Journal of Infection (2015) 70, 467—473

BIA
British Infection Association

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Predictors of recurrent cellulitis in five years. Clinical risk factors and the role of PTX3 and CRP

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Accepted 8 November 2014
Available online 15 November 2014

KEYWORDS
Cellulitis;
Erysipelas;
Recurrence;
PTX3;
CRP

Summary *Objectives:* To identify risk factors for recurrence of cellulitis, and to assess the predictive value of pentraxin 3 (PTX3) and C-reactive protein (CRP) measured at baseline.
Methods: A follow up study of 90 hospitalised patients with acute non-necrotising cellulitis was conducted. Clinical risk factors were assessed and PTX3 and CRP values were measured at baseline. Patients were contacted by phone at a median of 4.6 years after the baseline episode and the medical records were reviewed.

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http://dx.doi.org/10.1016/j.jinf.2014.11.002

Results: Overall, 41% of the patients had a recurrence in the follow up. Of the patients with a history of a previous cellulitis in the baseline study 57% had a recurrence in five year follow up as compared to 26% of those without previous episodes ($p = 0.003$). In multivariate analysis, only the history of previous cellulitis was identified as an independent predicting factor for recurrence. The levels of pentraxin 3 (PTX3) or C-reactive protein (CRP) in the acute phase did not predict recurrence.
Conclusions: Risk of recurrence is considerably higher after a recurrent episode than after the first episode. Clinical risk factors predisposing to the first cellulitis episode plausibly predispose also to recurrences.

Introduction

Acute bacterial cellulitis is an infection of the skin and subcutaneous tissue. Mostly it has a relatively benign course.[1] However, recurrences are common and may be considered as the main complication of acute cellulitis.[2] Overall recurrence rates have varied between 22 and 47% within two to three years follow up.[3–5] Preventive measures, such as compression stockings to reduce chronic leg oedema, or careful skin care to avoid skin breaks, have considered to be essential in reducing the risk of recurrence.[3,6,7] Prophylactic antibiotics have been used in order to prevent further cellulitis episodes in patients suffering many recurrences, and recently, low-dose penicillin has been shown to be effective.[8] Yet, the optimal patient selection for prophylactic antibiotic use, antibiotic dosing regimen and actual effectiveness of other preventive measures remain to be proven.[2,8–11] It has been shown that the risk for a recurrence is greater for those patients who already have suffered recurrent cellulitis, as compared to those who have had only one episode.[3,4] Prior leg surgery,[12] dermatitis, cancer, and tibial localisation[5] have been associated with the risk of recurrence after the initial episode. Risk factors for acute and recurrent cellulitis have been investigated in several studies.[6,7,12–17]

In our previous case control study[15,18] assessing the clinical risk factors for acute non-necrotising cellulitis, we have shown that chronic oedema of the extremity, disruption of the cutaneous barrier and obesity are associated with acute cellulitis. Furthermore, in the baseline study[15] patients presenting with a recurrent cellulitis had a stronger inflammatory response, as measured by peak CRP level and leukocyte count and longer stay in hospital, than those with their first cellulitis episode. Based on these findings, we conducted a five year follow up study to investigate demographic and clinical risk factors for recurrent cellulitis. Also, we assessed the value of short and long pentraxins, i.e. CRP and pentraxin 3 (PTX3) as laboratory markers of inflammation in predicting recurrence of cellulitis in five years follow up.

Materials and methods

Patients and methods

Study population consisted of patients hospitalised due to acute cellulitis and participated in the baseline study.[15] The patient population is previously described in detail.[15] In short, adult (≥18 yr) patients with an acute onset of fever or chills and a localised erythema of the skin in one extremity or in the face were recruited in the baseline study (see figure legend, Fig. 1). Patients were contacted by phone during March and April 2009 and asked if they had had any new cellulitis episodes after the initial study period (from April 2004 to March 2005). Medical records concerning the recalled recurrent episodes were obtained. Also, the available electronic health records of all patients of the previous study were examined to detect possibly unrecalled episodes and collecting data concerning patients not reached by phone. One patient had declined to participate in the follow up study after the initial recruitment. Seventy-eight (88%) of 89 patients were alive at the follow up, and 67 patients could be reached by phone.

In the baseline study patients and matched controls were clinically examined and the possible clinical risk factors were recorded. The history of previous cellulitis episodes was recorded for the patients, i.e. whether the cellulitis episode at the baseline study was the first for the given patient (negative history of cellulitis, NH) or a recurrent episode (positive history of cellulitis, PH). Thus, for NH patients the recorded recurrence during the follow up of the present study was their first recurrence. The number of possible multiple recurrences during the follow up was not recorded. CRP levels were measured according to the clinical practice on the hospital days 1–5, where day 1 is the day of admission, as described earlier.[15] Serum and EDTA-plasma samples for subsequent analysis were obtained in the acute phase (on admission or on the next working day following admission) and convalescent phase and stored in aliquots at −20 °C. PTX3 levels were measured from the thawed EDTA-plasma samples by a commercially available immunoassay (Quantikine, R&D Systems, Inc., Minneapolis, MN) according to the manufacturer's instructions. Acute phase sera were collected within less than three days after admission in 65 (75%) of the 87 cases as follows: day 1 (admission) in three cases, day 2 in 52 cases and day 3 in 10 cases. These 65 cases were included in acute phase PTX3 analyses. Convalescent phase sera were obtained from 73 patients one month after admission (median 31 days, range 12–67 days, except for one patient 118 days).

Statistical analysis

For continuous variables, median, maximum and minimum values are given. Statistical analysis was performed with