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Jacobs Journal of Experimental Dermatology and Research

Research Article

Reduced Recurrence Rate after a Three Week Clindamycin for the Initial Lower Limb Cellulitis

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Received: 03-08-2015

Accepted: 03-27-2015

Published: 06-04-2015

Abstract

Background: Recurrences are frequent, difficult to manage and contribute considerably to cellulitis disease burden. It remains uncertain whether treatment selections for the initial cellulitis episode modify the risk of subsequent recurrences.

Objectives: Aim of the present study was to report recurrences in patients treated with a prolonged (21 days) clindamycin scheme for initial lower limb cellulitis episode.

Material/Methods: Inpatients were administered clindamycin (3x600 mg/d i.v.; 3x300mg/d p.o. after release) and were followed up for up to 8 years. A subgroup received a 21 days penicillin scheme. Cellulitis recurrence rates reports were also mined through a PubMed search.

Results: Eighty nine patients were included in the recurrence analysis (N=80 received clindamycin, N=9 penicillin). Demographics and disease characteristics were equivalent between treatment groups. Nine recurrences occurred: 6/80 after clindamycin and 3/9 after penicillin (91.1%±3.6 and 66.7%±15.7 recurrence-free rates at the end of follow-up respectively; p= 0.012). In addition, significantly fewer recurrences occurred in the present clindamycin cohort compared to that anticipated from most corresponding literature data.

Conclusions: The treatment for the initial cellulitis episode seems to impact on the risk of subsequent recurrences. Realizing the rationale behind this relationship would contribute to the better understanding of recurrence pathogenesis, prevention and treatment of cellulitis.

Keywords: Cellulitis; Erysipelas; Clindamycin; Penicillin; Recurrence; Lower Limb; Leg

Introduction

Cellulitis is a common bacterial skin infection [1-3] that in > 70% of all cases involves the skin of the lower extremities [4-6]. The disease typically presents as a tender, rapidly expanding inflammatory area with a variable degree of systemic manifestations [1,7]. Presently the term 'cellulitis' will be preferred over 'erysipelas' [1,7] to interchangeably designate all laterally spreading skin infections with above characteristics that affect either exclusively the uppermost part of the dermis ('erysipelas') or extend also in the deeper dermis-subcutis tissue layers ('cellulitis')[8]. Different mi-

croorganisms have been described to cause cellulitis, however, most cases are due to Gram positive aerobes. Streptococci (particularly in cases of uncomplicated erysipelas) [9] and *Staphylococcus aureus* (including community-acquired methicillin resistant strains, especially in the USA) are considered to be the most common pathogens [10-14]. Rather short (5 to maximum 10 days) treatment schemes with beta-lactamic antimicrobials are widely recommended to initiate empirical treatment for this condition [8,10]. However, in line with emerging evidence, antimicrobials that target *S. aureus* (including clindamycin) are increasingly recommended for the initiation of the treatment of skin infections in recent treatment guideline updates [8]. Clindamycin is an antimicrobial agent with multifaceted pharmacological actions; it penetrates easily into cells and tissues and is a potent suppressor of the synthesis of bacterial virulence factors and toxins [15,16].

Cellulitis recurrences are frequent: they affect, according to different studies, 14-29% of the patients in the first three years after a disease episode [2,17-19]. In addition they are an established risk factor for further recurrences [20,21] and contribute significantly to overall burden of this condition [1,17,22]. The prevalent explanation for the pathogenesis of cellulitis recurrences is still that of a re-infection in a susceptible skin area. Several antimicrobial prophylaxis regimens that primarily target this mechanism have been evaluated in the literature [17,23-26]. However, the results of these studies are notably variable and generally unsatisfactory. Therapeutic strategies based on alternative approaches to the pathophysiology of recurrence prophylaxis of cellulitis have been not methodically addressed to date. Particularly, whether the selection of the treatment for the initial disease episode could modify the risk of subsequent recurrences has not been explored in the literature, probably with one exception: A solitary study found that a prolonged (≥28 days) treatment schedule seem to reduce the risk of subsequent recurrences [27].

We presently identified recurrences in a cohort of adult patients, who were hospitalized for the initial lower limb cellulitis episode and were followed up for as long as 8 years thereafter. We found significantly fewer recurrences among those who were administered a three-week clindamycin scheme compared both (a) with a parallel smaller benzyl-penicillin group and (b) with most corresponding literature data. We suggest that the treatment selection for the initial cellulitis episode may decisively impact on the risk of subsequent recurrences and this should be considered in the planning of therapeutic trials in the future.

Materials and Methods

Patients and disease definitions

This single center study reports recurrences that occurred in a cohort of adult patients (≥18 years old) hospitalized from January 01, 2006 to December 31, 2012 for the treatment of an initial community-acquired episode of lower limb cellulitis. Institutional (University Hospital of Ioannina) Ethics and Clinical Trials Review Committee permission was granted according to the Declaration of Helsinki Principles.

'Cellulitis' was presently defined as a spreading, sharply demarcated, unilateral, erythematous, tender and/or painful skin area with accompanying malaise and/or fever and/or chills and an elevated finding in at least one of the following three blood tests at admission: total white blood cells count (WBC), serum C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). Patients with surgery-related cellulitis or a co-localized abscess were excluded.

In authors' Institution, patients with cellulitis are treated in the Dermatology ward. Starting in 2006, patients with cellulitis were all initiated on a 21-days clindamycin regimen, consisting of an initial period of intravenous application (3x600 mg/d) during hospitalization followed by an ambulatory oral treatment period (3x300mg/d) for the rest of the scheduled therapy duration. Some of the patients, who had initially consulted other specialties, were initiated on intravenous benzyl-penicillin (daily $24x10^6$ IU i.v. in 4 doses). These patients, as far as they responded to the treatment, were continued on penicillin after their transfer to Dermatology. These latter patients were prescribed phenoxymethylpenicillin ($4.5x10^6$ I.U./d p.o.) for the rest of the 3-week treatment period after hospitalization ('penicillin' treatment group).

Recurrences were defined as cellulitis episodes that occurred in the same lower limb more than one month after the end of treatment for the initial episode. Episodes that occurred earlier than 1 month after the end of treatment were excluded as 'treatment failures'. None of the patients received 'recurrence prophylaxis' after the initial cellulitis disease episode. Among the patients who completed the treatment of the initial disease episode per protocol recurrences were identified based on (i) hospital records review and (ii) two structured telephone questionnaires (conducted in February 2012 and in February 2014) and focused files search in the case of cellulitis relevant answers.

Literature search

For identifying studies that report recurrence rates of cellulitis (and erysipelas) a PubMed based literature search (assessed at October 28, 2014) was performed with the following strategy: Articles that fulfilled the search string "(cellulitis OR erysipelas) AND (recurrence OR recurrent OR relapse OR relapsed)" were initially identified. 'Case reports' were excluded, and the remaining papers were selected for full-text evaluation regarding quantitative information on recurrence rates (recurrence incidence). The selected articles were further cross-searched for additional appropriate references. Only papers that reported recurrence rates

of cellulitis (or erysipelas) after defined follow-up periods (one, two or three years) were considered. Reports of cellulitis (or erysipelas) collected for a particular clinical feature (e.g. with lymphedema) or cases that exclusively affected a non-lower limb anatomic localization were excluded.

Data evaluation and statistical analysis

Means/medians and standard errors were employed to summarize continuous variables; frequency counts and percentages for categorical ones. For the comparison of repeat measurements of categorical and continuous variables in the same patient McNemar and Wilcoxon signed rank tests were employed respectively. Fisher's exact test, chi-squared test, one way analysis of variance (ANOVA) and Mann-Whitney U-test were used depending upon data structure to determine differences in the distribution of factors of interest in individuals who received different antimicrobial schemes and who suffered cellulitis recurrences or not. Interactions of predictors of recurrence were further assessed with logistic regression. Kaplan-Meier calculations with log-rank (Mantel-Cox) tests were applied to determine 'times to recurrence' and yearly and cumulative 'recurrence rates' and also to compare the outcomes between subgroups of patients. Recurrence rates from the literature were adopted as quoted by the authors. If not provided in the publication, binomial recurrence rates (and 95% confidence intervals) were calculated from the available material (number of recurrences and number of patients at risk). Two-sided P-values <0.05 were considered to indicate statistical significance. SPSS 22.0 edition (Chicago, IL, USA) was used for statistical calculations.

Results

Study population

Between January 2006 and December 2012 ninety-three consecutive adult patients were hospitalized for community-acquired initial lower limb cellulitis. Eighty-three of them were administered clindamycin and 10 the penicillin scheme. Four patients were excluded from follow-up analysis: In three cases (2 clindamycin and 1 penicillin) the initial treatment was revised because of failing disease control (cure was achieved by adding ceftriaxone) and one patient (on clindamycin) with adequate disease control developed drug eruption: The overall treatment failure rate was 3.6% (3/83 patients) on the clindamycin and 10% (1/10 patients) on the penicillin scheme. Complete sets of all three laboratory inflammation markers were available in 76/89 (85.4%) of the patients who were considered for follow-up. There were no statistically significant differences between the two treatment groups for any of the above inflammation parameters, neither at admission nor at release (Mann-Whitney U test; details not shown). However, a significant improvement (lowering) of all three markers (WBC, CRP and ESR) between the first and last days of hospitalization underscores the satisfactory treatment outcome (Figure 1).

Eighty patients on clindamycin and nine on penicillin completed the 21 days treatment schemes. There were no statistically significant differences between the two treatment groups with regard to the distribution of core demographic and disease parameters (Table 1). After a follow-up period of at least one year (1-8 years) nine recurrences (all *in loco*) occurred among the 89 patients, 6 in the clindamycin and 3 in the penicillin group. Significantly fewer recurrences were observed among patients on clindamycin (recurrence free: 91.1%±3.6; Figure 2) compared to the smaller penicillin group (66.7%±15.7; p= 0.012). In addition to the antimicrobial scheme, according to a univariable analysis (Table 2) the recurrence risk increases with the recurrence score of the prognostic model of McNamara et al [19] (p=0.036; Figure 3). However, in a logistic regression model only the antimicrobial treatment scheme achieved independent statistical significance (p=0.048).

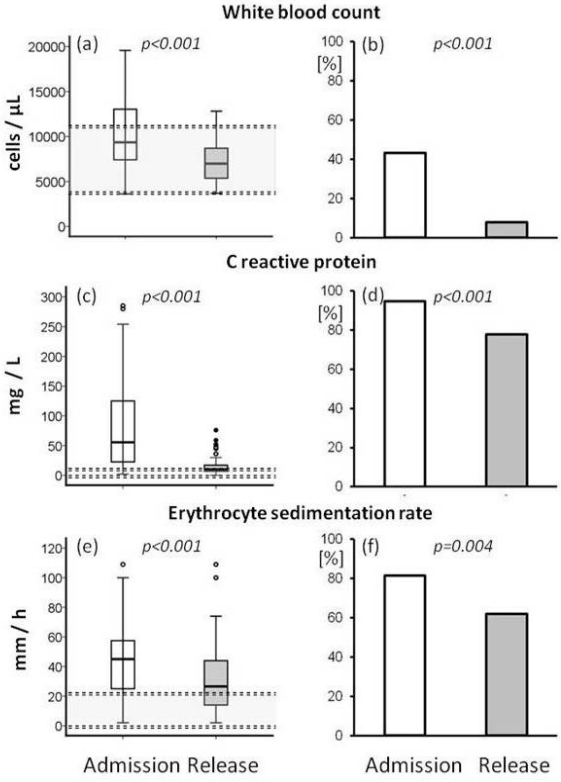

Figure 1. Comparison of core laboratory serum inflammation markers of patients with initial lower limb cellulitis episode between first and last days of stationary treatment (admission and release from hospitalization). Left side panels (a, c and e): Box plot diagrams of marker measurements; dashed region: normal range. Right side panels (b, d and f): Percent of patients with a pathologic value. There is a statistically significant improvement (decrease) of all three serum inflammation markers between admission and release (Wilcoxon signed rank test for continuous, McNemar test for categorical data; corresponding p-values of statistical significance are displayed above each panel). White blood count (WBC, normal range: 4,500 -10,500 cells/µL), C reactive protein in serum (CRP, normal range: <6 mg/L), Erythrocyte sedimentation rate (ESR, normal range: <20 mm/h).

Table 1. Core clinical data of the patients with community-acquired initial lower limb cellulitis episode stratified according to the antimicrobial scheme.

		Treatment[a]		
Attribute	**Total**	**Clindamycin**	**Benzyl-penicillin**	**p-value[b]**
***Patients*: N (%)**	**89 (100)**	**80 (92.5)**	**9 (7.5)**	**--**
***Gender*: N (%)**				**0.739**
Male	45 (50.6)	41 (51.3)	4 (44.4)	
Female	44 (49.4)	39 (48.7)	5 (55.6)	
***Age (years)*:** median [range]	66 [19-87]	66 [19-87]	63 [30-81]	**0.489**
***Localization*: N (%)**				**1.000**
Tibial	82 (92.1)	73 (91.3)	9 (100.0)	
Non-tibial	7 (7.9)	7 (8.7)	0 (00.0)	
***Recurrence score*[c]: N (%)**				**0.282**
0	4 (4.5)	4 (5.0)	0 (0.0)	
1	71 (79.8)	65 (81.3)	6 (66.7)	
2	12 (13.5)	9 (11.3)	3 (33.3)	
3	2 (2.2)	2 (2.5)	0 (0.0)	
***Follow up (months)*:** Mean [S.E.M.]	50.9 [2.75]	51.6 [2.9]	44.9 [9.9]	**0.466**

[a] Treatment regimens: **Benzyl-penicillin**: Benzyl-penicillin $24x10^6$ IU/d in 4 doses i.v. during hospitalization and phenoxymethylpenicillin $4.5x10^6$ IU/d p.o. for the rest of a total of the 21 days treatment period. **Clindamycin**: Clindamycin 3x600 mg/d i.v. initially during hospitalization and subsequently clindamycin 3x300 mg/d p.o. for the rest of a total of the 21 days treatment period.

[b] For the comparison between the two treatment groups: Chi-square or Fisher's exact test for categorical, Mann-Whitney U-test for continuous (age and length of follow up) data.

[c] Recurrence score according of the predictive model of McNamara et al. for lower limb cellulitis. [19]

Table 2. Recurrences after the initial community-acquired lower limb cellulitis disease episode: Prognostic significance of core demographic and disease parameters. Note that treatment scheme is the only among the herein considered factors that reached independent prognostic significance for disease recurrences in the logistic regression model.

Attribute	Total	Recurrence free	Recurrences	Univariable analysis[a]	Logistic regression[a]
***Patients*: N (%)**	89	80 (89.9)	9 (10.1)	–[b]	–
***Gender*: N (%)**				0.752	0.704
Male	45	40 (88.9)	5 (11.1)		
Female	44	40 (90.9)	4 (9.1)		
***Recurrence score*[c]: N (%)**				0.036	0.099
0	4	4 (100.0)	0 (0.0)		
1	71	66 (93.0)	5 (7.0)		
2	12	8 (66.7)	4 (33.3)		
3	2	2 (–)	0 (–)		
***Treatment*[d]: N (%)**				0.012	0.048
Benzyl-penicillin	9	6 (66.7)	3 (33.3)		
Clindamycin	80	74 (92.5)	6 (7.5)		
Age of patient (years): mean [S.E.M.]	63.0 [1.67]	63.2 [1.8]	61.4 [5.4]	0.748	0.704

[a] Univariable analysis of variance (ANOVA)

[b] –: Not relevant

[c] Calculated for this cohort according to the recurrence prognostic model of lower limb cellulitis of McNamara et al. [19]

[d] Treatment schemes: For details see Table 1 and text.

Table 3. Recurrence rates of cellulitis (binomial estimation [95% confidence intervals]) after 1, 2, 3 or 5 years follow-up (bold: present study). The studies have been grouped according to disease features for better comparison.

Cellulitis subset Study[a]	Patients (N)[b]	Follow up / Observation period after cellulitis episode[g] 1 year	2 years	3 years	5 years
Lower limb cellulitis, initial					
Present (clindamycin)[c]	**80**	**0.0370 [0.002-0.078]**	**0.0510 [0.0016-0.1004]**	**0.0660 [0.0087-0.1416]**	**0.0890 [0.0179-0.1601]**
McNamara 2007 [19]	209		0.1675 [0.1226-0.2243]*		
Lower limb cellulitis, all					
Eriksson 1996 [28]	177			0.2200 [0.1653-0.2873]*	
Cox 1998 [18]	70			0.1429 [0.0775-0.2454]	
Wang 1997 [29]	84	0.1905 [0.1197-0.2883]**			
Cellulitis, all initial					
Bergkvist 1998 [23]	103	0.1845 [0.1206-0.2711]**			
Cellulitis, all					
Jorup-Rönström 1987 17]	143			0.2900 [0.2187-0.3659]**	
Ellis Simonsen 2006 [2]	5780	0.1107 [0.1029-0.1191]*	0.1467 [0.1378-0.1561]*	0.1799 [0.1702-0.1900]**	
Inghammar 2014 [30]	502		0.0916 [0.0692-0.1203]		
Cellulitis, recurrent[d,e]					
Patch I+II 2012 [24,25] [f]	201			0.3582 [0.2951-0.4266]	
Sjoblom 1993 [49]	20			0.4000 [0.2183-0.6140]	

[a]First author or study protocol designation and year of publication; the numbers in brackets correspond to the numbers of publications in the References' list.
[b]Numbers of cases in follow-up for cellulitis recurrences in the corresponding studies.
[c]Bold: Present clindamycin-treated cohort.
[d]For comparison, data of cellulitis cases with history of recurrence are included. Only papers selected in the meta-analysis of cellulitis prophylaxis interventional trials by Oh et al. [26]
[e]Comparison with present data not applicable.
[f] The data of the conceptually similar PATCH I and II studies [24,25] have been unified (compare also [26]).
[g] *: p<0.05 and **: p<0.01, for the comparison between the present recurrence rate and the recurrence cellulitis data from the literature (Fisher's exact test).

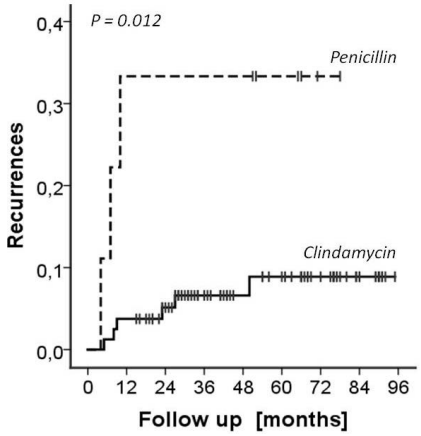

Figure 2. Cumulative cellulitis recurrence rate of patients treated with a three-week antimicrobial scheme for initial community-acquired lower limb disease episode as a function of the time after the end of treatment in months (for details of treatment schemes see: Table 1 and text). Bars correspond to censor events; p=0.012 for equality of distributions (Kaplan-Meier / log-rank test).

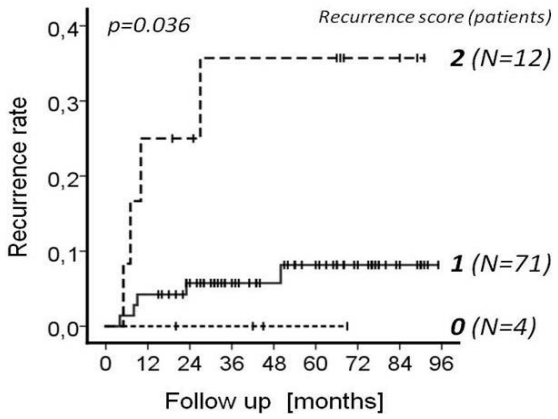

Figure 3. Cummulative cellulitis recurrence rates of the patients stratified according to the prediction score of the recurrence model of McNamara et al. for initial lower limb cellulitis [19]: The recurrence risk of a patient increases as recurrence predictors accumulate (p=0.036 for equality of distributions; Kaplan-Meier / log-rank test). The numbers in bold italics (0, 1 and 2) denote recurrence score levels; numbers in parentheses the numbers of patients with the corresponding attribute. Bars: time points of censor events. Note that only one patient (N=1) had score '3' (not shown). In one case the score was not available.

Literature review

From the 71 articles that entered the last step of full-text evaluation only eight publications reported data on the incidence of cellulitis recurrences ([2,17-19,23,28-30]; Table 3). Comparatively fewer recurrences occurred in our cohort of patients who were administered the three-week clindamycin scheme. Cumulative recurrence rates of 3.70%, 5.10%, 6.60% and 8.90% were determined after 1, 2, 3 and 5 years respectively. Notably, studies that included already relapsed cases found even higher recurrence rates.

Discussion

Cellulitis is one of the most frequent causes of hospital admissions due to a microbial agent, with considerable costs for the health care systems [12,31,32]. Tendency to recurrences is an important feature of cellulitis, especially of that cases that involve the lower limb [17,19]. Our present study indicates that a moderately protracted clindamycin treatment scheme for the initial episode of lower limb cellulitis may partly prevent subsequent disease recurrences. The pathophysiology of cellulitis recurrences is still poorly understood. In the literature, recurrent cellulitis has been mainly ascribed to the development of local predisposing host factors that favor access and growth of pathogens that spread to affected locations from microorganism reservoirs elsewhere in the body (toes webs, [33,34] anal canal, [35] nostrils [36]). Furthermore, bacterial toxins released during cellulitis are supposed to augment tissue damage in the affected skin areas [37-39]. It is thought that this latter results into defectively restituted tissue sites (fibrosis and secondary lymphoedema) that predispose to recurrences [27,40]. In line with this mechanism, clindamycin which is a potent bacterial protein synthesis inhibitor [41] may limit toxin production more effectively than penicillin, thus permitting improved tissue convalescence.

In addition, the duration of the treatment might also modify recurrence cellulitis risk. Based on moderate trials evidence [42,43] current guidelines [8] propose relatively short periods (5 to maximum 10 days) for the treatment of cellulitis. However, the PATCH II trial underscores the impact of antimicrobial 'prophylaxis' for cellulitis patients already after the initial disease episode [25,26]. This finding corroborates our present observation and scarce data in the literature [27] that longer antimicrobial courses for the initial cellulitis episode may partly prevent subsequent disease recurrences.

The main limitation of this retrospective observational study is the small number of patients included, particularly in the outlier penicillin group. However, for the clindamycin group this limitation (N=80 included patients) is partly compensated by the long follow-up period (one to eight years). In addition, our inclusion strategy homogenized the patients' population with respect to important recurrence risk factors (initial episode, tibial localization). Finally, pathogen identification data were not available for the patients in this study. Although this is in line with most corresponding evidence in the literature, [5,44-46] however, the suggestion that different antimicrobial agents for the initial cellulitis episode might differentially impact on the risk of subsequent recurrences indicate to the possibility that recurrent cellulitis might be associated with infections by some pathogen more than by others. We propose that the likelihood of this relationship should be explored in future studies.

An intriguing finding of our literature search is the scarcity of quantitative studies that report recurrence rates of cellulitis (erysipelas), a medical condition with considerable population health impact [1,47,48]. Oh et al. [26] made recently a similar observation in their meta-analysis of cellulitis prophylaxis studies. Probably the fact that the responsibility for the management of cellulitis is shared by different medical specialties does not favor focused research activities.

Conclusion

In conclusion, our observations support the hypothesis that "stronger" and "longer" antibiotic treatment of the initial lower limb cellulitis episode may reduce lymphatic damage caused by the infection and decrease the risk for subsequent disease recurrences. We propose that for optimization of the management of cellulitis future treatment trials, besides assessing short-term infection control outcomes, should be also designed to determine recurrence rates as additional primary study end-points. In this way, given the central role of recurrences for the burden of this disease, the overall cost-effectiveness of different therapeutic interventions (including treatment strategies for the initial cellulitis episode) could be determined more efficiently.

Acknowledgements

This study was partially supported by the University of Ioannina Research Committee Account No 22195.

Conflict of interest statement

Conflicts of interest: None

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