Clinical and Laboratory Factors Associated with Prolonged Hospital Stay among Patients with Cellulitis/Erysipelas

Fatores Clínico-Laboratoriais Associados ao Internamento Prolongado em Doentes com Celulite/Erisipela

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ABSTRACT

Introduction: Cellulitis and erysipelas represent the most frequent cause of hospitalization in the dermatology department of Santa Maria Hospital in Lisbon, Portugal. The aim of this study was to investigate whether patient demographics, comorbidities, previous episodes of cellulitis/erysipelas, the presence of complications, laboratory markers at admission, microbial isolation or previous use of antibiotics, are associated with prolonged stays.

Material and Methods: Retrospective analysis, including patients admitted with cellulitis/erysipelas in the inpatient dermatology department of Santa Maria Hospital between July 1st 2012 and June 30th 2017.

Results: There were 372 admissions, corresponding to 348 patients. The median length of stay was 11 days. Increased age (p = 0.002, OR 1.03, 95% CI 1.01 – 1.04), previous episode of cellulitis/erysipelas requiring hospitalization (p = 0.005, OR 4.81, 95% CI 1.63 – 14.23), the presence of cellulitis/erysipelas-associated complications (p = 0.001, OR 3.28, 95% CI 1.63 – 6.59), leukocytosis (p = 0.049, OR 1.81, 95% CI 1.00 – 3.30), high levels of C-reactive protein (p = 0.035, OR 1.03, 95% CI 1.00 – 1.06) and a positive culture result (p = 0.002, OR 2.59, 95% CI 1.41 – 4.79) were associated with prolonged hospitalization.

Discussion: Prolonged hospitalization for cellulitis/erysipelas is associated with higher costs, additional clinical investigation, invasive treatments, prolonged courses of antibiotic therapy, risk of nosocomial infections, and delayed return to activities of daily living. Thus, the investigation of clinical-laboratory factors associated with prolonged hospitalization for cellulitis / erysipelas is essential and may be useful for the construction of a severity score.

Conclusion: The knowledge of the characteristics that are associated with prolonged stay among patients with cellulitis/erysipelas may be relevant to improve health care, by reducing the length of hospital stay and associated risks and costs.

Keywords: C-Reactive Protein; Cellulitis; Erysipelas; Hospitalization; Leukocytosis

RESUMO

Introdução: A celulite e a erisipela constituem a causa mais frequente de internamento no Serviço de Dermatologia do Hospital Santa Maria. Este estudo teve como objetivo investigar se as características demográficas, as comorbilidades, a existência de episódios prévios de celulite/erisipela, a presença de complicações associadas, os parâmetros laboratoriais na admissão, o isolamento de microrganismo em cultura ou o uso prévio de antibióticos estão associados a internamentos prolongados.

Material e Métodos: Estudo retrospetivo, incluindo os doentes internados no Serviço de Dermatologia do Hospital Santa Maria com o diagnóstico de celulite/erisipela, entre 1 de julho de 2012 e 30 de junho de 2017.

Resultados: Existiram 372 internamentos, correspondendo a 348 doentes. A mediana do tempo de internamento foi de 11 dias. A idade (p = 0,002, OR 1,03, 95% IC 1,01 – 1,04), a existência de internamento prévio por celulite/erisipela (p = 0,005, OR 4,81, 95% IC 1,63 – 14,23), a presença de complicações associadas à celulite/erisipela (p = 0,001, OR 3,28, 95% IC 1,63 – 6,59), a leucocitose (p = 0,049, OR 1,81, 95% IC 1,00 – 3,30), valores elevados de proteína C reativa (p = 0,035, OR 1,03, 95% IC 1,00 - 1,06) e o isolamento de microrganismo em cultura (p = 0,002, OR 2,59, 95% IC 1,41 – 4,79) estiveram associados a internamentos prolongados.

Discussão: A par dos maiores custos associados, o internamento prolongado por celulite/erisipela está frequentemente associado à necessidade de investigação clínica adicional, a tratamentos invasivos, a cursos prolongados de antibioterapia, ao risco de infeções nosocomiais e ao atraso no retorno às atividades da vida diária. Assim, o estudo dos fatores clínico-laboratoriais associados ao internamento prolongado por celulite/erisipela é fundamental e poderá ser útil para a construção de um *score* de gravidade.

Conclusão: O conhecimento de características clínicas e laboratoriais associadas ao internamento prolongado poderá ser relevante para melhorar os cuidados de saúde, através da redução dos tempos de internamento e dos seus riscos e custos associados.

Palavras-chave: Celulite; Erisipela; Hospitalização; Leucocitose; Proteína C-Reactiva

INTRODUCTION

A Cellulitis and erysipelas are the leading causes of admission to the Department of Dermatology of the *Hospital Santa Maria*, corresponding to around 18% of annual admissions.

Even though cellulitis can be differentiated from erysipelas, this is mainly based on unclear clinical criteria and is irrelevant regarding the approach to treatment and management. Therefore, both terms are interchangeably used in clinical practice.[1]

Up to date, little is known on the factors with an influence

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on hospital length of stay (LOS) of patients with cellulitis/erysipelas. This study was aimed at defining the association between prolonged LOS and patient's demographic characteristics, comorbidities, the presence of previous episodes of cellulitis/erysipelas or previous complications associated with both conditions, laboratory parameters on admission, positive cultures or previous antibiotic treatment.

MATERIAL AND METHOD

This was a retrospective study involving patients aged 18 or older admitted to the Department of Dermatology of the *Hospital de Santa Maria* between 1 Jul 2012 and 30 Jun 2017 and diagnosed with cellulitis / erysipelas, regardless of the location of the affected area.

The following explanatory variables were assessed: demographic characteristics, including patient's age and gender, the presence of comorbidities, namely diabetes mellitus, peripheral vascular disease (affecting veins, arteries and lymphatic vessels), immune impairment (associated with infectious, haematological and pharmacological disease); history of cellulitis/erysipelas, namely the presence of at least one previous episode of cellulitis/erysipelas, at least one previous admission due to cellulitis/erysipelas and compliance with antibiotic prophylaxis; the presence of complications associated with cellulitis/erysipelas (including abscess, lymphangitis, necrosis, skin ulcers, blisters, osteoarticular involvement); the presence of a portal of entry [all the conditions involving skin barrier disruption, including fungal infections of the skin, hair and nails, viral (herpetic infections), bacterial (folliculitis, boils), traumatic wounds, surgical wounds, insect bites and stings]; laboratory parameters on admission, namely white blood cell count, neutrophil count, C-reactive protein (CRP) level; positive culture (ulcer or abscess exudate and/or blood culture); antibiotic treatment of the current episode of cellulitis/erysipelas on the week previous to admission.

The selection of variables was based on the pathophysiology of the disease and its hypothetical relationship with the length of stay in hospital.

Statistical analysis

Categorical variables were presented in the descriptive analysis as frequencies and rates and continuous variables as means and standard deviations, or medians and interquartile range, depending on the type of data (normally or non-normal distributed, respectively). The Shapiro-Wilk test of normality was used and cut-off based [-1; 1] skewness and kurtosis values were analysed.

Hospital admissions were divided into two different groups, depending on the length of stay (greater than 14 days of 14 days and less); this dichotomisation was based on the median LOS of our group of patients and was subsequently defined. A length of hospital stay greater than 14 days was considered as a prolonged LOS.

Chi-square or Fisher's exact test were used in bivariate analysis in order to check for an association between categorical variables and Student's t-test was used for the assessment of continuous variables.

Finally, an improved logistic regression model was developed, with a stepwise data entry method, including statistically significant variables in bivariate analysis, aimed at defining which variables were associated with prolonged LOS.

Only two-tailed *p*-values were reported, with a 0.05 significance level (α). Data analysis was made by use of the SPSS, version 23 software.

Table 1 – Univariate analysis of the characteristics of patients admitted with cellulitis/erysipelas

	General (n = 372)	Short stay (n = 247)	Prolonged stay (n = 125)	*p*-value
Age – mean (SD) (years)	61.2 (18.4)	59.5 (18.7)	64.5 (17.4)	**0.01**
Female gender – n (%)	191 (51%)	122 (49%)	69 (55%)	0.29
Diabetes mellitus – n (%)	86 (23%)	50 (20%)	36 (29%)	0.06
Peripheral vascular disease – n (%)	96 (26%)	55 (22%)	41 (33%)	**0.03**
Immune impairment – n (%)	47 (13%)	29 (12%)	18 (14%)	0.47
Previous local surgery – n (%)	83 (22%)	51 (21%)	32 (26%)	0.28
Previous episode(s) of cellulitis/erysipelas – n (%)	79 (21%)	50 (20%)	29 (23%)	0.51
Previous hospital admission due to cellulitis/erysipelas – n (%)	24 (6%)	8 (3%)	16 (13%)	**< 0.001**
Antibiotic prophylaxis	15 (4%)	9 (4%)	6 (5%)	0.59
Complications – n (%)	66 (18%)	32 (13%)	34 (27%)	**0.001**
Defined portal of entry – n (%)	193 (52%)	129 (52%)	64 (51%)	0.85
Leukocytosis – n (%)	188 (51%)	109 (44%)	79 (63%)	**0.001**
Neutrophilia – n (%)	221 (59%)	135 (55%)	86 (69%)	**0.009**
CRP – mean (SD) (mg/dL)	12.4 (9.9)	11.2 (8.9)	14.8 (11.5)	**0.002**
Positive culture* – n (%)	82 (22%)	37 (15%)	45 (36%)	**< 0.001**
Antibiotic treatment on the week previous to admission – n (%)	111 (30%)	67 (27%)	44 (35%)	0.11

Table 2 – Complications associated with cellulitis/erysipelas

	General (n = 66)	Short stay (n = 32)	Prolonged stay (n = 34)
Abscess – n (%)	33 (50%)	11 (35%)	22 (64%)
Lymphangitis – n (%)	22 (33%)	18 (56%)	4 (12%)
Skin ulcer – n (%)	4 (6%)	1 (3%)	3 (9%)
Necrosis – n (%)	1 (2%)	0 (0%)	1 (3%)
Skin blister – n (%)	2 (3%)	1 (3%)	1 (3%)
Osteoarticular involvement – n (%)	4 (6%)	1 (3%)	3 (9%)

RESULTS

A total of 372 hospital admissions were recorded during the study period, corresponding to 348 patients, with an 11-day median length of stay, mostly affecting the lower limb (n = 284, 76%), followed by the face (n = 42, 11%) and the upper limb (n = 36, 10%). Forty four percent of the hospital admissions were considered as prolonged LOS (n = 125).

Patient's characteristics are shown in Table 1. A significantly higher mean age was found in the group of patients with prolonged LOS [64.5 (17.4) *vs.* 59.5 (18.7); $p = 0.01$] while no significant differences were found as regards patient's gender ($p = 0.29$), even though mostly female patients with prolonged LOS were found. Rates of 29% *vs.* 20%, 33% *vs.* 22%, 14% *vs.* 12% and 26% *vs.* 21% were found as regards prolonged *vs.* short stay, respectively, in patients with diabetes mellitus, peripheral vascular disease, immune impairment and previous local surgery. A previous history of cellulitis/erysipelas was found in 21% of hospital admissions and at least one previous hospital admission due to the same reason was found in 6% of the cases. As regards the episode of cellulitis/erysipelas underlying the hospital admission, the presence of complications was significantly more frequent in patients with prolonged LOS (27% *vs.* 13%; $p = 0.001$). The complications associated with cellulitis/erysipelas are shown in Table 2. The identification of a portal of entry was similar in both groups (52% *vs.* 51%). Cultures were carried out in 262 admissions, which were positive in 31% (n = 82) of the cases (72 cases with a positive exudate culture, seven with a positive blood culture and three with both positive exudate and blood cultures). The microorganisms that were grown are shown in Fig. 1. Finally, no significant differences were found as regards an antibiotic treatment on the week previous to admission, even though this was more frequently found in the group with a prolonged LOS (35% *vs.* 27%) ($p = 0.11$).

The adjustment of the model of logistic regression has allowed for the identification of patient's age ($p = 0.002$), previous admission with cellulitis/erysipelas ($p = 0.005$), presence of complications ($p = 0.001$), leukocytosis ($p = 0.049$), CRP value ($p = 0.035$) and positive culture ($p = 0.002$) as factors associated with prolonged LOS (Table 3). The presence of previous admission with cellulitis/

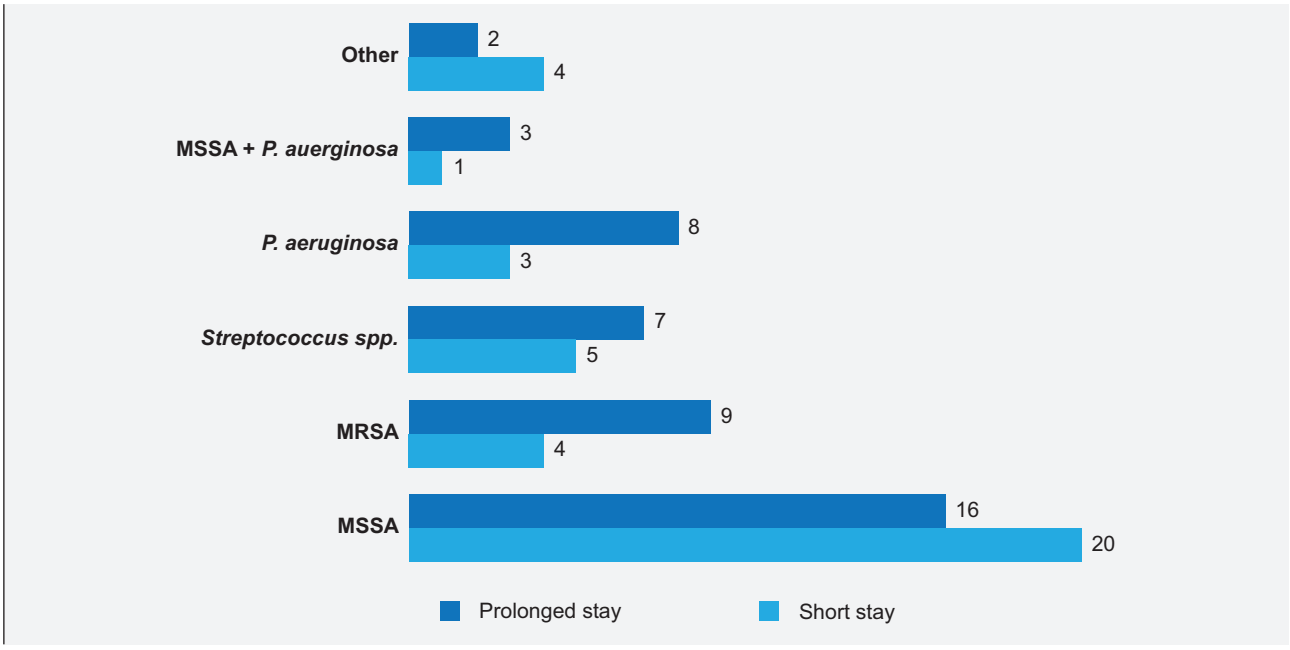

Figure 1 – Microorganisms grown in culture.
MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; *P. aeruginosa*: *Pseudomona aeruginosa*; *spp.*: species. Others, including: *Serratia marcescens* (n = 3), E. coli (n = 1), *Klebsiella pneumoniae* (n = 1), *Pantoea agglomerans* (n = 1)

Table 3 – Improved logistic regression, including 70% of data (262/372), due to missing values

	p-value	Adjusted odds ratio	95% confidence interval
Age	0.002	1.03	1.01 – 1.04
Previous hospital admission due to cellulitis/ erysipelas	0.005	4.81	1.63 –14.23
Peripheral vascular disease	0.42	1.30	0.69 – 2.46
Complications	0.001	3.28	2.63 – 6.59
Leukocytosis	0.049	1.81	1.00 – 3.30
CRP	0.035	1.03	1.00 – 1.06
Positive culture*	0.002	2.59	1.41 – 4.79

erysipelas and the presence of complications were the most significant variables.

The authors declare having followed the ongoing protocols at the healthcare institution as regards the publication of any personal data. An anonymised dataset has been used and none of the authors had any access to any identification elements of the patients. The study was carried out according to the Helsinki Declaration of the World Medical Association.

DISCUSSION

This is the first Portuguese study on the clinical and laboratorial factors associated with prolonged LOS of patients admitted with cellulitis/erysipelas. Therefore, it was found that patient's age, the presence of at least one previous hospital admission with cellulitis/erysipelas, the presence of complications, leukocytosis, CRP value on admission and a positive culture were associated with a long hospital stay.

In addition to higher associated costs, prolonged LOS due to cellulitis/erysipelas is frequently associated with the need for additional clinical evaluation with diagnostic tests (including imaging), with invasive procedures, including surgical drainage or debridement, long-term antibiotic treatment, with the risk of nosocomial infections and delayed recovery of the activities of daily living, with an impact on the patient's quality of life.

Despite no ideal antibiotic regimen has ever been established, a therapeutic protocol based on the presence of comorbidities and previous antibiotic treatment is followed in our department. Even though clinical guidelines have already been recommended for the approach and treatment of patients with cellulitis/erysipelas, there are still few data allowing for the identification of patients at risk of prolonged LOS and, in addition, that could benefit from a more aggressive treatment.[2,3]

In line with our study, other studies have looked for the characteristics of patients with cellulitis/erysipelas associated with prolonged LOS. According to the North-American multi-centric study by Gang *et al.* on 4,224 hospital admissions due to lower limb cellulitis/erysipelas, variables such as patient's age, female gender, diabetes mellitus, tachycardia, hypotension, leukocytosis, neutrophilia and elevated serum creatinine were associated with prolonged LOS.[4] In a study from New Zealand, involving 51 patients admitted with lower limb cellulitis, it has been found that an elevated neutrophil count, the score of oedema and the use of diuretics were independently associated with prolonged LOS.[5] In 2003, Carratalà *et al.* have examined 332 patients admitted with cellulitis, regardless of its location and have reached the conclusion that patients with multiple comorbidities, hypoalbuminaemia, kidney failure or skin necrosis on admission remained longer in the hospital.[6] In addition, an Australian study involved 395 episodes of cellulitis/erysipelas affecting different anatomical locations has found that over 60 years of age, symptoms lasting more than 4 days, the presence of hypoalbuminaemia, the presence of bacteraemia and methicillin-resistant *Staphylococcus aureus* (MRSA) were associated with prolonged LOS. On the other hand, neutrophilia and elevated serum creatinine were not associated with prolonged LOS in this analysis.[7] Finally, a Canadian study based on the national database of 65,454 patients admitted with cellulitis has shown that over 65 years of age, female gender and congestive heart failure were factors associated with prolonged LOS.[8]

Heterogeneous results still exist and could be influenced by the absence of clearly defined criteria for the diagnosis and approach to patients with cellulitis/erysipelas, leading to different approaches in the different centres, as well as regarding the average LOS.[9–11] However, Gang *et al.* argued that the results of these studies could represent an important tool for the construction of a severity score,[4] in line with the scores applied to pneumonia that led to the reduction of the rates of hospital admission, as well as LOS and associated complications.[12–15]

The presence of potential confounding factors for prolonged LOS is one of the major limitations of this observational study, including unfavourable social background or other complications not directly related to the episode of cellulitis/erysipelas. However, the application of an improved logistic regression model, with a stepwise data entry method, was aimed at reducing the statistical impact of confounding factors.

CONCLUSION

In conclusion, the knowledge of the predictive clinical and laboratorial characteristics could be relevant to improved healthcare delivery, aimed at reducing the length of stay and associated risks and costs.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and

Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data. Informed consents were obtained.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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