1946, and Jan 31, 2017, found only a single randomised controlled trial of OPAT in children, and its primary outcome was

Research in context

Evidence before this study

We searched MEDLINE from Jan 1, 1946, to Oct 2, 2018, and Embase from Jan 1, 1974, to Oct 3, 2018, using the search terms "cellulitis/ or soft tissue infections/", "ceftriaxone", "outpatient", "home care/", and "ambulatory care/". We limited the search to studies in children aged 18 years and younger; no language restrictions were applied. This search did not identify any randomised controlled trials investigating the efficacy or safety of home or ambulatory management of cellulitis. The only randomised controlled trial to compare home-based versus hospital-based care primarily investigated quality of life. However, several retrospective and observational studies were identified, which indicated widespread use of home or ambulatory care in children, despite the absence of robust evidence of its efficacy and safety. These studies found that some children with moderate or severe cellulitis could be successfully treated via a home or ambulatory care pathway, with readmission rates ranging from 0% to 20%.

Added value of this study

This is the first randomised controlled trial of any acute infection requiring intravenous antibiotic therapy in children to compare the efficacy and safety of home or ambulatory treatment with standard management in hospital. Findings from our study provide robust evidence that children with moderate to severe cellulitis can be effectively treated at home without the need for hospital admission. Additionally, we have shown that this management pathway is highly acceptable to families and has cost-saving benefits for the hospital. Of equal importance to clinicians, there was no sign of increased colonisation with antibiotic-resistant nasal or gastrointestinal bacteria when ceftriaxone was used for outpatient parenteral antimicrobial therapy.

Implications of all the available evidence

Our study provides the first unbiased evidence to support the existing literature and increasing practice of treating childhood infections with intravenous antibiotics outside the hospital environment. It promotes the broader uptake of home or ambulatory management of moderate to severe cellulitis so that children can avoid hospital admission. For centres without a pre-existing home-care or ambulatory service, these findings enable advocacy for resources for a similar treatment pathway. For those with existing services, this study acts as a platform to be replicated in other acute infections to increase the evidence base for home or ambulatory care.

quality of life. The inability to mask patients and clinicians to treatment location might have discouraged trials in this field. However, most randomised controlled trials of standard in-hospital versus at-home care in adult patients have used an open-label approach,[9] and this strategy could also be used in clinical trials of OPAT in children.

The scarcity of evidence has not stopped clinicians from using OPAT, with an increasing number of reports of its use in institutional practice, including use of OPAT for patients directly from the emergency department, completely avoiding admission to hospital.[4,10,11–13] The antibiotic most frequently used for OPAT in children, particularly for admission avoidance management pathways, is ceftriaxone, a broad-spectrum cephalosporin.[1,2,13] The reasons for using ceftriaxone are that it can be administered once daily; it is given as a single dose, allowing a peripheral cannula to be inserted in the emergency department; and it is effective against many pathogens that cause common childhood infections.[14] However, broad-spectrum cephalosporin use has been temporally associated with isolation of antibiotic-resistant bacteria in studies in adult inpatients.[15–17] Although this finding has not been observed when ceftriaxone has been used at home, the global crisis of antibiotic resistance raises legitimate concerns, which have not been addressed for OPAT in children. It is unclear whether the benefits of OPAT outweigh the disadvantages of ceftriaxone use in this setting.

We therefore designed the first randomised controlled trial of OPAT for admission avoidance in children, using ceftriaxone to treat moderate to severe cellulitis as a paradigm. Cellulitis, a skin infection, is a common presentation to the emergency department, often but not always affecting the limbs. Although most children with cellulitis can be treated with oral antibiotic therapy, many children with moderate to severe cellulitis require intravenous antibiotic therapy; skin and soft-tissue infections in these children account for more than 74 000 hospital admissions each year in the USA.[18] Cellulitis in children admitted to the hospital is usually managed with narrow-spectrum, intravenous antibiotics, such as flucloxacillin. However, flucloxacillin is administered every 6 h and so is not compatible with ambulatory use through a peripheral cannula, with ceftriaxone being the only viable alternative. For a trial of OPAT to have useful outcomes that are translatable to clinical practice, it must compare a feasible OPAT option with standard hospital treatment.

We aimed to compare the efficacy and safety of home-based treatment with intravenous ceftriaxone with that of standard treatment in hospital with intravenous flucloxacillin for children with cellulitis.

Methods

Study design and participants

The Cellulitis at Home or Inpatient in Children from the Emergency Department (CHOICE) trial was a single-centre, randomised, controlled, open-label, non-inferiority trial.[19] Patients were enrolled from The Royal Children's Hospital, a tertiary paediatric hospital in

Melbourne, VIC, Australia. The study protocol was published previously.[19]

Briefly, eligible participants were aged 6 months to 1 year and had presented to the emergency department at The Royal Children's Hospital with moderate to severe cellulitis. Inclusion criteria included a diagnosis of cellulitis that required administration of intravenous antibiotics by an experienced clinician (senior trainee) in the emergency department. Reasons for intravenous antibiotics included no response to oral antibiotics (no improvement despite 24 h of treatment); rapidly spreading redness; moderate to severe swelling, erythema, or pain; systemic symptoms or signs; and difficult-to-treat areas (eg, facial or periorbital). Children were excluded if they had complicated cellulitis (eg, an undrained abscess), toxicity (eg, tachycardia when afebrile), underlying comorbidities (eg, immunosupression), or mild cellulitis; they were younger than 6 months; or intravenous access could not be obtained (a full description of the exclusion criteria is in the appendix).

Written informed consent was obtained from a parent or guardian, and from the child when appropriate, by a study investigator or research nurse. Ethical approval was obtained from the human research and ethics committee at The Royal Children's Hospital, reference number HREC34254.

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio with a web-based randomisation tool to receive either intravenous flucloxacillin in hospital (50 mg/kg every 6 h) or intravenous ceftriaxone at home (50 mg/kg once daily). Randomisation was done in randomly permuted blocks of variable length, stratified by age (6 months to 8 years *vs* 9 years to 18 years) and presence of periorbital cellulitis. These stratification factors were previously identified as reasons for clinicians' hesitation in using OPAT. Preparation of the randomisation sequence was completed by a data management coordinator who was independent of the research team and had no further role in the trial. The trial statistician was masked to treatment assignment until the primary outcome was analysed. The nurses and clinicians who administered the treatments, as well as the patients, were not masked to group assignment.

Procedures

All children had an intravenous peripheral cannula inserted and the first dose of antibiotic administered in the emergency department. Blood cultures and skin swabs were collected from patients with discharge from the infected area. A line was drawn on the skin in the emergency department to demarcate the cellulitis. In all patients, the decision to cease intravenous antibiotics was made when deemed clinically appropriate by the hospital or home-care medical registrar, reflecting normal clinical practice.

Patients in the hospital group received intravenous flucloxacillin every 6 h on the hospital ward. A hospital ward medical registrar (senior trainee) reviewed the patient for clinical progress each day, and nursing staff assessed and recorded vital signs at least every 4 h. All children in the hospital group had continuous infusion of normal saline through an intravenous cannula between antibiotic doses, as per standard practice.

Children in the home group were referred to the home-care team, who were available 24 h a day, 7 days a week. After receiving the first dose of ceftriaxone in the emergency department and meeting a home-care nurse, the patient went home with the peripheral cannula in situ until intravenous antibiotics were ceased. Families were provided with a contact telephone number for a home-care nurse. A nurse visited the child at home and administered intravenous ceftriaxone 50 mg/kg over a period of 3–5 min once daily until the child was deemed suitable for oral therapy. A home-care medical registrar (senior trainee) reviewed the child in person at least once during treatment, daily by teleconferencing, and when necessary, by reviewing digital photographs.

See Online for appendix

Stool and nasal samples were collected at baseline and 7–14 days and 3 months after start of intravenous antibiotic therapy to test for the potential acquisition of extended-spectrum β-lactamase (ESBL)-producing bacteria, vancomycin-resistant enterococci (VRE), meticillin-resistant *Staphylococcus aureus* (MRSA), and *Clostridium difficile*. Microbiological laboratory methods are described in detail in the appendix.

Outcomes

The primary outcome was treatment failure, which was defined as no clinical improvement or occurrence of an adverse event, resulting in a change of initial empiric antibiotics within 2 days (48 h) of administration of the first antibiotic dose in the emergency department. Clinical improvement was an objective measure: either continuous or binary assessments of fever, cellulitis area, severity of swelling, and erythema, as per the trial protocol. No clinical improvement was defined as no improvement in any of these four assessment criteria compared with baseline, and it resulted in a discussion between the registrar and consultant (and usually other members of the team), which led to a discussion with the parents or guardian of the child before changing the antibiotic.

Secondary outcomes, assessed up to 14 days after discharge from care, were length of stay in the emergency department, cessation of erythema spread within 24 h (by observing spread of erythema from the demarcated line), duration of intravenous antibiotic therapy, number of intravenous catheterisations during treatment, length of stay in medical care, re-presentation to the emergency department, hospital readmission, and safety measures (adverse events and complications). The hospital and home-care registrars were trained to do assessments in a

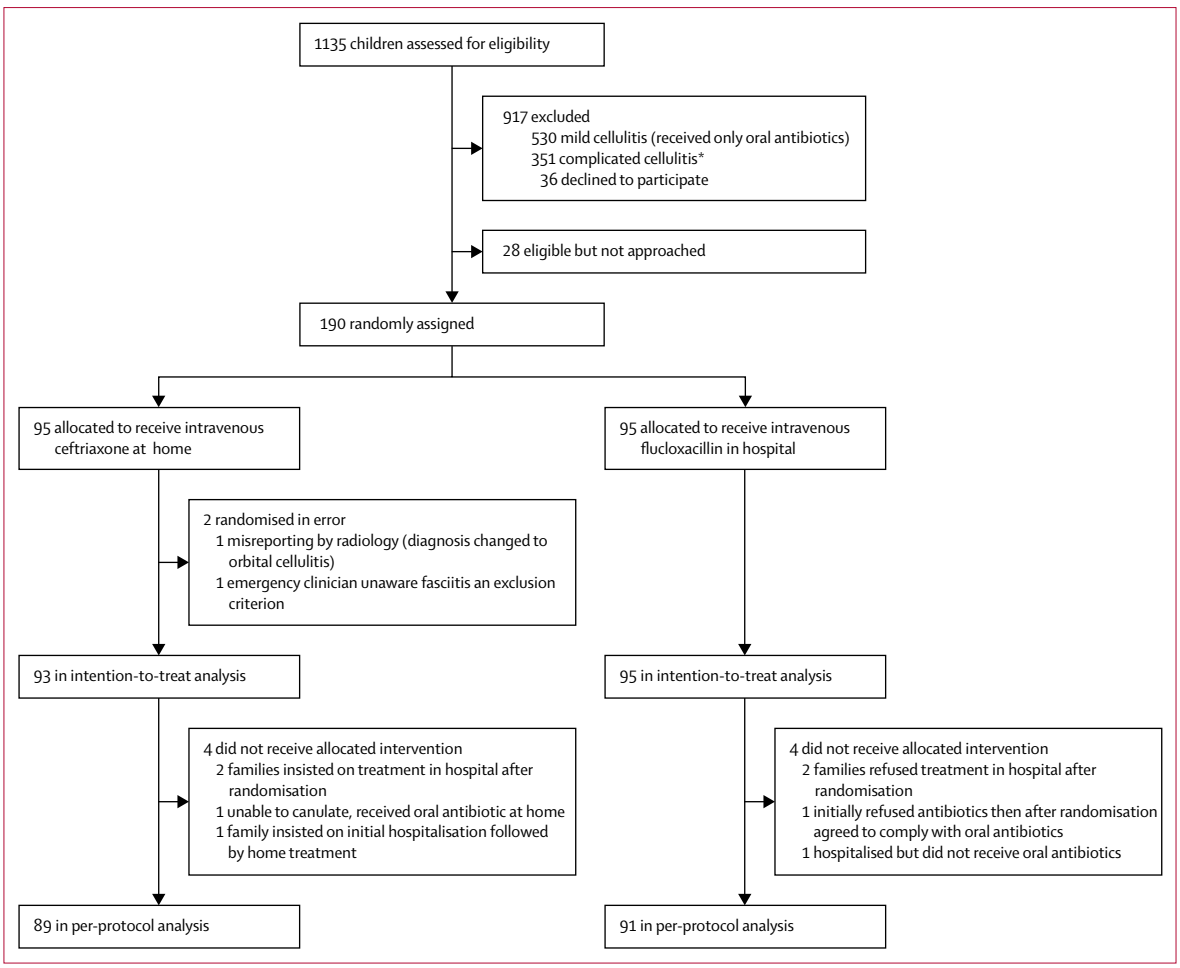

Figure: **Trial profile**
*Included abscess requiring surgical drainage (n=73), toxicity (tachycardia when afebrile, hypotension, or poor central perfusion; n=18), orbital cellulitis (n=15), comorbidities (n=124), requirement for further imaging or surgical management (n=89), or age younger than 6 months (n=32).

standardised way and documented their assessment of the child daily with regards to clinical improvement, adverse events, complications, and cessation of cellulitis spread.

Microbiological outcomes were assessed in a subgroup of patients who consented. Patients were tested for antibiotic-resistant bacteria and *C difficile* at baseline and 7–14 days and 3 months after treatment initiation; acquisition was defined as detection of at least one of ESBL-producing bacteria, VRE, MRSA, and *C difficile* at a timepoint after intravenous antibiotic therapy in patients who had previously tested negative. This substudy was optional, and not providing samples did not preclude patients from the study.

To assess quality of life, 7–14 days after discharge from medical care parents were asked to anonymously rate their experience (1–5 on the Likert scale, with 1 meaning very poor and 5 meaning very good) and disruption to routine (score of 1–3, with 1 meaning no disruption, 2 meaning slight disruption, and 3 meaning substantial disruption), and to state their preference for either hospital-based or home-based treatment.

An institutional cost comparison was done, including the cost of nursing and medical resources (which included availability of the home-care team for referral or telephone calls 24 h a day, 7 days a week), consumable items, indirect overhead costs (including administrative time), information technology, and use of hospital vehicles for visiting patients. A full cost-effectiveness analysis was planned and done alongside this trial, of which the results will be published separately.

Statistical analysis

A previous study[11] at The Royal Children's Hospital showed that treatment failure occurred in 5–7% of children with cellulitis who were treated with flucloxacillin in hospital. Thus, for this study, we assumed that about 7% of children treated in hospital would have treatment failure and estimated that treatment failure would occur in about 10% of children treated at home. We specified

that for the home group to be non-inferior to the hospital group (and clinically acceptable based on the literature[13] and discussions with clinicians in the emergency department), the upper margin of the two-sided 95% CI of the difference in the primary outcome between the home and hospital groups should be no greater than 15%. In other words, OPAT would be deemed acceptable to clinicians and families if 80% of children can be successfully treated at home. On the basis of this premise, we required 89 participants per group to provide a statistical power of 80%. Allowing for a dropout rate or crossover between treatments of 5%, 94 participants were required in each treatment group.

We calculated a risk difference between groups in the primary outcome, and its two-sided 95% CI, using a binomial regression model, adjusted for the stratification factors (age at randomisation and presence of periorbital cellulitis) as predictors. Binary secondary outcomes were also compared between groups with this model. For continuous secondary outcomes, we calculated odds ratios using a linear regression model adjusted for the stratification factors.

Primary and secondary outcomes were assessed in the intention-to-treat and per-protocol populations, whereas microbiological outcomes were assessed in the per-protocol population only. The intention-to-treat analysis included all randomised participants with outcome data. The per-protocol analysis included all individuals who received treatment as allocated and did not have any major protocol violations, such as receiving treatment in the hospital if randomised to the home group, receiving treatment at home if randomised to the hospital group, or not receiving any study treatment. Participants who were found to be randomised in error were excluded from the analysis.

An independent data safety monitoring board provided trial oversight and reviewed data, including adverse events and protocol violations, by treatment group every 6 months for the duration of the recruitment period.

All analyses were done with Stata version 15.0. This trial is registered with ClinicalTrials.gov, number NCT02334124.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The first and corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Ceftriaxone at home (n=93)	Flucloxacillin in hospital (n=95)
Age, years	7·01 (4·98)	7·08 (4·20)
Age category		
6 months to <9 years	66 (71%)	67 (71%)
9 years to <18 years	27 (29%)	28 (29%)
Sex		
Male	56 (60%)	46 (48%)
Female	37 (40%)	49 (52%)
Previous oral antibiotic therapy	54 (58%)	43 (45%)
Systemic features*	37 (40%)	42 (44%)
Febrile in emergency department†	3 (3%)	18 (19%)
Febrile at home or in general practice†	19 (20%)	16 (17%)
Reported fever	2 (2%)	3 (3%)
Vomiting	2 (2%)	3 (3%)
Lethargic	7 (8%)	13 (14%)
Rigors	2 (2%)	1 (1%)
Other‡	10 (11%)	7 (7%)
Site of cellulitis		
Lower limb	40 (43%)	48 (51%)
Periorbital	25 (27%)	28 (29%)
Upper limb	20 (22%)	10 (11%)
Head and neck	2 (2%)	0
Trunk	0	2 (2%)
Chest	1 (1%)	0
Back	1 (1%)	2 (2%)
Face	3 (3%)	5 (5%)
Perineum	1 (1%)	0
Cellulitis features		
Body surface area, %	1·0 (1·5)	0·8 (0·8)
Functional impairment	53 (57%)	52 (55%)
Moderate to severe swelling	65 (70%)	63 (66%)
Comorbidities	13 (14%)	13 (14%)
Eczema	4 (4%)	6 (6%)
Developmental	4 (4%)	3 (3%)
Asthma	1 (1%)	1 (1%)
Ventricular septal defect	1 (1%)	1 (1%)
Other§	3 (3%)	2 (2%)

Data are mean (SD) or n (%). *Several patients had more than one systemic feature. †Febrile was defined as body temperature >38°C. ‡Other systemic features were irritability (n=3), generalised aches (n=5), and rash (n=2) in the ceftriaxone at home group, and headache (n=3) and generalised aches (n=4) in the flucloxacillin in hospital group. §Other comorbidities were inguinal hernia (n=1), cleft lip or palate (n=1), and other skin disorder (n=1) in the ceftriaxone at home group and laryngomalacia (n=1) and haematological disorder (n=1) in the flucloxacillin in hospital group.

Table 1: **Baseline demographics and clinical characteristics of the intention-to-treat population**

Results

Between Jan 9, 2015, and June 15, 2017, 1135 children were screened for eligibility, of whom 190 were randomly assigned to receive treatment at home with ceftriaxone (n=95) or in hospital with flucloxacillin (n=95; figure). Two patients in the home group were found to be ineligible and were excluded post-randomisation. Thus, the intention-to-treat population comprised 188 children, including 93 in the home group and 95 in the hospital group.

Median duration of follow-up was 7 days (IQR 7–8). Baseline characteristics of the intention-to-treat population are shown in table 1. 79 (42%) of 118 patients

	Ceftriaxone at home (n=93)	Flucloxacillin in hospital (n=95)	Risk difference (95% CI)*	p value
Treatment failure (primary outcome)				
Intention-to-treat analysis	2/93 (2%)	7/95 (7%)	−5·3 (−11·3 to 0·8)	0·088
Per-protocol analysis	1/89 (1%)	7/91 (8%)	−6·5 (−12·4 to −0·7)	0·029
Secondary clinical outcomes†				
Length of stay in emergency department, h	4·3 (1·9)	5·5 (3·1)	−1·2 (−1·9 to −0·4)	0·0019
Cellulitis stopped spreading within 24 h	76 (82%)	61 (64%)	16·8 (4·8 to 28·8)	0·0062
Adverse event during care	2 (2%)	10 (11%)	−9·8 (−19·5 to −0·1)	0·048
Complications during care	6 (6%)	6 (6%)	0·0 (−6·9 to 6·9)	0·99
Required intravenous cannula reinsertion during care	3 (3%)	17 (18%)	−16·7 (−28·2 to −5·3)	0·0043
Duration of intravenous antibiotics, days	2·2 (2·4)	1·7 (1·1)	0·5 (0·0 to 1·1)	0·045
Duration of oral antibiotics after intravenous antibiotics, days	6·1 (2·8)	6·3 (2·5)	−0·3 (−1·0 to 0·5)	0·49
Total duration of antibiotics, days	8·1 (5·0)	8·3 (2·9)	0·2 (−1·0 to 1·4)	0·73
Duration of medical care, days	2·7 (2·4)	2·0 (1·1)	0·6 (0·1 to 1·2)	0·0020
Re-presented to emergency department within 14 days of discharge for same cellulitis	2 (2%)	2 (2%)	0·0 (−4·1 to 4·2)	0·98
Secondary quality-of-life outcomes‡				
Returned satisfaction questionnaire	73/93 (78%)	62/95 (65%)	1·9 (1·0 to 3·7)	0·044
Reported very good experience	69/73 (95%)	45/62 (73%)	6·5 (2·1 to 20·6)	0·0014
Reported very poor experience	0	0	NA	NA
No disruption to parental routine	48/73 (66%)	25/62 (40%)	2·8 (1·4 to 5·7)	0·0035
No disruption to child routine	49/73 (67%)	22/62 (35%)	3·7 (1·8 to 7·8)	0·0003
Would choose treatment in same location	58/60 (97%)	16/38 (42%)	21·1 (4·5 to 99·3)	0·0001

Data are n/N (%), n (%), or mean (SD). NA=not appropriate. *Risk difference is reported for binary outcomes, mean difference for continuous outcomes, and odds ratios for questionnaire responses. †Secondary clinical outcomes are shown for the intention-to-treat population. ‡Secondary quality-of-life outcomes are shown for participants in the intention-to-treat population who returned questionnaires; questionnaire responses were not adjusted for stratification factors.

Table 2: **Comparison of primary and secondary outcomes, adjusted for stratification factors**

presented with systemic features, primarily fever (table 1). The proportion of patients who were febrile in the emergency department was lower in the home group than in the hospital group (table 1). 97 (52%) participants had previously received oral antibiotic therapy, with a median number of four doses (IQR 3–8). No patient had received intravenous antibiotics before randomisation.

Two (2%) of 93 patients in the home group had treatment failure compared with seven (7%) of 95 patients in the hospital group (risk difference −5·2%, 95% CI −11·3 to 0·8; table 2); thus, the prespecified criterion for non-inferiority was met. Of the two patients in the home group with treatment failure, one developed a localised abscess 1 day after initial presentation to the emergency department. This patient was found to have a family history of MRSA infection and so was admitted to hospital for intravenous vancomycin; MRSA was detected in a skin swab from this patient 3 days after initial admission. The second patient with treatment failure in the home group was treated in hospital with intravenous flucloxacillin after randomisation. This patient developed a rash consistent with flucloxacillin allergy after 24 h and was, therefore, switched to intravenous ceftriaxone. In the hospital group, five of the seven patients with treatment failure had no clinical improvement, which prompted an additional antibiotic to be added to the treatment regimen within 48 h (intravenous ceftriaxone in three, intravenous vancomycin in one, and oral clindamycin in one). The remaining two patients were changed to a different antibiotic: one to benzylpenicillin because of no clinical improvement after 47 h and the other to ceftriaxone after 24 h because of developing a rash consistent with flucloxacillin allergy. All patients had fully recovered within 14 days.

In the per-protocol analysis of the primary outcome, the proportion of patients with treatment failure was significantly lower in the home group than in the hospital group (one [1%] of 89 *vs* seven [8%] of 91; risk difference −6·5%, 95% CI −12·4 to −0·7).

The proportion of children in the intention-to-treat analysis who had an adverse event was lower in the home group than in the hospital group (2% [two of 93] *vs* 11% [ten of 95]; p=0·048; tables 2, 3). One patient in the hospital group had hypotension with intermittent low blood pressure (lowest reading 85/56 mm Hg, with normal blood pressure in between and without associated tachycardia), which was not associated with treatment. The same proportion of children in both groups had complications during treatment (p=0·99; table 2). These

	Ceftriaxone at home (n=93)	Flucloxacillin in hospital (n=95)
Rash	1 (1%)	0
Dosing error*	1 (1%)	0
Diarrhoea or vomiting	1 (1%)	7 (7%)
Headache	0	1 (1%)
Vasovagal episode	0	1 (1%)
Hypotension	0	0

Data are n (%). *Requested by the data safety monitoring board to be reported as an adverse event.

Table 3: **Adverse events**

comprised drainage of an abscess or blister in six patients in the home group and five in the hospital group, and removal of a foreign body in one patient in the hospital group.

Secondary outcomes favouring the home group were length of stay in the emergency department and rate of recatheterisation, whereas outcomes favouring the hospital group were duration of intravenous antibiotic therapy and medical care (table 2). 2% of children in both groups re-presented to the emergency department within 14 days after discharge (p=0·98). The per-protocol analysis of all secondary clinical outcomes yielded similar results to the intention-to-treat analysis (appendix). An exploratory analysis of patients who had failed on previous antibiotic therapy compared with those who had not received antibiotics previously did not show any differences in primary or secondary outcomes (appendix).

Blood cultures were taken from 170 patients, one (1%) of whom had a single positive blood culture for *S aureus*. This patient, who was in the home group, was subsequently diagnosed with osteomyelitis upon a bone scan. He continued to receive ceftriaxone at home because he was already clinically well by the time the culture was flagged as positive; repeated blood culture was negative. 159 patients provided at least one microbiological sample; 98 patients provided nasal samples and 86 provided stool samples at 7–14 days or 3 months (or both) after intravenous antibiotic therapy. Patients who provided stool samples were slightly younger than those who did not (appendix), and patients with treatment failure were less likely to provide follow-up stool samples than those without (appendix). At baseline, there was no difference between groups in the prevalence of ESBL-producing bacteria and *C difficile* in stool samples (table 4), and no patient tested positive for VRE. No difference was seen between groups in the proportion of patients who had acquired ESBL-producing bacteria or *C difficile* at 7–14 days or 3 months after intravenous antibiotic therapy (table 4), and no patient acquired VRE at either timepoint. No patient in either group had nasal carriage of MRSA at baseline, although MRSA was cultured from the abscess of one patient in the hospital group. No patient had acquired MRSA after intravenous antibiotic therapy (table 4).

	Ceftriaxone at home	Flucloxacillin in hospital	p value
Colonisation at baseline			
Stool sample			
ESBL-producing bacteria	7/46 (15%)	4/44 (9%)	0·52
C difficile	4/46 (9%)	5/44 (11%)	0·74
Nasal swab			
MRSA	0/68	0/63	NA
Colonisation after intravenous antibiotic therapy			
Stool sample			
7–14 days			
ESBL-producing bacteria	10/48 (21%)	4/33 (12%)	0·38
C difficile	6/48 (13%)	4/33 (12%)	1·00
3 months			
ESBL-producing bacteria	8/44 (18%)	7/35 (20%)	0·84
C difficile	4/44 (9%)	4/35 (11%)	0·57
Nasal swab			
7–14 days			
MRSA	0/49	0/35	NA
3 months			
MRSA	1/54 (2%)	0/34	0·31
Newly acquired after intravenous antibiotic therapy*			
Stool sample			
7–14 days			
ESBL-producing bacteria	3/41 (7%)	0/29	0·26
C difficile	3/43 (7%)	2/31 (6%)	1·00
3 months			
ESBL-producing bacteria	4/40 (10%)	3/31 (10%)	1·00
C difficile	3/43 (7%)	2/35 (6%)	1·00
Nasal swab			
7–14 days			
MRSA	0/49	0/35	NA
3 months			
MRSA	0/53	0/34	NA

ESBL=extended spectrum β-lactamase. *C difficile=Clostridium difficile*. MRSA=meticillin-resistant *Staphylococcus aureus*. NA=not appropriate. *Patients who were persistently colonised or colonised without baseline samples were excluded from this analysis.

Table 4: **Microbiological outcomes in a subgroup of 159 patients (per-protocol analysis)**

With regards to quality of life during treatment, 69 (95%) of 73 parents in the home group rated the experience of care as very good compared with 45 (73%) of 62 parents in the hospital group (p=0·0014; table 2). Disruption to parental and child routine was significantly greater in the hospital group than in the home group, and more parents in the home than in the hospital group reported they would choose treatment for their child in the same location again (table 2).

At our institution, the mean cost of treating a patient with moderate to severe cellulitis at home is AUS$530 (£308) per day, compared with $1297 (£752) per day for a hospital bed on a medical ward. Patients treated at home

in the intention-to-treat analysis were under medical care for a combined total of 242 days. Including the cost of hospital stay for the two patients who were assigned home treatment but had treatment failure and subsequently required treatment in hospital (total of 6 days in hospital), the cost for the home group was $1463 (£849) per patient per day. Patients in the hospital group in the intention-to-treat analysis stayed in hospital for a total of 190 days, costing $2594 (£1505) per patient per day. Thus, the 95 patients who received hospital-based treatment had an excess cost of $110 387 (£64 052) compared with the 93 patients who received home treatment. The cost analysis of the per-protocol population yielded a cost difference of $122 104 (£70 884), in favour of the home group. Full details of the cost analysis in the per-protocol population are reported in the appendix.

Discussion

In this study, intravenous ceftriaxone at home was non-inferior to intravenous flucloxacillin in hospital for the primary outcome of treatment failure. In the per-protocol analysis, treatment failure was lower in the home group than in the hospital group. This difference was unlikely to be due to differences in the number of children who were febrile in the emergency department as, although more children in the hospital group than in the home group were febrile in the emergency department, only two of the 18 children who were febrile had treatment failure.

Treatment of cellulitis at home with ceftriaxone appeared to be safe, as indicated by the significantly lower frequency of adverse events in the home group than in the hospital group. Moreover, the proportions of participants who had complications during treatment or who re-presented to the emergency department were similar between groups. Although the frequency of formal reporting of adverse events was daily for both groups, children in hospital had more opportunities than children at home to report adverse events to clinicians or nurses. It is highly likely that symptomatic adverse events, such as vasovagal syncope, diarrhoea, and vomiting, were reported by parents in the home group. The worst outcome experienced by a patient at home was return to hospital for drainage of an abscess. No patient with moderate to severe cellulitis developed sepsis, consistent with previous studies.[11,20,21]

With antimicrobial resistance increasing globally, investigating acquisition of antimicrobial-resistant micro-organisms is as important as investigating clinical efficacy and safety. In this study, the risk of acquiring antibiotic-resistant nasal or gastrointestinal bacteria or *C difficile* was not significantly increased in patients treated at home with ceftriaxone compared with those treated with flucloxacillin in hospital, and no patient acquired MRSA. The association between third-generation cephalosporin use and colonisation with antibiotic-resistant microorganisms in children is less strong than in adults and predominantly comes from studies of antibiotic policy in neonatal units.[22,23] Although most of these studies were retrospective or observational, making exclusion of confounding factors difficult, a single prospective, crossover, intervention trial[22] showed that an antibiotic policy including cefotaxime was associated with colonisation of neonates with cefotaxime-resistant Enterobacteriaceae. However, a prospective longitudinal study[24] of antibiotic use in a single unit showed a steady increase over 25 years in resistance to third-generation cephalosporins, despite third-generation cephalosporins not being used. Similarly, studies investigating the association between use of third-generation cephalosporins and acquisition or colonisation with VRE, *C difficile*, or MRSA have either been in sick or inpatient populations with prolonged antibiotic use[15] or have not shown an association.[16] No previous studies associating ceftriaxone use with increased bacterial resistance were in previously healthy children receiving OPAT at home, and none investigated short-course use.[17,24–27] Therefore, we propose that our findings are due to a different population and different antibiotic duration.

Other factors to consider when interpreting the microbiological findings of our study include that Victoria has a low prevalence of antibiotic resistance in children, particularly MRSA, although this situation reflects many paediatric populations worldwide. Thus, the generalisability of the trial's findings might be limited to regions with low prevalence of antibiotic resistance in children.

Only around half of patients provided longitudinal samples for resistance analysis, so this result might not be representative of the entire study population. However, the tested patients were, for the most part, clinically indistinguishable from those who did not provide a sample (appendix). Our findings suggest, therefore, that short-term ceftriaxone use at home in previously healthy children is not associated with acquisition of resistance. However, as our study was powered for efficacy and not microbiological outcomes, larger studies are now needed of longer-term use in the outpatient or home setting.

Length of stay in the emergency department was longer in the hospital group than in the home group, likely reflecting the time spent waiting for a hospital bed, an important finding with increasing pressure to reduce waiting times in the emergency department.[28] Intravenous cannulation was also repeated more often in the hospital group than in the home group. This finding might be related to the use in hospital of low-volume, continuous infusion to keep the vein open or to the direct irritant effect of intravenous flucloxacillin.[29] The duration of intravenous treatment and consequent length of medical care were longer in the home group than in the hospital group by half a day, likely reflecting that the home-care staff had only one opportunity per day to stop treatment or discharge the patient because of the antibiotic dosing interval.

Parents reported high satisfaction rates with home management, and disruption to routine was

significantly lower at home than in hospital for both parents and patients. Although previous studies[4,13] have shown satisfaction for children treated via ambulatory pathways, this study is the first to compare satisfaction between home and hospital groups in non-preselected patients.

The strengths of this study are that it is the first randomised study of OPAT in children directly from the emergency department. The study is powered for clinical efficacy, with as low a risk of bias as is possible in a randomised controlled trial of OPAT. It is also the first to address the effects of ceftriaxone on antibiotic resistance when used in the short term for OPAT.

The main limitation of this study is the applicability of the findings to centres without a home-care visiting team. However, other studies[12,13] have shown that other ambulatory pathways (eg, day treatment centres and patients returning daily to the emergency department to be seen by and receive antibiotics from clinicians) are cost-effective and preferred by patients to treatment in hospital. We designed this study to be as widely applicable as possible to other health-care systems—for example, by administering ceftriaxone once daily rather than twice daily in the home group, by having junior doctors make the daily assessments, and by having medical doctors rather than study doctors assessing the patients. Additionally, patients who required abscess drainage were directed to the emergency department with minimal waiting time because they already had a management pathway identified.

Another limitation was the absence of a gold standard for the diagnosis of cellulitis requiring intravenous antibiotics. However, the proportion of children at The Royal Children's Hospital who receive intravenous antibiotics for uncomplicated cellulitis is lower than at other institutions,[30] and it decreased from 184 (26%) of 700 children in an earlier observational study[11] to 190 (22%) of 881 children in this trial. Moreover, we found that more than half of children included in this study had already failed on oral antibiotics.

Owing to the deliberate design of this study to compare two locations with two different antibiotics, the findings cannot be attributed solely to the location of treatment or to the different antibiotics. For example, the increased adverse events in hospital compared with at home could be due to location, antibiotic, or a combination of the two. This decision was made to ensure a combination of best practice and translatability. Lastly, clinicians assessing the primary outcome could not be masked to treatment assignment, which could have introduced bias. However, we determined that for the outcomes of this trial to be translatable into clinical practice it was important that medical clinicians were assessing the patients in real time. We believe we have minimised the risk of bias by having both pre-determined criteria for ceasing intravenous antibiotics and multiple clinicians in both groups making the assessments.

For children who require intravenous antibiotics for cellulitis, this study provides evidence that treatment at home with short-course ceftriaxone is efficacious, safe, preferred by patients, and less costly, allowing children to avoid hospital admission along with the accompanying advantages (such as avoidance of hospital-acquired infections). In previously healthy children, the use of ceftriaxone at home did not show a signal of increased acquisition of antibiotic-resistant microorganisms, although larger studies are needed. Regardless, this finding should not be extrapolated to longer courses of ceftriaxone and robust antimicrobial stewardship should remain a mainstay of OPAT programmes.

Contributors

LFI conceptualised, designed, and coordinated the study; did the data analysis; drafted the initial manuscript; and revised subsequent drafts. PAB, FEB, and SMH contributed to study design and data analysis, and reviewed and revised the manuscript. FO planned the statistical analysis, contributed to study design and data analysis, and revised the manuscript. AJD contributed to design of the microbiological analyses and reviewed and revised the manuscript. All authors approved the final manuscript for submission.

Declaration of interests

We declare no competing interests.

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References

1 Fernandes P, Milliren C, Mahoney-West HM, Schwartz L, Lachenauer CS, Nakamura MM. Safety of outpatient parenteral antimicrobial therapy in children. *Pediatr Infect Dis J* 2018; **37:** 157–63.

2 Hodgson KA, Huynh J, Ibrahim LF, et al. The use, appropriateness and outcomes of outpatient parenteral antimicrobial therapy. *Arch Dis Child* 2016; **101:** 886–93.

3 Elema A, Zalmstra TA, Boonstra AM, Narayanan UG, Reinders-Messelink HA, van der Putten AA. Pain and hospital admissions are important factors associated with quality of life in nonambulatory children. *Acta Paediatr* 2016; **105:** e419–25.

4 Orme LM, Babl FE, Barnes C, Barnett P, Donath S, Ashley DM. Outpatient versus inpatient IV antibiotic management for pediatric oncology patients with low risk febrile neutropenia: a randomised trial. *Pediatr Blood Cancer* 2014; **61:** 1427–33.

5 Hulten KG, Kaplan SL, Lamberth LB, et al. Hospital-acquired *Staphylococcus aureus* infections at Texas Children's Hospital, 2001–2007. *Infect Control Hosp Epidemiol* 2010; **31:** 183–90.

6 Sartain SA, Maxwell MJ, Todd PJ, Haycox AR, Bundred PE. Users' views on hospital and home care for acute illness in childhood. *Health Soc Care Community* 2001; **9:** 108–17.

7 Hansson H, Kjaergaard H, Johansen C, et al. Hospital-based home care for children with cancer: feasibility and psychosocial impact on children and their families. *Pediatr Blood Cancer* 2013; **60:** 865–72.

8 Bryant PA, Katz NT. Inpatient versus outpatient parenteral antibiotic therapy at home for acute infections in children: a systematic review. *Lancet Infect Dis* 2018; **18:** e45–54.

9 Caplan GA. A meta-analysis of "hospital in the home". *Med J Aust* 2013; **198:** 195–96.

10 Sartain SA, Maxwell MJ, Todd PJ, et al. Randomised controlled trial comparing an acute paediatric hospital at home scheme with conventional hospital care. *Arch Dis Child* 2002; **87:** 371–75.

11 Ibrahim LF, Hopper SM, Babl FE, Bryant PA. Who can have parenteral antibiotics at home? A prospective observational study in children with moderate/severe cellulitis. *Pediatr Infect Dis J* 2016; **35:** 269–74.

12 Brugha RE, Abrahamson E. Ambulatory intravenous antibiotic therapy for children with preseptal cellulitis. *Pediatr Emerg Care* 2012; **28:** 226–28.

13 Gouin S, Chevalier I, Gauthier M, Lamarre V. Prospective evaluation of the management of moderate to severe cellulitis with parenteral antibiotics at a paediatric day treatment centre. *J Paediatr Child Health* 2008; **44:** 214–18.

14 Frenkel LD. Once-daily administration of ceftriaxone for the treatment of selected serious bacterial infections in children. *Pediatrics* 1988; **82:** 486–91.

15 Washio M, Mizoue T, Kajioka T, et al. Risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) infection in a Japanese geriatric hospital. *Public Health* 1997; **111:** 187–90.

16 McKinnell JA, Kunz DF, Chamot E, et al. Association between vancomycin-resistant Enterococci bacteremia and ceftriaxone usage. *Infect Control Hosp Epidemiol* 2012; **33:** 718–24.

17 Meletiadis J, Turlej-Rogacka A, Lerner A, et al. Amplification of antimicrobial resistance in gut flora of patients treated with ceftriaxone. *Antimicrob Agents Chemother* 2017; **61:** e00473–17.

18 Lopez MA, Cruz AT, Kowalkowski MA, Raphael JL. Trends in resource utilization for hospitalized children with skin and soft tissue infections. *Pediatrics* 2013; **131:** e718–25.

19 Ibrahim LF, Babl FE, Orsini F, Hopper SM, Bryant PA. Cellulitis: home or inpatient in children from the emergency department (CHOICE): protocol for a randomised controlled trial. *BMJ Open* 2016; **6:** e009606.

20 Bryant PA, Babl FE, Daley AJ, Hopper SM, Ibrahim LF. Blood cultures in cellulitis are not cost effective and should prompt investigation for an alternative focus. *Paediatr Infect Dis J* 2016; **35:** 118.

21 Malone JR, Durica SR, Thompson DM, Bogie A, Naifeh M. Blood cultures in the evaluation of uncomplicated skin and soft tissue infections. *Pediatrics* 2013; **132:** 454–59.

22 de Man P, Verhoeven BA, Verbrugh HA, Vos MC, van den Anker JN. An antibiotic policy to prevent emergence of resistant bacilli. *Lancet* 2000; **355:** 973–78.

23 Pessoa-Silva CL, Meurer Moreira B, Câmara Almeida V, et al. Extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* in a neonatal intensive care unit: risk factors for infection and colonization. *J Hosp Infect* 2003; **53:** 198–206.

24 Carr D, Barnes EH, Gordon A, Isaacs D. Effect of antibiotic use on antimicrobial antibiotic resistance and late-onset neonatal infections over 25 years in an Australian tertiary neonatal unit. *Arch Dis Child Fetal Neonatal Ed* 2017; **102:** F244–50.

25 Knudsen PK, Brandtzaeg P, Hoiby EA, et al. Impact of extensive antibiotic treatment on faecal carriage of antibiotic-resistant enterobacteria in children in a low resistance prevalence setting. *PloS One* 2017; **12:** e0187618.

26 Prevot MH, Andremont A, Sancho-Garnier H, Tancrede C. Epidemiology of intestinal colonization by members of the family Enterobacteriaceae resistant to cefotaxime in a hematology–oncology unit. *Antimicrob Agents Chemother* 1986; **30:** 945–47.

27 Adams DJ, Eberly MD, Rajnik M, Nylund CM. Risk factors for community-associated *Clostridium difficile* infection in children. *J Pediatr* 2017; **186:** 105–09.

28 Melo MR, Ferreira-Magalhaes M, Flor-Lima F, et al. Dedicated pediatricians in emergency department: shorter waiting times and lower costs. *PloS One* 2016; **11:** e0161149.

29 Paquet F, Marchionni C. What is your KVO? Historical perspectives, review of evidence, and a survey about an often overlooked nursing practice. *J Infus Nurs* 2016; **39:** 32–37.

30 Khangura S, Wallace J, Kissoon N, Kodeeswaran T. Management of cellulitis in a pediatric emergency department. *Pediatr Emerg Care* 2007; **23:** 805–11.