Treatment failure in emergency department patients with cellulitis

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ABSTRACT

Objective: To identify the rate of treatment failure in emergency department patients with cellulitis.

Methods: This prospective observational convenience study enrolled adult patients with uncomplicated cellulitis. Physicians performed a standardized assessment prior to treatment. To calculate the interrater reliability of the assessment, duplicate data collection forms were completed on a small subsample of patients. Treatment failure was defined as the occurrence of any one of the following events after the initial emergency department visit: incision and drainage of abscess; change in antibiotics (not due to allergy/intolerance); specialist consultation; or, hospital admission. Comparison of means and proportions between the 2 groups was performed with univariate associations, using parametric or non-parametric tests where appropriate.

Results: Seventy-five patients were enrolled; 57% were male, the mean age was 48 (standard deviation 19), 71 (95%) patients had extremity cellulitis and 10 (13%) had abscess with cellulitis. Fourteen episodes (18.7%, 95% confidence interval [CI] 11%–28%) were classified as treatment failures, with an oral antibiotic failure rate of 6.8% (95% CI 2%–22%) and an emergency department–based intravenous antibiotic failure rate of 26.1% (95% CI 16%–40%). Patients with treatment failure were older (mean age 59 yr v. 46 yr, $p = 0.02$) and more likely to have been taking oral antibiotics at enrolment (50% v. 16.4%, $p = 0.01$). Patients with a larger surface area of infection were also more likely to fail treatment (465.1 cm^2 v. 101.5 cm^2, $p < 0.01$). Interrater agreement was high for the presence of fever (kappa 1.0) and the size of surface area of infection (intraclass correlation coefficient 0.98), but low for assessments of both severity (kappa 0.35) and need for admission (kappa 0.46).

Conclusions: The treatment of cellulitis with daily emergency department–based intravenous antibiotics has a failure rate of more than 25% in our centre. Cellulitis patients with a larger surface area of infection and previous (failed) oral therapy are more likely to fail treatment. Further research should focus on defining eligibility for treatment with emergency department–based intravenous antibiotics.

Key words: cellulitis; skin and soft tissue infections; treatment failure

RÉSUMÉ

Objectif : Déterminer le taux d'échec dans le traitement des patients atteints de cellulite au département d'urgence.

Méthodes : Cette étude d'observation prospective d'un échantillon de commodité incluait des patients adultes atteints de cellulite non compliquée. Les médecins effectuèrent une évaluation standardisée avant le traitement. Afin de calculer la fiabilité inter-évaluateurs de l'évaluation, des doubles de formulaires de collecte de données furent remplis pour un petit sous-groupe de

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patients. L'échec du traitement fut défini comme la survenue de n'importe quel des événements qui suivent après la visite initiale au département d'urgence : incision et drainage d'un abcès; changement d'antibiotiques (non dû à une allergie ou à une intolérance); consultation auprès d'un spécialiste; ou hospitalisation. Une comparaison des moyennes et des proportions entre les deux groupes fut effectuée au moyen d'associations univariées, en utilisant des tests paramétriques et non paramétriques au besoin.

Résultats : Soixante-quinze patients furent inclus dans l'étude; 57 % de ces patients étaient des hommes et l'âge moyen était de 48 ans (écart-type 19); 71 de ces patients (95 %) souffraient de cellulite des extrémités et 10 (13 %) présentaient un abcès avec la cellulite. Quatorze épisodes (18,7 %, intervalle de confiance [IC] de 95 % 11 %–28 %) furent classifiés comme des échecs de traitement, avec un taux d'échec de l'antibiothérapie per os de 6,8 % (IC de 95 % 2 %–22 %) et un taux d'échec de l'administration d'antibiotiques au département d'urgence de 26,1 % (IC de 95 % 16 %–40 %). Les patients chez qui le traitement avait échoué étaient plus âgés (âge moyen de 59 ans v. 46 ans, $p = 0,02$) et plus susceptibles d'être sous traitement à l'aide d'un antibiotique per os au moment de leur inclusion dans l'étude (50 % v. 16,4 %, $p = 0,01$). Le traitement était également susceptible d'échouer chez les patients dont la région d'infection était plus grande (465,1 cm^2 v. 101,5 cm^2, $p < 0,01$). La concordance inter-évaluateurs était élevée quant à la présence de fièvre (kappa 1,0) et à la taille de la surface d'infection (coefficient de corrélation intraclasse de 0,98), mais faible quant à l'évaluation de la gravité (kappa 0,35) et du besoin d'hospitalisation (kappa 0,46).

Conclusions : Le traitement de la cellulite au moyen d'antibiotiques intraveineux administrés quotidiennement au département d'urgence présente un taux d'échec de plus de 25 % à notre centre. Chez les patients atteints de cellulite présentant une plus grande surface d'infection et ayant déjà reçu une antibiothérapie per os qui a échoué, le traitement est plus susceptible d'échouer. Des recherches plus poussées devraient se pencher sur la détermination de l'admissibilité au traitement à l'aide d'antibiotiques intraveineux au département d'urgence.

Introduction

Emergency departments (EDs) have experienced a shift in the philosophy of patient care, becoming increasingly involved in the assessment and primary outpatient management of conditions historically requiring inpatient management. One such example is the management of patients with cellulitis. Many of these patients are now being treated without being admitted, using intravenous (IV) therapy through the ED or Day Hospital setting.[1–5]

Problems may arise from such a change in patient care. The use of a wide variety of antibiotics, doses and dosing schedules, and involvement of multiple physicians with different practice patterns may have made the treatment both haphazard and confusing for patients and physicians. Even in EDs with standardized protocols for these patients there exist varied opinions over who should be eligible, what constitutes "improvement," and when the IV regimen may be switched to an oral one.

To evaluate the practice of ED-based IV antibiotic therapy in clinical studies, several questions must be answered: Which patients require hospital admission? Which infections require IV as opposed to oral antibiotic therapy? How do we develop standardized definitions of cure, improvement or treatment failure? Despite the common nature of cellulitis and an obvious recent shift in practice, there is a surprising lack of published research and no clear answers to these questions.[6,7]

The primary objective of this study was to prospectively document the rates of treatment failure for patients treated with oral and IV antibiotics, in preparation for a planned clinical trial comparing oral antibiotics with ED-based IV antibiotics. Secondary objectives included the identification of the historical features and physical findings associated with treatment failure, and assessment of the interrater reliability of the signs and symptoms of cellulitis.

Methods

Design and setting

This prospective observational convenience study was conducted at 2 tertiary care hospital EDs with a combined annual census of more than 90 000 ED visits and a 20% admission rate. Patients were recruited between November 1999 and July 2000. We estimated enrolment of approximately 100 patients over a 6-month period. This sample size was based on feasibility; however the study time frame was extended to 8 months due to lower than anticipated enrolment. The Queen's University Research Ethics Board approved this project.

Eligibility and recruitment

Patients with acute (defined as less than 1 week duration) signs and symptoms consistent with cellulitis, erysipelas, or abscess with associated cellulitis (after incision and drainage) were eligible for study. A research nurse approached all eligible patients who registered between 0800 and 2200, Monday to Friday.

Exclusion criteria

The target population for this study was patients with uncomplicated skin infection expected to respond to standard anti-streptococcal and anti-staphylococcal antibiotics. Patients with the following conditions were therefore excluded from enrolment: suspected necrotizing fasciitis, osteomyelitis or septic arthritis; infected diabetic or decubitus ulcers; postoperative wound infection; or infected animal or human bite wounds. Children <16 years old, pregnant or breast-feeding women, and patients allergic to study medication were also excluded.

Antibiotic treatment

Patients were treated either with IV or oral antibiotics according to the decision of the attending emergency physician. If the physicians decided to treat with IV antibiotics they were given a choice of 1 of 2 standardized regimens, each given once daily in the ED: cefazolin 2 g, co-administered with 1 g of oral probenecid; or ceftriaxone 1 g alone. These 2 treatment regimens are both widely used in the ED treatment of cellulitis and allow for once daily visits and antibiotic dosing.[1–3,8] Patients treated with oral antibiotics alone were prescribed cephalexin 500 mg 4 times daily for 7–10 days.

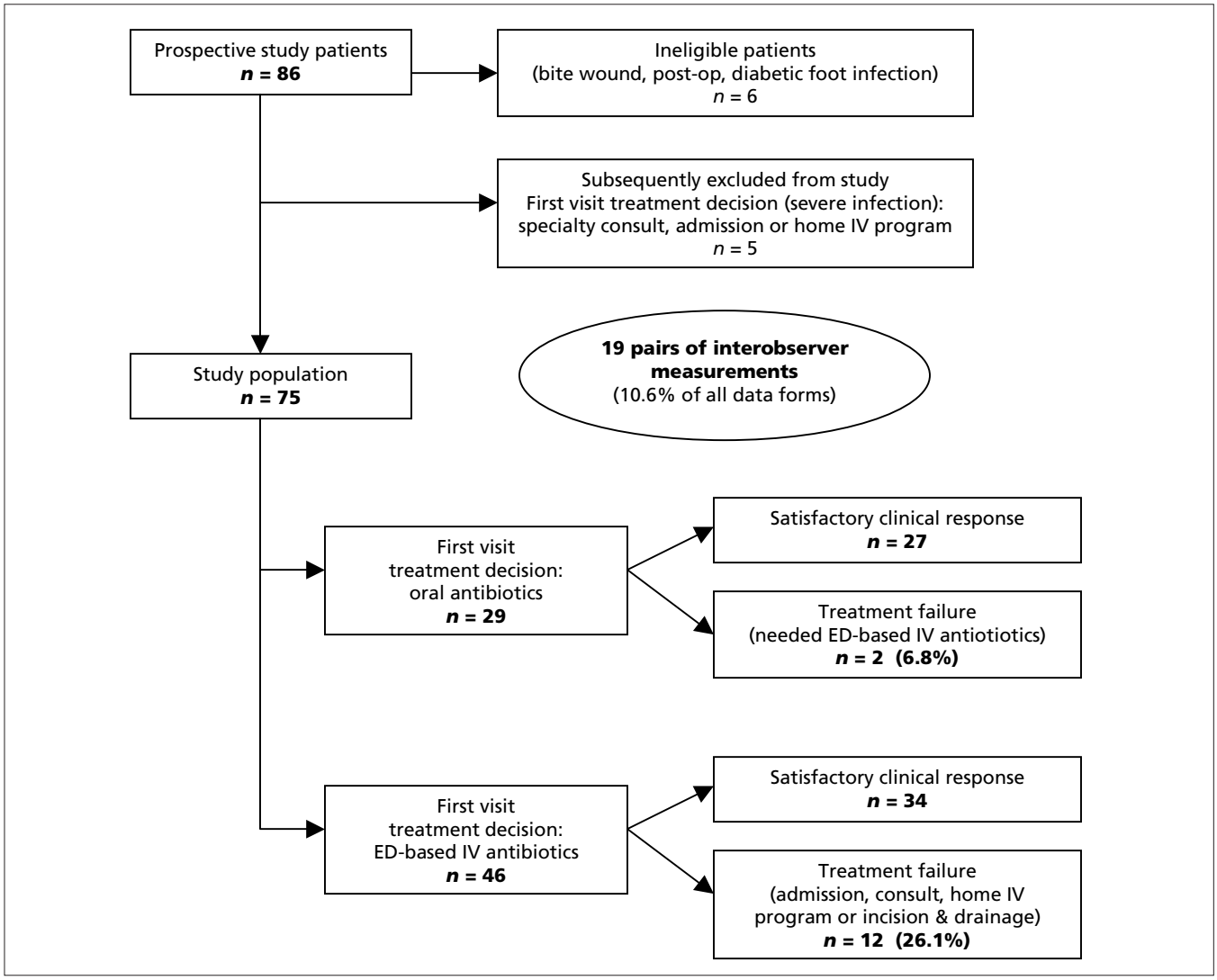

Fig. 1. Flow chart of patient enrolment, treatment decisions and outcomes for prospective study patients. IV = intravenous; ED = emergency department.

Table 1. Patient and infection characteristics, treatments and outcomes for the 75 study patients and the convenience subsample of 19 of the study patients

Variables	No. (and %)* of patients: All study patients *N* = 75	Inter-observer subsample *n* = 19
Patient characteristics		
Age range, yr	16–89	27–89
Mean age, yr (and SD)	48 (19)	57 (21)
Male	43 (57.3)	8 (42.1)
Patient medical history		
Intravenous drug use	6 (8.0)	0
Diabetes mellitus	6 (8.0)	3 (15.8)
Peripheral vascular disease	6 (8.0)	3 (15.8)
Peripheral edema	9 (12.0)	6 (31.6)
Dermatologic disorder	7 (9.3)	2 (10.5)
Previous cellulitis	18 (24.0)	6 (31.6)
Previous antibiotic treatment	18 (24.0)	3 (15.8)
Infection characteristics		
Trauma prior to infection	35 (46.7)	6 (31.6)
Laceration	10 (13.3)	0
Abrasion / Scratch / Blister	7 (9.3)	2 (10.5)
Puncture wound	10 (13.0)	2 (10.5)
Blunt trauma (no skin break)	8 (10.6)	2 (10.5)
Location of infection		
Head / Neck	1 (1.3)	0
Arm	24 (32.0)	3 (15.8)
Hand	5 (6.7)	1 (5.3)
Trunk	3 (4.0)	0
Leg	31 (41.3)	7 (36.8)
Foot	11 (14.7)	5 (26.3)
First ED visit findings		
Fever	19 (25.3)	4 (21.1)
Nausea or vomiting	21 (27.8)	6 (31.6)
Lymphangitis or lymphadenopathy	20 (26.5)	1 (5.3)
Mean area erythema, cm^2 (and SD)	556 (655)	468 (373)
Mean largest single diameter, cm (and SD)	23.9 (14.2)	24.6 (11.6)
Treatments and outcome		
Intravenous antibiotic	48 (64.0)	14 (73.8)
Complications		
Olecranon bursitis	10 (13.3)	2 (10.5)
Abscess at study enrolment	10 (13.3)	1 (5.3)
Abscess formation at any time	13 (17.3)	3 (15.8)
Admitted to hospital	6 (8.0)	3 (15.8)
Treatment failure requiring 2nd intervention	14 (18.7)	3 (15.8)
Second intervention		
Incision and drainage	3 (4.0)	1 (5.3)
Change in antibiotic	6 (8.0)	0
Specialty consultation	6 (8.0)	2 (10.5)

*Unless otherwise indicated; SD = standard deviation

Data collection

A standardized data collection form recorded patient demographics and associated medical conditions, history of the infection and any previous attempts at treatment (including prior antibiotics and incision and drainage). Infection-specific baseline data included the diameter and area of erythema, skin surface temperature (with skin surface probe), patient pain (visual analog scale [VAS] score), intensity of erythema, patient and physician perception of severity (all 5-point Likert scales), and the presence of regional lymphangitis, lymphadenopathy, fever and nausea or vomiting.

Two physicians completed blinded duplicate data collection forms on a convenience subsample to allow measurement of interrater agreement.

Outcome measures

The primary outcome was the rate of treatment failure. There are currently no validated definitions of treatment failure for cellulitis in the published literature. We devised an evidence-based definition relying on expert opinion and on our own observation of treatment patterns in this centre.[1,3,9–13] Patients were labelled treatment failures if they required any of the following: specialist consultation, hospital admission, a change in antibiotics or a surgical procedure (e.g., incision and debridgement). A change in antibiotics was defined as an "upgrade" to IV antibiotics from oral, or a change from one IV antibiotic to another; however, patients who required a change in antibiotics due only to an adverse effect from their antibiotic were classified as clinical responders if they did not have any of the other criteria listed under treatment failure.

Patient follow-up

Study personnel attempted telephone contact of all enrolled patients 1 week after discharge to ensure that their infection had continued to resolve as expected. Patients without complete resolution of their symptoms or who reported a worsening in symptoms were asked to return to the ED for a re-evaluation. The hospital medical records of all study patients not contacted were reviewed 1 month after their final visit to ensure that they had not had further ED visits for re-evaluation of their infection.

Data analysis

Univariate associations between historical features, co-existent illness, clinical characteristics and the primary outcome of treatment failure were calculated using SPSS. Proportions were compared using chi-squared and Fisher's exact tests, and the means of continuous variables were

compared using Student's *t* tests and Mann–Whitney *U* tests where appropriate.

The reliability of the selected cellulitis measurements was evaluated on the sample of patients who had duplicate data forms completed. The percentage agreement for each variable was calculated. Kappa statistics were calculated for dichotomous variables and intraclass correlation coefficients (one way random effects model) for the continuous variables.

Results

During the 8-month study period 86 patients were enrolled. Eleven patients were subsequently excluded from analysis because they had infections deemed ineligible (1 bite wound, 3 post-op, 2 diabetic foot infections) or were referred or admitted at the first ED visit (5 patients), leaving a study population of 75 patients. A summary of treatment decisions and patient outcomes is displayed in a flow chart in Figure 1 (see page 230). Of the 70 patients ultimately discharged from ED care, 48 (68.6%) were successfully contacted and reported their infection to be completely resolved or significantly improved. None of the remaining 22 patients returned to either centre within 1 month of their treatment, and thus these patients were classified as clinical responders.

The demographic data and comorbidities of the 75 study patients are shown in Table 1. The historical features and physical exam findings are summarized in Table 1. Of note, 18 patients (24%) in the study group reported a previous episode of cellulitis, the majority occurring in the same anatomic location.

Of the 75 study patients, 29 (38.6%) were treated initially with oral antibiotics and 46 (61.4%) were given ED-based IV antibiotics. Fourteen patients met the definition for treatment failure, for an overall failure rate of 18.7% (95% CI 11%–28%). There were 2 treatment failures in the oral antibiotic group (6.8%, 95% CI 2%–22%), compared with 12 of the 46 patients (26.1%, 95% CI 16%–40%) in the IV group. Table 2 describes the type and timing of the treatment failure outcome.

Nineteen patients had duplicate data collection forms completed, by a total of 11 different physicians. Calculated measures of agreement for these data are summarized in Table 3. The agreement between physicians on the presence of fever, the presence of systemic symptoms and the likelihood of abscess were high, with kappas of 1.0 and 0.73, respectively. There was poor agreement for both physician assessment of severity (kappa 0.35) and the physician assessment of need for admission (kappa 0.46). The relatively large standard error suggests that a larger sample is required to confirm this trend. The continuous measurements (surface temperature, diameter of erythema and VAS pain score) taken of the patients' infections appeared highly reliable, with intraclass correlation coefficients of 0.90, 0.98 and 0.95.

Table 4 shows the patient characteristics of infections (i.e., host factors) that failed treatment compared with those that responded successfully. It also shows the infection charac-

Table 2. Type and timing of second treatment intervention in the 14 study patients whose initial treatment failed

	Day of treatment,* no. of patients treated						
Action taken	1	2	3	4	5	After Day 5	Total†
Incision and debridement performed	0	2	1	0	0	0	3
Change in antibiotic	0	3	1	0	1	1	6
Specialist consultation	0	0	0	0	0	1	1
Hospital admission	0	4	1	0	0	0	5
Total	0	9	3	0	1	2	15

*Initial emergency department visit and initiation of treatment was counted as Day 0.
†Total is greater than 14 because some patients had more than 1 intervention.

Table 3. Summary of calculated measures of agreement between physicians for interobserver subsample (19 patients)

Variable	Agreement, %	Kappa (SE) or ICC (95%CI)
Fever	100	1.0 (0)
Other systemic symptoms	90	0.73 (0.17)
Lymphadenopathy / Lymphangitis	83	–0.09 (0.06)
Admission	89	0.46 (0.31)
Severity (mild / moderate / severe)	76	0.35 (0.26)
Abscess (yes / unsure / no)	100	1.0 (0)
Intensity (not / little red/very red)	100	1.0 (0)
Intensity of erythema	100	0.89 (0.73–0.96)
Physician impression of severity	76	0.39 (0.01–0.72)
Likelihood of abscess	100	0.81 (0.55–0.92)
Surface temperature (within 1°C)	82	0.90 (0.82–0.94)
Diameter erythema (within 2 cm)	87	0.98 (0.96–0.99)
VAS pain score (within 1 cm)	79	0.95 (0.84–0.99)

SE = standard error; ICC = intraclass correlation coefficient; CI = confidence interval; VAS = visual analogue scale

teristics of the treatment failure group compared with those patients who responded successfully. Older patients were significantly more likely to fail treatment. Other characteristics associated with failure included prior antibiotic treatment and the initial size of the infection, as measured both by the single largest diameter and the area of erythema.

Discussion

Our high rate of treatment failure is concerning, and reinforces the need for further evaluation of this therapy. Identifying patients who are likely to fail treatment is an important step in evaluating eligibility for any treatment plan. Patients who are older or have peripheral vascular disease seem more likely to fail treatment, as do patients previously treated with oral antibiotics for cellulitis or who have a larger size of infection at first ED presentation. These findings should be verified in future studies. The higher rate of treatment failure seen in our ED-based IV treatment group was possibly due to the increased severity of those infections. We may be underestimating which patients seen in the ED require hospital admission. Currently there are no guidelines defining the indications for either IV therapy or hospital admission. Further study into the indicators of infection severity and clarification of which infections require inpatient treatment is needed.

Table 4. Comparison of characteristics of the study patients who were clinical responders (*n* = 61) with those study patients whose initial treatment was a failure (*n* = 14)

	No. (and %)* of patients		
Variables	Clinical responders *n* = 61	Treatment failure *n* = 14	*p* value
Patient characteristics			
Mean age, yr (and SD)	46 (19)	59 (17)	0.02
Male	35 (57.4)	8 (57.1)	0.61
Patient medical history			
Intravenous drug use	6 (9.8)	0	0.28
Diabetes mellitus	4 (6.6)	2 (14.3)	0.31
Peripheral vascular disease	3 (4.9)	3 (21.4)	0.80
Peripheral edema	6 (9.8)	3 (21.4)	0.22
Dermatologic disorder	6 (9.8)	1 (7.1)	0.61
Previous cellulitis	13 (21.3)	5 (35.7)	0.21
Previous antibiotic treatment	10 (16.4)	7 (50.0)	0.01
Infection characteristics			
Trauma prior to infection	30 (49.2)	4 (28.6)	0.16
Laceration	7 (11.4)	2 (14.2)	–
Abrasion / Scratch / Blister	9 (14.8)	1 (7.1)	–
Puncture wound	7 (11.4)	0	–
Blunt trauma (no skin break)	7 (11.4)	1 (7.1)	–
Location of infection			
Head / Neck	1 (1.6)	0	–
Arm	19 (31.1)	5 (35.7)	–
Hand	4 (6.6)	1 (7.1)	–
Trunk	3 (4.9)	0 (0)	–
Leg	24 (39.3)	7 (50.0)	–
Foot	10 (16.4)	1 (7.1)	–
First ED visit findings			
Fever	14 (22.9)	4 (28.5)	0.49
Nausea or vomiting	14 (22.9)	6 (42.9)	0.12
Lymphangitis or lymphadenopathy	16 (26.2)	4 (28.6)	0.73
Largest diameter erythema, cm (and SD)	22.6 (13.0)	30.5 (18.4)	0.07
Complications			
Olecranon bursitis	6 (9.8)	4 (28.6)	0.06
Abscess at study enrolment	7 (11.5)	3 (21.4)	0.38

*Unless otherwise indicated; SD = standard deviation

Published estimates of treatment failure in cellulitis vary. The failure rate in a retrospective chart review[9] of 170 patients treated with ED-based IV antibiotics in our centre over a different 1-year period — using the same criteria for treatment failure — was 27.4%. A 1999 abstract comparing a protocol of ED-based IV antibiotics versus a single dose of IV antibiotics followed by oral therapy found a failure rate of 32.4%.[14] Another group reported a treatment failure rate of only 12% in 346 patients when looking at the efficacy of ED-based IV therapy using cefazolin and probenecid.[15] A Canadian study examined the treatment strategies in 5 Canadian urban centres and found an overall treatment failure rate of 12% in 416 patients treated for cellulitis over a 1-year period.[2] This study (which included both oral and IV antibiotic regimens) noted more than 25 different initial antibiotic choices and dose regimens in the study patients, and did not publish the IV treatment failure rate. An ED-based trial comparing IV cefazolin and probenecid with IV ceftriaxone reported similar failure rates in both arms (7% v. 8%). However the cause of cellulitis in the majority of the trial population was IV drug use and, due to concerns about follow-up, all patients in both arms were also treated with oral antibiotics throughout the trial.[1] Another clinical trial comparing home-based IV cefazolin plus probenecid with IV ceftriaxone reported a treatment failure rate of 14% in the cefazolin arm and 4% in the ceftriaxone arm.[3] In that study, a large proportion of patients had an "indeterminate clinical outcome" in both arms. If these indeterminate patients had been considered treatment failures, then failure rates would have been 32.5% in

the cefazolin group and 30% in the ceftriaxone group.

Our study is the first to examine the interrater agreement of the characteristics of cellulitis. The agreement between physicians on these characteristics is very strong when objective measurements are used (such as fever or diameter of erythema), and the agreement appears to be poor to moderate when physicians are asked for a subjective clinical impression (such as an impression of severity). This finding demonstrates the need to record the objective manifestations of these infections and to clarify the features of severity and the admission requirements.

Limitations

Our study has some important limitations. Due to the availability of the research nurses, patients were not enrolled during night shifts and weekends. Two-thirds of our patients were treated with IV antibiotics, suggesting that many patients treated with oral antibiotics were not enrolled. Enrolment was slower than expected, and even with extension of the study time frame, we still did not meet our target of 100 patients. There is the potential for selection bias and, consequently, an overestimation of the treatment failure rates. Our small sample size was not adequate for a multivariate analysis. Some of the features that appeared to be associated with treatment failure did not reach statistical significance in our univariate analysis, and this may also be due to the small sample size.

Despite these limitations, this is the first ED study to prospectively identify specific patient and infection characteristics. Our definition for treatment failure was also prospectively defined and implemented after an extensive review of the cellulitis literature. There have not been any previous attempts to examine the interrater reliability of the features of cellulitis, and although our sample size was small, we have been able to show disagreement between physicians on many of the more subjective features of cellulitis. These findings will be used to assist with the design of future research to establish which patients should be eligible and will benefit most from treatment with ED-based IV antibiotics.

Conclusions

The treatment of cellulitis with daily ED-based IV antibiotics has a treatment failure rate of more than 25% in our centre. A clinical trial of this practice is needed to determine which patients may benefit from more intensive IV therapy, as is possible with admission. Older patients and patients with previous (failed) oral therapy and those infections over a larger area are more likely to fail ED treatment for cellulitis. Physicians show high interrater reliability for the objective findings of skin and soft-tissue infections (such as fever and estimated size) but poor interrater reliability for subjective decision (such as infection severity and need for hospital admission). Further research should also be focused on identifying infection characteristics for clinical decision-making that are reliable and reproducible.

Competing interests: None declared.

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