ORIGINAL ARTICLE

The risk factors of lower limb cellulitis: A case-control study in a tertiary centre

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Abstract

Introduction: Lower limb cellulitis is a common superficial skin infection that leads to morbidity and mortality. Cellulitis risk factors have been well studied in many countries, but to date, not in Malaysia. Geographical and climate variables may affect risk factors. Early identification of the preventable risk factors is vital to prevent cellulitis and improve holistic patient care.
Objective: To determine the risk factors of lower limb cellulitis amongst hospitalized patients at a tertiary center.
Methods: A prospective case-control study of hospitalized patients with a clinical diagnosis of lower limb cellulitis was conducted at UKM Medical Centre, January–August 2015. Each patient was compared to two age and gender-matched control patients. All patients were interviewed and examined for risk factors of cellulitis.
Results: A total of 96 cellulitis patients and 192 controls participated in this study. The cellulitis patients included 61 males and 35 females with a mean age of 62.07±15.43 years. The majority of patients were experiencing their first episode of cellulitis. Multivariate analysis showed a previous history of cellulitis (OR 25.53; 95% CI 4.73–137.79), sole anomalies (OR 16.32; 95% CI 6.65–40.06), ulceration (OR 14.86; 95% CI 1.00–219.39), venous insufficiency (OR 10.46 95% CI 1.98–55.22), interdigital intertrigo (OR 8.86; 95% CI 3.33-23.56), eczema (OR 5.74; 95% CI 0.96.–34.21), and limb edema (OR 3.95; 95% CI 1.82–8.59) were the significant risk factors for lower limb cellulitis.
Conclusion: Previous cellulitis and factors causing skin barrier disruption such as sole anomalies, ulceration, venous insufficiency, eczema, intertrigo, and limb edema were the risk factors for lower limb cellulitis. Physician awareness, early detection, and treatment of these factors at the primary care level may prevent hospital admission and morbidity associated with cellulitis.

Introduction

Cellulitis is a common bacterial skin infection presented as a painful, ill-defined erythematous patch. According to data published in the United Kingdom, in 2009, there were 82,113 hospital cellulitis admissions in England and Wales1, and it was estimated that £133 million was spent on hospital stays alone.2 Cellulitis accounted for 1.6% of emergency hospital admissions in the United Kingdom in 2008–2009.3 In Singapore, cellulitis was ranked as one of the top ten causes of hospital admissions in 2012, contributing 2% of total admissions.4 In Malaysia, the epidemiological data for cellulitis is scarce; however, unpublished data from 2016 in our tertiary center indicated approximately 1% of total hospital admissions in both medical and surgical wards was due to cellulitis (UKM Medical Centre unpublished patient census, 2016).

Cellulitis can be debilitating, potentially life-threatening, and cause a considerable economic burden to healthcare. Risk factors of cellulitis in lower limbs are treatable and could prevent recurrent infection. These risk factors are generally divided into two major categories. The first category is local risk factors that cause disruption in the skin and compromise its barrier function. These factors include local wounds, ulcers, dermatitis, tinea infection, and maceration of interdigital spaces, all of which provide a portal for skin bacteria to enter the tissue. The second category is systemic factors that are thought to weaken the host immune defense either systemically or locally, e.g., uncontrolled diabetes mellitus (DM).[5] Despite vast treatment options, the complications of cellulitis are still considerably high and have been documented as high as 31% in hospitalized patients.[6]

Previous studies have shown that risk factors for cellulitis are interdigital intertrigo, lymphedema, leg edema, leg eczema,

and sole abnormalities (e.g., tinea pedis, onychomycosis, and dermatitis).[10,11,16,18] To date, there has been no prospective study on the risk factors of lower limb cellulitis in Malaysia. It is vital to identify these risk factors in our local population and to ascertain whether they are considerably different from those studied around the globe. We hypothesized that tropical climate and genetic diversity may influence some of the risk factors involved. Although this study is more focused on the risk factors of lower limb cellulitis which is more severe and requires hospitalization, we believe that the same risk factors are applicable for milder cases. The result of this study will provide more meaningful information in identifying and treating these risk factors, which ultimately contribute to cellulitis prevention.

Considering the large number of patients treated by primary care physicians for various conditions, most of these risk factors would have been detected in a primary care setting. Also, the non-severe cellulitis cases would most likely be seen at the onset in a general practitioners' office. Therefore, it is necessary to create awareness amongst primary care physicians regarding the importance of these risks in the development of cellulitis. An increase in physician awareness will lead to early identification and treatment to prevent cellulitis, particularly in patients with multiple risk factors. Early detection and treatment at the primary care setting will prevent admission to tertiary care facilities and may help reduce healthcare costs, morbidity, and mortality associated with cellulitis.

Materials and methods

This was a prospective, case-control study carried out January–August 2015 at the UKM Medical Centre (UKMMC) including all patients 12 yo and above admitted to all wards with a clinical diagnosis of lower limb cellulitis. Sample size calculation is shown in appendix 1. Patients were identified from hospital admission records readily available in the medical and surgical wards. Patients with cellulitis associated with surgical wounds, surgical instrumentation, abscesses, and necrotizing fasciitis were excluded. Each study case was age and sex-matched to control patients which were admitted to any medical and surgical wards at UKMMC within 48 hours of the case patients due to diagnoses other than cellulitis. The patients were not racially matched as previous studies have shown that race is not a contributing factor to cellulitis risk. A ratio of 1 case to 2 controls was applied in this study to increase the accuracy and to minimize confounders to the identified risk factors.

All case and control patients were interviewed and underwent a thorough clinical examination within 48 hours of admission. The face-to-face interview and clinical examination were carried out by the same dermatology-trained medical officer and it included skin examinations of the upper and lower limbs, looking for any evidence of erosion, intertrigo, eczema, or psoriasis and any nail changes which may indicate onychomycosis. Interdigital intertrigo includes maceration and fissuring of the interdigital spaces. Sole anomaly in this study was defined as scaling, callus, erosion, wound, or erythema at the dorsum of the foot. Lower limb peripheral pulses were also determined. Immunocompromised individuals were defined as those on systemic corticosteroids, chemotherapy, immunosuppressive medication, and diagnosed with AIDS. This study was approved by the Research Ethics Committee from UKM Medical Centre (Approval No: FF-2014-356). Demographic data collected were expressed as mean ± standard deviation (SD), number and percentage in parenthesis where appropriate. The categorical variables in the case and the control groups were compared using the chi-square test. The risk factors with $p < 0.05$ on univariate analysis were included in further multivariate analysis. Multivariate analysis with multiple logistic regression was performed on the identified risk factors. A value of $p < 0.05$ was considered statistically significant.

Results

A total of 96 case patients were recruited in this study. Most patients were admitted with their first episode of cellulitis (76.1%), 15.6% were experiencing their second episode, 5.2% their third and 3.1% their fourth. The majority had cellulitis on one leg (77.1%) and the remaining were bilateral. The demographic data of both case and control patients are summarized in **Table 1**.

Table 1: Demographic Characteristics of Case and Control Patients

	Case (N=96) (Mean ± SD)/N (%)	Control (N=192) (Mean ± SD)/N (%)
Age (years)	62.07 ± 15.43	61.90 ± 15.36
Gender		
Female	35 (36.5)	70 (36.5)
Male	61 (63.5)	122 (63.5)
Ethnicity		
Malay	52 (54.2)	87 (45.3)
Chinese	30 (31.3)	86 (44.8)
Indian	14 (14.5)	17 (8.9)
Others	0 (0)	2 (1.0)

Table 2 summarizes all the systemic risk factors identified in the case patients compared to control. From the univariate analysis, only diabetes and previous cellulitis were found to be significant. Intravenous drug users and the immunocompromised were excluded from OR analysis due to small numbers. As for the local risk factors, interdigital intertrigo, leg edema, venous insufficiency, ulceration, peripheral vascular disease and sole anomalies were found to be significant in the univariate analysis (**Table 3**).

Table 2: Univariate Analysis for Systemic Risk Factors of Lower Limb Cellulitis

	Cellulitis		p-value*
	Control (N=192)	Case (N=96)	
Systemic risk factors			
Diabetes	84 43.6%	57 59.4%	<0.05
Overweight 25<BMI(kg/m2)<30 Obesity BMI(kg/m2)>30	11 5.7% 27 14.1%	7 7.2% 20 20.8	
Alcoholic	3 1.6%	2 2.1%	0.75
IV drug use	0 0.0%	2 2.1%	
Cirrhosis	2 1.0%	5 5.2%	0.19
Heart failure	23 12.0%	12 12.5%	0.80
Immunocompromised[a]	1 0.52%	3 3.1%	
Smoking	48 25.0%	24 25.0%	0.92
Previous cellulitis	2	18	<0.05

[a] Immunocompromised defined as patients on systemic corticosteroid, chemotherapy, immunosuppressive medication, and AIDS.

* Chi-Square Test

Table 3: Univariate Analysis for Local Risk factors of Lower Limb Cellulitis

	Control (N=192)	Case (N=96)	p-value*
Local risk factors			
Eczema/ psoriasis	4 1.9%	4 6.8%	0.16
Dry skin	18 8.8%	13 13.5%	0.41
Blisters	0 0.0%	2 2.1%	
DVT	0 0.0%	4 4.2%	
Interdigital intertrigo[c]	12 6.3%	35 36.5%	<0.05
Edema	45 23.4%	59 61.5%	<0.05
Venous insufficiency	4 2.1%	11 11.5%	<0.05
Ulceration	1 0.5%	8 8.3%	<0.05
PVD	1 0.5%	8 8.3%	<0.05
Sole anomalies[d]	9 4.7%	46 47.9%	<0.05

* chi-square test

[c] Interdigital intertrigo includes maceration and fissuring of the interdigital spaces

[d] Sole anomalies defined as scaling, callus, erosion, wound, or erythema at the dorsum of foot

Table 4: Multivariate Analysis with Binary Logistic Regression for Significant Risk Factors of Lower Limb Cellulitis

Risk factors	OR	95%CI	p-value
Previous cellulitis	25.53	4.73–137.79	<0.05
Sole anomalies	16.32	6.65–40.06	<0.05
Ulceration	14.86	1.00–219.39	<0.05
Venous insufficiency	10.46	1.98–55.22	<0.05
Interdigital intertrigo	8.86	3.33–23.56	<0.05
Eczema	5.74	0.96–34.21	<0.05
Edema	3.95	1.82–8.59	<0.05
Diabetes mellitus	0.81	0.36–1.82	0.61

NA: not applicable; IV: intravenous; DVT: deep vein thrombosis; PVD: peripheral vascular disease; OR: odds ratio; CI: confidence interval

Multivariate analysis identified seven risk factors that had strong association with cellulitis. Of the potential systemic factors, only previous history of cellulitis (OR 25.53, 95% CI 4.73–137.79) was significant. For local risk factors, sole anomalies including scaling, callus, erosion, wound, and erythema at the dorsum of foot (OR 16.32, 95% CI 6.65–40.06), ulceration (OR 14.86, 95% CI, 1.00–219.39), venous insufficiency (OR 10.46, 95% CI 1.98–55.22), interdigital intertrigo (OR 8.86, 95% CI 3.33–23.56), eczema (OR 5.74, 95% CI 0.96–34.21), and limb edema (OR 3.95, 95% CI 1.82–8.59) were significant.

Discussion

Most previous studies exploring risk factors of cellulitis were retrospective in nature, which

relies on medical record documentation. This may result in recall bias or underestimation due to a lack of documentation. Hence, we conducted a prospective case-control study to provide more accurate, real-time data regarding the risk factors for cellulitis. The results of this study supported previous studies from other parts of the world. Our results demonstrated that tropical climate and genetic diversity in Malaysia did not influence the risk factors. All the significant risk factors for cellulitis in our study and previous studies such as sole anomalies, interdigital intertrigo, ulceration, eczema, venous insufficiency, limb edema, and previous history of cellulitis are commonly found in the lower limbs, explaining why it is the most common site for the condition.

In this study, previous cellulitis and sole anomalies had the two highest odds ratios (OR) for local risk factors, similar to that of a previous study.[9] This is expected as a majority of the time, patients with a previous episode of cellulitis also had at least one of the other risk factors.

Venous insufficiency, dermatitis, and ulceration were also found to be significant and these findings concur with results from many other studies.[7,8,9,10] Sole anomalies, dermatitis and ulceration contribute to cellulitis as they provide a direct portal for the invasion of pathogens through the skin.[11]

Among the risk factors studied, interdigital intertrigo is most consistently associated with cellulitis, either singly or combined. This is not surprising because in intertrigo, there is the presence of scaling, maceration, and fissures which all create direct portals of entry for bacterial invasion. Results from Iceland[9] and England[10] reported OR values of 0.32 and 5.35, respectively, slightly lower than our result. The wide variation in OR may be influenced by climate and location. The higher temperature and level of humidity in Malaysia may be contributing factors for the development of interdigital intertrigo.

Our study and many other studies have also shown that limb edema plays a role in cellulitis. Damage to the venous system and lymphatic vessels which cause limb edema hinders clearance of bacteria which leads to the propagation of infection.[12,13] These conditions also have been shown to predispose patients to Streptococci infection by providing optimal conditions for bacterial infection.[14] Chronic venous insufficiency, which may also lead to limb edema, is postulated to lead to the development of venous microangiopathy, which subsequently causes growth factor trapping and white blood cell decline, which impairs healing process.[15] It is essential to highlight that cellulitis itself will lead to limb edema which will predispose the individual to another episode of cellulitis.

It is interesting to note that being neither overweight nor obese were significant risk factors in this study, in agreement with previous studies.[8,10] We hypothesize that it is not the excess weight but rather the complications related to venous stasis, stasis eczema, and leg edema that were the main cellulitis risk factors. Both leg dermatitis and edema were shown to be significant risk factors in this study. However, other studies have concluded that obesity was linked to cellulitis.[7,16] It has been suggested that obesity causes impairment in cutaneous vascular supply predisposing those individuals to cutaneous infection.[17] The WHO classification for overweight and obese categories was used instead of Malaysian classification to facilitate comparison to other studies by using the same classification.

Diabetes mellitus, which is almost synonymous with skin and soft tissue infection such as necrotizing fasciitis, was found to be significant in univariate analysis but not in the multivariate analysis. This is because poor diabetes control and not diabetes itself is a risk factor for cellulitis. There is evidence that poor glycemic control poses a risk to skin infection such as cellulitis[5], and higher *Staphylococcus aureus* colonization has been found in patients with poor DM control.[19] Our results are the opposite of that found in a few other studies.[7,8,9,18] It may be that our DM patients had better glycemic control compared to those in other studies but we are unable to conclude this as we did not assess the DM control in our patients, such as via HBA1c measurements.

Conclusions regarding cellulitis risk factors may be limited in this study as there were no confirmatory investigations such as ankle-brachial pressure index (ABPI) measurements or ultrasound doppler studies done for patients with a diagnosis of peripheral vascular disease. The cellulitis diagnosis was based on previous investigation or via clinical examination. This might lead to an under or overestimation of the condition.

The findings of this study highlight the importance of local risk factors, as opposed to systemic risk factors, to lower limb cellulitis. Therefore, our findings emphasized the importance of aggressive treatment of these conditions to prevent the occurrence of cellulitis. Patients with sole anomalies and leg eczema need to be treated with appropriate topical treatment. Interdigital intertrigo needs more comprehensive care combined with systemic or topical antibiotics and antifungals. Leg edema and lymphoedema, which seem harmless before the onset of cellulitis, will need to be investigated and treated with diuretics and compression therapy.[20,21] These measures were mentioned in previous studies and may seem imperative however, no study has evaluated their effectiveness in preventing cellulitis and its recurrence. Many cellulitis prevention studies focused more on the use of antibiotic prophylaxis in preventing cellulitis.[22]

The results of this study can be translated into clinical practice in a primary care setting by early screening of these factors in patients at risk of cellulitis, e.g. those with chronic leg edema and uncontrolled DM. In first episode or recurrent cellulitis patients, using a pre-printed clerking proforma which includes these important risk factors may facilitate physician awareness, better identification, and treatment.

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Conflict of Interest

All authors declared there were no conflict of interest in this study.

Appendix

Appendix 1

Sample Size Determination

Based on the formula

$$P_{case} = \frac{OR \times Pcontrol}{P\ control\ (OR-1) + 1}$$

$$P_{case} = \frac{2.6 \times 0.1}{0.1(2.6-1)+1}$$

$$P_{case} = 0.224$$

$$P_{average} = \frac{Pcase + Pcontrol}{2} = \frac{0.224 + 0.1}{2} = 0.162$$

$$N = \frac{(R+1)\ X\ (P_{average})(1-P_{average})(Z_{\beta} + Z_{\alpha/2})^2}{2\qquad (P_{case} - P_{control})}$$

$$N = \frac{(2+1)\ X\ (0.162)(1-0.162)(0.84+1.96)^2}{2\qquad (0.224-0.1)^2}$$

N= 103

P_{case} = Prevalence of the case
$P_{control}$ = Prevalence of the control, based on previous study, it is 10%
$P_{average}$ = Average of Prevalence of the case and Prevalence of the control
OR = Odd ratio of the control, based on previous study is 2.6
N = Number of cases needed for the study
R = Ratio of the control to the case
Z_{β} = For 80% power, Z_{β}= 0.84
$Z_{\alpha/2}$ = For 0.05 significance, $Z_{\alpha}^{/2}$= 1.96

A total of 103 case patients and 206 of control patients are needed. (Ratio is 1 case : 2 control)

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