# THE RISK FACTORS AND CLINICAL CHARACTERISTICS OF CELLULITIS: A HOSPITAL-BASED CASE-CONTROL STUDY IN SINGAPORE

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**ABSTRACT:** Bacterial cellulitis is a worldwide problem and may lead to potentially fatal complications. The aim of this study was to identify the risk factors associated with, and the clinical characteristics of, cellulitis. A hospital-based case-control study of 150 patients and 150 unmatched controls was conducted. The mean age was 56.5 (±16.5) years in cases and 59.2 (±19.0) in controls, (p=0.195). There were 63.3% males in cases and 40.0% in controls (p<0.001) and 21.3% Singaporean Indians in cases and 7.3% in controls (p=0.001). Diabetes mellitus (DM) was found in 33.3% of cases and in 13.3 % of controls (p<0.001). Skin disruption was present in 32.7% cases and controls 6.0% of controls, (p<0.001). Lower limb cellulitis was found in 67.3% of cases, bacteraemia in 6.4%, and recurrence of cellulitis in 31.3%. Ninety percent of cases improved with antibiotic or after surgery, over 30% needed surgery and the death rate was 2%. Length of stay was increased in those with DM, hypoalbuminaemia, skin disruption, and with increasing age. Risk factors for cellulitis were increasing age, male gender, Singaporean Indian ethnicity, DM, skin disruption, breast cancer, renal impairment and previous episode of cellulitis. A multi-disciplinary team should manage patients and a guideline on the use of antibiotics in cellulitis should be updated. The National Health Education Program should include foot-care and care of simple wounds with special emphasis for diabetics.

**Keywords:** cellulitis, health burden, necrotizing fasciitis, Singapore

**INTRODUCTION:** Cellulitis is a deep infection of the skin characterized by a painful area of redness, warmth with accompanying fever[1,2]. It occurs worldwide and early treatment with oral or intravenous antibiotics is indicated[1,3-12]. *Streptococcus pyogenes* and *Staphylococcus aureus* are the common organisms involved[1,3]. Rarer organisms include *Erysipelothrix rhuseopathiae* in patients dealing with fish or pigs, or *Vibrio vulnificus* when patients had been in contact with seawater or crustaceans[13,14]. Virulent organisms cause rapid extension of cellulitis resulting in necrotising fasciitis, septicaemia, septic shock and death. Risk factors for cellulitis include diabetes mellitus (DM), trauma or surgery to limbs, damage of lymphatics by surgery or radiotherapy, infections and malignant processes[15]. Rarely, a malignancy of the bone may present as recurrent cellulitis. If treatment is started late or if the patient is immuno-compromised, has DM, renal failure or is elderly, complications may set in[16]. These complications usually need surgical intervention, increase the length of stay (LOS) in hospital, and increase health costs. The aim of this study was to identify the risk factors associated with, and the clinical characteristics of, cellulitis.

**METHODS:** Patients with cellulitis admitted to the medical wards of Singapore General Hospital between the 1st of March 2005 and 31st December 2005 were recruited as cases. Patients admitted without cellulitis, in the same medical wards, between 1st July 2007 and 31st December 2007, were randomly selected as controls. By using StatCalc from EpiInfo Version 6 and assuming a confidence level of 95%, a power of 90%, an unmatched case control ratio of 1:1, a 20% frequency in controls and a 40% frequency in cases, the computed number was 118 for cases and 118 for controls. We expected that by using a sample size of 150 for the cases and 150 for the controls, we should be able to detect whether

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there was indeed an association or not for each of the potential risk factors.

A pilot project was undertaken and two trained investigators were given a questionnaire and each of them chose 20 files of patients with cellulitis at random. From these files the questionnaire was filled in with the appropriate data. The 20 completed questionnaires were used to iron out difficulties found by both investigators. A new modified and updated questionnaire was drafted in order to improve the clarity and expression of the contents, to avoid ambiguities and to make data collection easier. This modified questionnaire was then used for the study. A similar exercise was done for the questionnaire of the controls.

All patients admitted to medical wards with a confirmed diagnosis of cellulitis made by a consultant were included as cases. Excluded were patients with orbital cellulitis, necrotizing fasciitis, or with an infectious disease such as open tuberculosis, herpes zoster, methicillin resistant *Staphyloccocus areus* (MRSA) or vancomycin resistant enteroccocci (VRE) infections diagnosed on admission.

Hundred and fifty consecutive patients with cellulitis admitted in the medical wards between the 1st of March 2005 and 31st December 2005 were recruited as cases. A further 150 patients admitted without cellulitis, in the same medical wards, between 1st July 2007 and 31st December 2007, were randomly selected as controls. The files of the cases and the controls as well as the online results of laboratory investigations and radiological investigations were perused and information as indicated in a pre-tested questionnaire was extracted. The demographic data as well as the clinical characteristics of controls and cases were recorded. The variables identified as potential risks factors for cellulitis included the patients' age, sex, ethnic group, and co-morbid conditions that included DM, skin disruption, IV drug abuse, leukaemia/lymphoma, taking immuno-suppressants, solid malignancies, renal impairment, cirrhosis of the liver, nephrotic syndrome, congestive cardiac failure, hypoalbuminaemia, ischaemic heart disease and carcinoma of the breast were ascertained and recorded.

For the cases, the site of cellulitis, and a first attack or a recurrence were recorded. The type of organisms isolated, the antibiotics used, the course of the disease, the type of operation done, outcome and the length of stay in hospital were ascertained from the files or from online results and recorded in the questionnaire.

For risk factor analysis, bivariate and logistic regression analyses were performed on the data of cases and controls. For the analysis of the clinical characteristics of cellulitis only the data of the cases were used. The necessary percentages were computed and linear regression analyses performed. For continuous data that were normally distributed the mean and standard deviations were presented. For non-continuous data the median was presented. Categorical variables were tested with chi-square and logistic regression, looking at one factor at a time. The variables in the bivariate analysis with a p-value of <0.2 were included in logistic regression analysis to control for confounders.

**RESULTS:** The demographic data of cases and controls are shown in Table 1. The mean ages of the cases and controls were 56.5 (±16.5) and 59.2 (±19.0) years, respectively (p=0.195). The Chinese ethnic group, being the biggest, was used as the reference group when performing logistic regression analysis of ethnicity. The Indian ethnic group demarcated itself with an odds ratio of 3.379 (p=0.001).

Association of co-morbid disease with cellulitis is presented in Table 2. It was found that DM and

**Table 1** Demographic data of cases and controls

| Variables | Cases | | Controls | | P-value |
|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | |
| Sex (Male) | 95 | (61.3) | 60 | (38.7) | <0.001 |
| Age group < 45 years | 36 | (24.0) | 37 | (24.7) | 0.907 |
| Age group 45 to 74 years | 89 | (59.3) | 73 | (48.7) | 0.209 |
| Age group > 74 years | 25 | (16.7) | 40 | (26.7) | 0.037 |
| Ethnic group: Chinese | 115 | (53.7) | 99 | (46.3) | 0.275 |
| Ethnic group: Malay | 17 | (53.1) | 15 | (46.9) | 0.724 |
| Ethnic group: Indian | 32 | (74.4) | 11 | (25.6) | 0.002 |
| Ethnic group: "Others" | 2 | (81.8) | 9 | (81.8) | 0.054 |

**Table 2** Association of co-morbidities with cellulitis

| Co-morbidites | Case N (%) | Control N (%) | Crude Odds Ratio ( 95% CI) | P-value |
|---|---|---|---|---|
| Diabetes mellitus | 50 (33.3) | 20 (13.3) | 3.250 (0.172 - 0.550) | < 0.001 |
| Skin disruption | 49 (32.7) | 9 (6.0) | 7.598 (0.062 - 0.280) | < 0.001 |
| IV drug abuser | 4 (2.7) | 2 (1.3) | 2.027 (0.089 - 2.735) | 0.419 |
| Leukemia/lymphoma | 5 (3.3) | 1 (0.7) | 5.137 (0.022 - 1.686) | 0.137 |
| On immuno-suppressants | 9 (6.0) | 1 (0.7) | 9.466 (0.013 - 0.841) | 0.034 |
| Solid malignancies | 14 (9.3) | 12 (8.0) | 1.184 (0.377 - 1.892) | 0.682 |
| Renal impairment | 27 (18.0) | 33 (22.0) | 0.778 (0.728 - 2.268) | 0.387 |
| Cirrhosis of the liver | 7 (4.7) | 8 (5.3) | 0.869 (0.407 - 3.258) | 0.791 |
| Congestive cardiac failure | 9 (6.0) | 15 (10.0) | 0.574 (0.737 - 4.111) | 0.230 |
| Hypoalbuminaemia | 4 (2.7) | 25 (16.7) | 0.137 (2.474 - 21.542) | < 0.001 |
| Ischaemic heart disease | 13 (8.7) | 29 (19.3) | 0.396 (1.256 - 5.078) | 0.009 |
| Carcinoma of the breast | 5 (3.3) | 2 (1.3) | 0.255 (0.075 - 2.050) | 0.268 |

skin disruption were strongly and positively associated with cellulitis. The variables with a p-value of < 0.2 found in the bivariate analysis were: male gender, ethnicity, DM, skin disruption, leukaemia/lymphoma, on immuno-suppressants, hypoalbuminaemia and ischaemic heart disease. These were included in the binary regression analysis. The following variables retained their statistical significance: male gender, Singaporean Indian ethnicity, DM, skin disruption and hypoalbuminaemia. Therefore, risk factors for cellulitis were male gender, Singaporean of Indian origin, DM and skin disruption.

The clinical characteristics of cellulitis are shown in Table 3. On presentation, hypotension was present in 5.3% of the cases. The white cell count was 14.56 (±23.31) x $10^9$/L and the mean value for serum urea was 8.12 (±7.30) mmol/L. Ninety-three percent of the patients improved with antibiotics, with or without minor surgery. Complications encountered included abscess formation, necrotising fasciitis, gangrene and septicaemia. Over 30% of patients with cellulitis needed some form of surgery either minor or major; 20% needed incision and drainage because of abscess formation and another 4% developed necrotising fasciitis needing fasciotomy and extensive debridement. Four percent required an amputation of the lower limb and over 1% needed a disarticulation of a toe or metatarsal. Organisms cultured from wounds included methicillin sensitive *Staphylococcus aureus* (10.0%), *MRSA* (4.7%), *Pseudomonas aeruginosa* (2.1%). Other organisms grown were *Streptococcus pyogenes*, *Steptococcus millieri*, *Proteus mirabillis* and *Klesbsiella* species each accounting for 0.7%. Various types of organisms contributed to bacteraemia (8.7%), in which the most common species found were *Stapylococcus aureus*, *Streptococcus pyogenes and E. coli*. Thirty-six different types of antibiotics were used.

**Table 3** Characteristics of cellulitis

| Characteristic | No. (%) |
|---|---|
| Lower limb cellulitis | 101 (67.3) |
| Recurrence of cellulitis | 47 (31.3) |
| Organisms cultured from wounds | 28 (19.6) |
| Bacteraemia | 13 (8.7) |
| Initial progression of cellulitis | 90 (60.0) |
| Death rate | 3 (2.0) |

*Excluding amputation of limbs

**Table 4** Characteristics associated with length of hospital stay (days) in cellulitis patients, using linear regression analysis

| Variables | B Coefficient | 95% C.I. Lower | 95% C.I. Upper | P-value |
|---|---|---|---|---|
| (Constant) | 5.44 | 2.94 | to 7.94 | <0.001 |
| Presence of bacteraemia | 14.49 | 8.86 | to 20.11 | <0.001 |
| Chronic renal failure | 2.57 | -0.002 | to 5.14 | 0.050 |
| Diabetes mellitus | 3.02 | -0.51 | to 6.55 | 0.093 |
| Recurrence of cellulitis | 1.68 | -1.24 | to 4.61 | 0.257 |
| Skin disruption | 1.46 | -1.90 | to 4.82 | 0.392 |
| Age 75 years and above | 0.28 | -3.90 | to 4.47 | 0.894 |

The characteristics associated with prolonged length of stay are displayed in Table 4. Presence of bacteraemia, chronic renal failure and DM were strongly associated with prolonged length of stay.

**DISCUSSION:** The mean age of cases was not much different from the 58 years found by Lazzarini *et al.*[5]. The mean age in years was also not significantly different between the two groups

analyzed in the present study. On linear regression analysis age was found to be positively and marginally significantly associated with cellulitis with a p-value of 0.053, consistent again with the findings of Lazzarini.

The distribution of the sexes in the two groups was dissimilar, with male gender being predominant, (p<0.001). Ginsberg made the general statement that the disease affected predominantly males and made no mention of percentage[6]. In other words, male gender seems to be a risk factor for cellulitis. Bivariate logistic regression analysis done, with Chinese ethnic group as the reference, showed a significant p-value of 0.001 for the Indian ethnic group. Therefore, being a Singaporean Indian is a strong risk factor for developing cellulitis. To our knowledge there are no previous reports of cellulitis risk in relation to ethnicity.

DM was found in 33.3% in the cases and in 13.3% of the controls (p<0.001) and was therefore associated with cellulitis. However Dupuy *et al.* did not find this association but other authors such as Harris *et al.* did mention about this association as well as the association with abnormal glucose tolerance also[8,10]. In the present study DM turned out to be strongly associated with a prolonged hospital stay in patients with cellulitis. The mean length of stay in patients with and without diabetes mellitus were 12.9 days and 9.4 days, respectively (p=0.064, marginally significant). This indicates increased hospital costs in diabetics.

Skin disruption showed a strong association with cellulitis with an odds ratio of 7.6 (p<0.001). This association was also found by Dupuy *et al.* who estimated the odds ratio at 23.8[8]. In our study the patients with cellulitis had an increased length of stay of 17.9 days for those on antibiotic combination. Lazzarini *et al.* reported a length of 11 days for those on antibiotic combination[5].

Blood malignancies such as leukemias and lymphomas were marginally associated with cellulitis (p=0.137), however solid malignancies were weakly associated (p=0.682). Patients on immunosuppressants had an odds ratio of 9.51 (p=0.034), for having cellulitis, an association that was stronger than with solid malignancies.

Hypoalbuminaemia was negatively associated with cellulitis (p<0.001). This is a paradoxical situation where we would have expected to have greater number of persons with hypoalbuminaemia in cases rather than in controls. This observation could conceivably be explained by the fact that many of the controls were, in general, patients with chronic diseases and who might have had hypoalbuminaemia due to many other causes like poor nutrition, increased catabolism or increased loss of albumin in the urine. Being sick they might not have been as mobile as normal individuals and therefore at a less risk of injuring themselves and developing cellulitis. The same reasoning might explain why ischaemic heart disease also is negatively associated with cellulitis (p=0.009).

Ipsilateral upper limb cellulitis in patients with breast cancer and ipsilateral lymphoedema is associated with cellulitis, (p<0.001). Therefore lymphoedema seemed to be an important risk factor for the development of cellulitis as was reported by Dupuy *et al.* (1999) as well as Mokni *et al.*[8,9] (2006). This increased risk may be explained by the fact that the lymphoedema distorts the anatomy of the previously damaged tissues and prevents proper vascular supply that ultimately leads to decreased resistance to infection. It may also be that the pooling of static fluid in the tissues favors colonization by infectious organisms. Patients with renal failure, cirrhosis of the liver and congestive cardiac failure did not seem to have an increased risk of cellulitis. They all gave non-significant p-values on bivariate analysis.

The multivariable logistic regression analysis showed that male gender, Singaporean Indian ethnicity, diabetes mellitus and skin disruption retained their strong association with cellulitis. The majority of cellulitis (67.3%) occurred in the legs, replicating the results (66%) of Lazarrini *et al.*[5]. This might explain why some authors focused their work on the lower limbs[11,17,18]. The exact reason for the predilection for the lower limbs is not known though a possible explanation

might be infections following monilial colonization of webs of toes. In over 60% of cases, there was an initial progression of cellulitis before the disease responded to antibiotics and leaving minimal sequelae. Patients who responded promptly accounted for only 7.5% of the cases. Bacteraemia warranted prolonged use of intravenous antibiotics whereas chronic renal failure and DM are known to cause delayed healing. In the study by Cox *et al.* 47% of patients had recurrent cellulitis compared to 31.3% in this present study[7]. The same limb was affected in 28% of cases but McNamara *et al.* found 16.5 %[11]. An attack of cellulitis seems to be a risk factor for a subsequent attack of cellulitis in the same limb.

Complications of cellulitis included abscess formation, necrotising fasciitis, gangrene and septicaemia. Those needed some form of surgery either minor or major accounted for 29.3%. Twenty percent needed incision and drainage because of abscess formation and another 4% developed necrotising fasciitis needing fasciotomy and extensive debridement. Over 7% developed septicaemia and over 5% needed a disarticulation of a toe, metatarsal or needed an amputation of the lower limb. There were 3 (or 2%) deaths among patients implying that cellulitis was not as innocuous as previously thought.

In the series by Carratala *et al.*, 57.8% of patients required surgery whereas in our series it was 30%[16]. Their rate of complications including deaths was 31%. Rolston in 1986 proposed a multi-disciplinary team to look after these patients but unfortunately this concept did not gain widespread popularity probably due to logistic reasons[18]. Theoretically, such a proposal would ensure more efficient and faster management, leading to a decrease in hospital stay and thereby cutting costs related to admission.

The presence of bacteraemia was 15.3% in cases compared to 2% in the study of Lazzarini *et al.*[15]. Organisms cultured from the wounds were predominantly *staphylococcus* sp. and *streptococcus* sp. as found by Musettel *et al.*[12]. The contribution from resistant organisms such as *MRSA, P. aeroginosa, A. baumanii* and *Klebsiella* sp was 3.5%. Though colonization of the skin with *MRSA* need not be treated, bacteraemia should be treated aggressively with potent antibiotics. The recent vancomycin resistant *Enterococci* outbreak in the hospital is a cause for concern because exchange of genomic material between *Enterococci* and *MRSA* may result in *MRSA* resistant to vancomycin[19].

Physicians chose antibiotics according to the clinical setting and the probable organisms involved, resulting in 36 different types of antibiotics, either singly or in combination, being used. Therefore guidelines should be updated to ensure optimum antibiotic utilization. The average length of stay (LOS) for cases above 74 years of age was 11.65 days, and for those below 75 it was 9.85 days, whereas Dupuy *et al.* found a mean LOS of 8.7 days[16]. LOS increased with increasing age, hypoalbuminaemia, diabetes mellitus and skin rupture individually or in combination, recurrent cellulitis and bacteraemia.

The limitations to this study were that patients were a special cohort, physicians had the liberty to prescribe any antibiotic, and different groups of physicians, surgeons and orthopaedic surgeons were involved and their approach would probably have been different. Investigator's bias has been reduced to a minimum by using two trained investigators and using pre-tested questionnaire. Recall bias was unavoidable as some details needed might not have been documented properly in the files of patients. Since this was an unmatched case control study the problem of confounding could have arisen. However, care was taken to include more cases and control than the required sample size, and statistical analysis that included logistic regression analysis would have controlled some of the confounders. Our study did not take into account factors such as profession, socio-economic status, education and marital status. The clinical information did not give enough details regarding the degree of hypoalbuminaemia and its causes, and the severity of angina pectoris and the probable associated congestive cardiac failure. Research that includes measurement and assessment of these factors should be conducted. The reason

why Singaporean Indians are more likely to develop cellulitis than the other ethnic groups should also be further explored as should ethnic associations with cellulitis in general. The validity of the data is rather strong, our data and conclusions can be generalized for other big hospitals in Singapore but not for small institutions or the public in general.

**CONCLUSION AND RECOMMENDATION:** The risk factors for cellulitis were: increasing age, male gender, Singaporean Indian ethnicity, diabetes mellitus, skin disruption, breast cancer, renal impairment and previous episode of cellulitis. Complications led to increased morbidity, length of stay and hospital costs. A multi-disciplinary team should preferably manage these patients. A guideline on the use of antibiotics in cellulitis may be needed. The National Health Education Program should include foot-care and care of simple wounds with special emphasis for diabetics.

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