MAJOR ARTICLE

Risk Factors for Acute Cellulitis of the Lower Limb: A Prospective Case-Control Study

Sigrídur Björnsdóttir,[1] Magnús Gottfredsson,[1,3] Anna S. Thórisdóttir,[1] Gunnar B. Gunnarsson,[1] Hugrún Ríkardsdóttir,[1] Már Kristjánsson,[1] and Ingibjörg Hilmarsdóttir[2]

[1]Department of Medicine, Division of Infectious Diseases, and [2]Department of Microbiology, Landspítali University Hospital, and [3]University of Iceland School of Medicine, Reykjavik, Iceland

Background. Acute bacterial cellulitis is a potentially serious infection that commonly recurs. The identification of preventable risk factors could reduce infection-related morbidity and cost and improve patient management. The aim of this study was to identify the risk factors associated with lower-limb cellulitis, including both analysis of risk factors associated with cellulitis in either limb and risk factors in a single limb associated with cellulitis in the same limb. We placed particular emphasis on dermatophytic infections of the foot and bacterial infection and colonization of the toe webs.

Methods. We conducted a prospective case-control study of 100 subjects with cellulitis and 200 control subjects, matched for age and sex, who were admitted to a university hospital during the period October 2000–February 2004. Data were obtained with a questionnaire and from examination of lower limbs and microbiological analyses of samples from the feet.

Results. The median age of the participants was 66.5 years (interquartile range, 48.8–77.0). The following risk factors were strongly and independently associated with cellulitis: previous history of cellulitis (OR, 31.04; 95% CI, 4.15–232.20), the presence of *Staphylococcus aureus* and/or β-hemolytic streptococci in the toe webs (OR, 28.97; 95% CI, 5.47–153.48), presence of leg erosions or ulcers (OR, 11.80; 95% CI, 2.47–56.33), and prior saphenectomy (OR, 8.49; 95% CI, 1.62–44.52). Tinea pedis interdigitalis was associated with cellulitis only when toe web bacteria were excluded from the analysis (OR, 3.86; 95% CI, 1.32–11.27).

Conclusions. Risk factors for acute bacterial cellulitis in hospitalized patients include predisposing factors and the presence of sites of pathogen entry on legs and toe webs. These findings indicate that improved awareness and management of toe web intertrigo, which may harbor bacterial pathogens, and other skin lesions might reduce the incidence of cellulitis.

Cellulitis is an inflammatory condition of the skin and subcutaneous tissue, characterized by erythema, swelling, warmth, and pain. The etiologic agents are most often *Streptococcus pyogenes* and *Staphylococcus aureus,* followed by non–group A β-hemolytic streptococci and gram-negative bacilli [1, 2]. Cellulitis is a common medical emergency, the severity of which varies from mild to life threatening. The infection can occur on any body site; lower limbs are affected in ⩽70% of cases [1]. Risk factors for cellulitis of the lower limbs include the presence of sites of entry for the etiologic agent and predisposing factors, such as being overweight and having lymphedema [3, 4]. Sites of entry are commonly created by traumatic injury, leg ulcers, and, possibly, dermatophytic toe web intertrigo [3–5]. Two recent case-control studies addressing risk factors for cellulitis demonstrated a significantly higher rate of toe web intertrigo in the patient group [3, 4]. Although dermatophytes do not cause cellulitis, they lead to scaling and fissure formation and, by disruption of the skin, provide a niche for bacteria that could enter the body. Two reports have confirmed the presence of pathogenic bacteria, such as β-hemolytic streptococci and *S. aureus,* in abnormal toe webs of cellulitis patients [5, 6].

Cellulitis often requires hospitalization, especially for elderly patients, who frequently have comorbid conditions. The morbidity related to immediate complications and frequent recurrences and the cost of management warrant efforts to better understand the risk factors. We present data from a prospective case-control

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Reprints or correspondence: Dr. Ingibjörg Hilmarsdóttir, Dept. of Microbiology, Barónsstígur, Landspítali University Hospital, 101 Reykjavik, Iceland (ingibjh@landspitali.is).

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study on the risk factors for cellulitis in either lower limb and risk factors in a single limb associated with cellulitis in the same limb (hereafter, referred to as "general and ipsilateral risk factors"). This is, to our knowledge, the first study to include bacteriological and mycological examinations of the feet of case patients and control patients alike.

PATIENTS, MATERIALS, AND METHODS

Study design and population. The study was conducted at Landspítali University Hospital in Reykjavík, Iceland, from October 2000 to February 2004. The study population consisted of patients aged ⩾18 years who were hospitalized because of acute cellulitis on a lower limb. For each patient, 2 hospitalized control patients were recruited and matched for age (range, ±5 years) and sex. Case patients were identified on admission by physicians on call and enrolled by the investigators. Information from the hospital admission register was used to assess the number of eligible case patients who, for some reason, were not enrolled in the study, and the relevant patient files were examined. The study was approved by the hospital's ethics committee. All participants signed an informed consent statement.

Case and control definitions. Inclusion criteria for case patients were as follows: (1) presence of lower-limb cellulitis, defined as a demarcated cutaneous inflammation of sudden onset (over <72 h) that was associated with fever, chills or leukocytosis (leukocyte count, $>10.5 \times 10^9$ cells/L); and (2) absence of abscess formation or necrotizing fasciitis. The inclusion criterion for control patients was hospital admission for an acute or chronic disease, with the exception of cellulitis, within 72 h of their enrollment. Exclusion criteria for both groups were as follows: (1) the use of systemic antifungal treatment within the 4 weeks preceding hospital admission or use of topical antifungal treatment within 1 week, and (2) hospitalization within the 4 weeks preceding the present admission.

Data collection and microbiological analyses. The investigators completed a questionnaire for each patient, examined both lower extremities, and obtained samples from the affected limb. "Overweight" was defined as a body mass index of ⩾25 but <30, and "obese" was defined as a body mass index of ⩾30 [7]. Diabetes mellitus was recorded for patients with laboratory-confirmed disease. Alcohol misuse was considered present if consumption exceeded 14 units of alcohol per week for men and 7 for women [8] (there are 12 g of pure alcohol per unit). Any quantity or type of current smoking was recorded. "Swimming" was defined as regular leisure swimming in a pool. Presence of dry skin was recorded if skin on the legs showed fine scaling or lack of suppleness. Skin and toenail samples for microbiological analyses were obtained from the foot affected by cellulitis, for case patients, and from the corresponding (ipsilateral) foot, for control patients; samples from the contralateral foot were not obtained from either group. A swab specimen for bacterial culture was obtained from the most abnormal toe web or, if all toe webs appeared normal, from the fourth one. Skin and toenail scrapings for mycological examination were taken from the sole of the foot and from abnormal toe webs and toenails, or, if all sites seemed normal, from the fourth toe web and the nail of the big toe. Blood cultures were performed if it was deemed clinically indicated by the physician on call.

For bacterial culture, swabs were inoculated on 1 MacConkey agar plate and 3 horse-blood agar plates (with and without nalidixic acid and colistin sulphate); 1 plate was incubated in aerobic conditions, 1 plate was incubated in 5% CO_2, and 1 plate was incubated in an anaerobic jar. A tube coagulase test (BBL, Becton Dickinson) and a latex agglutination test (Streptex, Remel) were used to identify *S. aureus* and large-colony-forming β-hemolytic streptococci. Lancefield group C and group G β-hemolytic streptococci were further identified by the API 20 Strep system (bioMérieux); species belonging to the *Streptococcus anginosus* group were not included in the term "β-hemolytic streptococci," used hereafter in this article. Skin and nail scrapings were treated with 10% KOH and chlorazol black E for microscopy; hyaline hyphae and arthrospores seen on microscopy were considered to represent dermatophytes. Samples were plated on Sabouraud dextrose agar with chloramphenicol and mycobiotic agar and incubated at 30°C for 3 weeks. Identification of dermatophytes was based on macroscopic and microscopic characteristics and, if necessary, urease test results. The laboratory personnel were blinded to the status of case and control patients. Blood cultures were performed using the ESP culture system II (Difco Laboratories).

Statistical analysis. Power calculations using 2 control patients for each case indicated a need for 90–110 case patients to reach a power of 0.80 at 2-sided significance level of .05, to detect an OR of 2.50 for a factor with a known prevalence of 10%–15% in the local population (onychomycosis). Groups were compared using χ^2 tests for categorical variables, with Yates' correction where appropriate, and the Mann-Whitney *U* test was used for continuous variables. We used logistic regression, conditional on the matching of case patient to control patients, to calculate the OR for each risk factor. Multivariable analysis was performed with conditional logistic regression on 2 combinations of selected risk factors that appeared associated with cellulitis in the univariate analysis (OR, >2.50). In the first combination (model 1), swimming, toe web intertrigo, toenail dystrophy, and detection of dermatophytes at any site were excluded. The second combination (model 2) varied from the first in that detection of *S. aureus* and/or β-hemolytic streptococci in culture was also excluded. Finally, we performed a stepwise conditional logistic regression with forward selection including all the variables that were examined in the univariate

analysis. To compare risk factors on ipsilateral and contralateral limbs for each case patient, we used the κ statistic, which is a measure of agreement giving values between 0 and 1. A high number indicates good agreement (i.e., the risk factor is present on both limbs), whereas a low number indicates poor agreement (i.e., the risk factor is mostly present on the diseased limb). We classified the κ values for agreement between limbs as follows: <0.2, poor; 0.21–0.4, fair; 0.41–0.6, moderate; 0.61–0.8, good; and 0.81–1, very good [9]. For the data analysis we used SPSS software, version 10.5 (SPSS) and SAS software, version 6.12 (SAS).

RESULTS

One hundred cellulitis case patients—29 female and 71 male—and 200 matched control patients were included in the study; demographic and clinical characteristics are summarized in table 1. Admission diagnoses of control patients were cardiovascular disease in 101 patients, gastrointestinal disease in 20, pulmonary disease in 14, and miscellaneous medical conditions in 65. A total of 132 eligible case patients were identified. However, only 100 were recruited, mainly because of failure to notify the investigators. No significant differences were noted between those who participated in the study and those who did not with regard to age, sex distribution, length of hospitalization, or antibiotic use before hospital admission. However, participants had a lower incidence of recent trauma (23% vs. 44%; $P < .05$).

Table 2 shows univariate analysis of general and ipsilateral risk factors. Obesity was significantly more frequent in the case patient group, but being overweight was not. Alcohol consumption exceeding the definitions for safe levels was reported for only 8 case patients and 7 control patients, and was therefore not analyzed further. Several factors appeared to be strongly associated with cellulitis; the most prominent ones were previous history of cellulitis, leg ulcer, or saphenectomy; and the presence of possible sites of entry, such as dry skin, leg lesions, and toe web intertrigo. Further analysis of toe web intertrigo as a risk factor revealed that case patients were more likely than control patients to have fissures (OR, 3.44; 95% CI, 2.03–5.85), maceration (OR, 2.94; 95% CI, 1.67–5.16), and scaling (OR, 2.07; 95% CI, 1.24–3.47)on the ipsilateral foot or contralateral foot.

Table 1. Demographic and clinical characteristics of case and control patients enrolled in a study of lower-limb cellulitis at Landspítali University Hospital in Reykjavík, Iceland during the period October 2000–February 2004.

Characteristics	Case patients (n = 100)	Control patients (n = 200)
Age, median years (IQR)	66.5 (48.8–77.0)	66.5 (50–75)
BMI, median (IQR)	27.7 (25.1–32.8)[a]	25.8 (23.3–28.7)[a]
Concomitant diseases, no. (%) of patients		
Cardiovascular	55 (55)	136 (68)
Endocrine or metabolic	18 (18)	48 (24)
Gastrointestinal	7 (7)	34 (17)
Neurological	8 (8)	11 (5.5)
Rheumatic or orthopedic	19 (19)	38 (19)
Psychiatric	12 (12)	17 (8.5)
Pulmonary	7 (7)	19 (9.5)
Urinary	10 (10)	25 (12.5)
Other	1 (1)	7 (3.5)

NOTE. BMI, body mass index; IQR, interquartile range.

[a] $P < .001$

Dermatophyte infection (diagnosed using microscopy or culture) was more frequent among case patients than among control patients (table 3). Dematophytes were detected in culture of toenail specimens from 34 case and 34 control patients ($P = .001$), in culture of toe web specimens from 32 case and 28 control patients ($P < .001$), and in culture of sole specimens of 11 case and 12 control patients ($P = .13$). Of the 94 patients with cultures positive for dermatophytes (47 case patients and 47 control patients), 77 had *Trichophyton rubrum* isolated, 18 had *T. mentagrophytes* isolated, and 4 had *Epidermophyton floccosum* isolated; 5 patients had 2 species isolated. Bacteriological cultures of toe web specimens yielded known cellulitis pathogens (*S. aureus* and/or β-hemolytic streptococci) and gram-negative bacilli more frequently for case patients than for control patients (table 3).

An analysis of the case patient group with regard to the association of toe web intertrigo with the presence of bacteria in the toe web revealed that toe web intertrigo was associated with presence of *S. aureus* and/or β-hemolytic streptococci in 45 (58.4%) of 77 case patients, whereas only 3 (13.0%) of 23 case patients with healthy-looking interdigital spaces had bacteria in the toe web ($P < .001$). Furthermore, 34 (69%) of 49 patients with fissured toe webs and 28 (63%) of 44 patients with macerated toe webs had these bacteria, compared with 14 (27%) of 51 patients ($P < .001$) and 20 (36%) of 56 patients ($P = .006$) who did not have the toe web changes. Likewise, fungally infected toe webs of case patients harbored *S. aureus* and/or β-hemolytic streptococci in 27 (64.3%) of 42 patients, compared with 21 (36.2%) of 58 patients whose toe webs were not infected ($P = .005$).

Blood cultures were performed for 81 cellulitis cases; group A β-hemolytic streptococci were isolated in 4, group B and G streptococci in 1 and 3 cases, respectively, and gram-negative rods in 4 cases (*Hemophilus influenzae, Neisseria* species other than *N. meningitidis* or *N. gonorrhoeae, Escherichia coli,* and *Comomonas* species). In 2 cases, the same pathogen—group A and G β-hemolytic streptococci—was also isolated from the toe web. No other sites of entry were found on the limbs of these 2 patients.

Table 2. Univariate analysis of general and ipsilateral risk factors for cellulitis of the lower limb in hospitalized patients.

Risk factor	No. (%) of case patients (n = 100)	No. (%) of control patients (n = 200)	OR (95% CI)
Body mass index			
>25 and <30	37 (37)	86 (43)	1.38 (0.75–2.54)
⩾30	39 (39)	36 (18)	3.55 (1.88–6.70)
Swimming	54 (54)	62 (31)	2.65 (1.59–4.42)
Skin disease	26 (26)	28 (14)	2.16 (1.18–3.97)
Diabetes mellitus	11 (11)	23 (11.5)	0.95 (0.46–2.00)
Smoking	16 (16)	49 (24.5)	0.60 (0.32–1.10)
Patient history			
Chronic leg edema	56 (56)	66 (33)	2.65 (1.59–4.42)
Leg ulcer	17 (17)	7 (3.5)	5.44 (2.14–1.84)
Saphenectomy	21 (21)	4 (2)	10.50 (3.60–30.59)
Leg surgery[a]	25 (25)	35 (17.5)	1.60 (0.88–2.90)
Pedicure[b]	12 (12)	23 (11.5)	1.05 (0.49–2.27)
Cellulitis	35 (35)	3 (1.5)	23.33 (7.18–75.87)
Disorders at admission			
Varicose veins	20 (20)	39 (19.5)	1.04 (0.55–1.95)
Dry skin	33 (33)	26 (13)	4.00 (2.03–7.90)
Stasis dermatitis	14 (14)	16 (8)	1.83 (0.86–3.88)
Leg lesions[c]	40 (40)	21 (10.5)	7.02 (3.37–14.63)
Toe web intertrigo[d]	77 (77)	95 (47.5)	5.35 (2.73–10.48)
Toenail dystrophy	85 (85)	135 (67.5)	3.21 (1.60–6.42)
Sole abnormalities[d]	56 (56)	106 (53)	1.15 (0.68–1.94)

[a] Leg surgery other than saphenectomy.
[b] During the 4 weeks before hospital admission.
[c] Leg lesions include erosions, ulcers, and wounds on the legs and the dorsum of the foot.
[d] Toe web intertrigo and sole abnormalities include scaling, maceration, fissures, erythema, pruitus, and vesicles.

A multivariate analysis of model 1 showed that history of cellulitis, history of saphenectomy, the presence of *S. aureus* and/or β-hemolytic streptococci in toe webs, and presence of leg lesions were strongly and independently associated with cellulitis (table 4). When presence of these pathogens was excluded from the analysis (model 2), toe web dermatophytosis showed a significant association with cellulitis. A multivariate analysis with forward selection of the variables presented in table 2 revealed the same risk factors as model 1; however, the ORs were somewhat higher. The presence of *S. aureus* and/or β-hemolytic streptococci in toe webs showed by far the strongest association with cellulitis (OR, 69.6; 95% CI, 9.61–504.86), followed by prior cellulitis (OR, 21.8; 95% CI, 4.36–108.93), leg lesions (OR, 21.2; 95% CI, 5.27–85.53), and history of saphenectomy (OR, 12.2; 95% CI, 2.44–60.93).

To further investigate whether recurrent cellulitis is induced by persistent risk factors or cellulitis per se, we compared the 35 case patients who reported a history of ipsilateral cellulitis with the remaining 65 case patients. No significant differences were detected among ipsilateral factors, with the exception of prior leg surgery (other than saphenectomy), which was reported by 15 (43%) of the 35 case patients with a history of cellulitis, compared with 10 (15%) of the other 65 patients (P = .003); the difference remained significant after correction for age. When these groups were compared with their corresponding control patients, the majority of general and ipsilateral risk factors that were associated with cellulitis (OR, >2.50) in the undivided patient group remained so. Persistent risk factors could thus explain repeated attacks of cellulitis; however, it is also possible that prior cellulitis could predispose patients to subsequent episodes. The comparison of data for case patients' ipsilateral and contralateral limbs (table 5) revealed that previous cellulitis had occurred more often on the ipsilateral limb—the κ value showed "poor" agreement between the limbs—which indicated that the infection may predispose the patient to future episodes of infection on the affected limb.

DISCUSSION

Our findings indicate that previous history of cellulitis and a history of saphenectomy are major predisposing factors for cellulitis and that leg lesions or toe webs that are colonized by

Table 3. Dermatophytes and bacteria isolated from the limb affected by cellulitis in case patients, and from the corresponding limb in control patients.

Microorganism and body site	No. (%) of case patients (n = 100)	No. (%) of control patients (n = 200)	OR (95% CI)
Dermatophytes[a]			
On foot	58 (58)	67 (33.5)	2.96 (1.72–5.06)
In toenails	47 (47)	52 (26)	2.62 (1.54–4.47)
In toe webs	42 (42)	39 (19.5)	3.72 (1.98–6.99)
On sole of the foot	17 (17)	28 (14)	1.27 (0.65–2.49)
S. aureus and/or BHS in toe webs[b]			
Any	48 (48)	11 (5.5)	28.07 (8.71–90.24)
Group A BHS	4	1	…
Group B BHS	2	1	…
Group C BHS	3	0	…
Group G BHS	28	2	…
S. aureus	30	8	…
Gram-negative bacilli in toe webs	21 (21)	23 (11.5)	2.07 (1.07–3.99)

NOTE. BHS, β-hemolytic streptococci; *S. aureus, Staphylococcus aureus.*

[a] Seen on microscopic examination of a sample from any site or isolated in culture.

[b] Nineteen case patients and 1 control patient had >1 species isolated.

or infected with potential bacterial pathogens are significant sites of entry for the causative organisms. Toe web dermatophytosis only appeared as a risk factor when presence of bacterial pathogens in toe webs was excluded from the analysis, which indicates that the colonization of toe webs by bacterial pathogens is more strongly associated with cellulitis than is fungal infection.

Recent case-control studies of the risk factors for lower limb cellulitis reported that being overweight, history of cellulitis, chronic leg edema, disruption of the cutaneous barrier, and toe web dermatophytosis were independent risk factors. [3, 4] These studies did not include bacterial analysis of toe web samples or distinguish saphenectomy from other types of leg surgery. A few case series have suggested that saphenectomy might predispose a patient to cellulitis [6, 10]. This observation has now been confirmed by our study.

Patients who are affected by cellulitis of the lower limbs constitute a heterogeneous group, with regard to risk factors. The young, healthy individual who develops cellulitis after trauma differs from the middle-aged patient whose comorbid conditions may predispose him or her to recurrent attacks, with or without an apparent site of pathogen entry. Predisposing factors do not, per se, cause bacterial cellulitis. The infection originates from the entry of pathogens through a disruption of the cutaneous barrier that may or may not be identified on physical examination.

The role of various predisposing factors, such as previous cellulitis, leg edema, and saphenectomy, in the pathogenesis of cellulitis, has not yet been elucidated. Although these factors do not cause infection, they probably facilitate its development by impairing local defense mechanisms. The prevalence of predisposing factors may vary between patient populations, and this could, in part, explain discordant findings among case-control studies. Disruption of the cutaneous barrier appears to be a consistent risk factor across studies. Lesions involving a break in the skin on the leg and dorsum of the foot were significantly associated with cellulitis in our study. Because the lesions were not systematically sampled, it is not possible to estimate their bacterial carriage rate and relative role in infection.

This is, to our knowledge, the first study of risk factors for cellulitis of the lower limbs that includes both bacteriological and mycological examination of the foot in case and control patients. The results demonstrated a remarkably high prevalence of β-hemolytic streptococci and *S. aureus* in the toe webs of patients with cellulitis. Tinea pedis has long been thought to provide the site of entry for pathogens that cause cellulitis and, in 2 cases, the cessation of recurrent cellulitis after treatment of tinea pedis has been reported [10]. Other studies have documented the presence of β-hemolytic streptococci and *S. aureus* on abnormal toe webs of cellulitis patients [5, 6]. Semel et al. [5] isolated *S. aureus* and β-hemolytic streptococci from the toe webs of 20 (83%) of 24 cellulitis case patients, compared with 7 (23%) of 30 control patients. Clinical signs of tinea pedis

Table 4. Multivariate analysis of general and ipsilateral risk factors for cellulitis of the lower limb among hospitalized patients.

Risk factor	OR (95% CI)	
	Model 1	Model 2
Body mass index ⩾30	1.98 (0.44–8.79)	2.96 (0.94–9.26)
Patient history		
Chronic leg edema	1.51 (0.53–4.28)	1.58 (0.65–3.83)
Leg ulcer	0.44 (0.06–3.11)	0.80 (0.16–3.94)
Saphenectomy	8.49 (1.62–44.52)	10.56 (1.77–62.86)
Cellulitis	31.04 (4.15–232.20)	33.08 (6.43–170.27)
Disorders at admission		
Dry skin	3.52 (0.82–15.10)	2.66 (0.82–8.65)
Leg lesions[a]	11.80 (2.47–56.33)	7.70 (2.36–25.10)
Dermatophytes in toenails[b]	0.69 (0.18–2.63)	1.42 (0.48–4.22)
Dermatophytes in toe webs[b]	1.49 (0.39–5.69)	3.86 (1.32–11.27)
S. aureus and/or BHS in toe webs	28.97 (5.47–153.48)	Not included

NOTE. Model 1 is a combination of selected risk factors that appeared associated with cellulitis in the univariate analysis (OR, >2.50); swimming, toe web intertrigo, toenail dystrophy, and detection of dermatophytes at any site were excluded. In model 2, cultures revealing *S. aureus* and/or β-hemolytic streptococci were excluded in addition to the exclusions made in model 1. BHS, β-hemolytic streptococci; *S. aureus, Staphylococcus aureus.*

[a] Leg lesions include erosions, ulcers, and wounds on the legs and the dorsum of the foot.

[b] Dermatophytes were demonstrated by microscopy of the patient specimen or isolated in culture.

Table 5. Comparison of case patients' ipsilateral and contralateral limbs with regard to risk factors associated with cellulitis, determined with the κ measure of agreement.

Risk factor	No. of case patients with or without risk factor(s) on lower limb(s), by site				
	Neither limb	Ipsilateral limb	Contralateral limb	Both limbs	κ
Patient history					
Cellulitis	59	32	6	3	0.00
Chronic leg edema	44	12	0	44	0.76
Leg ulcer	81	12	2	5	0.35
Leg surgery[a]	71	15	4	10	0.41
Saphenectomy	78	14	1	7	0.42
Disorders at admission					
Varicose veins	76	8	4	12	0.60
Stasis dermatitis	84	6	2	8	0.62
Dry skin	67	7	0	26	0.83
Leg lesions[b]	57	20	3	20	0.48
Toe web intertrigo[c]	19	27	4	50	0.35
Toenail dystrophy	13	12	2	73	0.57
Sole abnormalities[c]	44	12	0	44	0.76

[a] Leg surgery other than saphenectomy.
[b] Leg lesions include erosions, ulcers, and wounds on the legs and the dorsum of the foot.
[c] Toe web intertrigo and sole abnormalities include scaling, maceration, fissures, erythema, pruritus, and vesicles.

were present in the majority of case patients, but no mycological tests were done; fungal infection was confirmed in 17 (57%) of 30 control patients by microscopy of KOH-prepared skin samples [5]. Studies of the microbial flora of toe webs have, indeed, confirmed that there are qualitative and quantitative changes in the bacterial flora of fungally infected toe webs. Leyden and Kligman [11] demonstrated an expansion of the aerobic microflora and an increased recovery of *S. aureus* and gram-negative bacilli from patients with interdigital athlete's foot, compared with individuals with normal interdigital spaces. They concluded that maceration of an uncomplicated and often subclinical fungal infection leads to overgrowth of the interdigital bacterial flora and to the development of a complex and symptomatic disease [11, 12]. Likewise, our study showed that both maceration and fungal infection were associated with the isolation of *S. aureus* and β-hemolytic streptococci from case patients' toe webs. These bacteria are all recognized etiologic agents of cellulitis [1, 2, 13–16]. Thus, fungal infection might cause optimal conditions for bacterial overgrowth and facilitate bacterial entry through skin breaks. The strong association between the presence of bacteria in the toe webs and cellulitis suggests that toe web intertrigo deserves attention and should be identified and treated in select patient populations. This was further supported by the κ measure of agreement (table 5), which indicates that, among case patients, toe web intertrigo was more common on the leg affected by cellulitis than on the healthy leg (the κ value indicated there was less than "moderate" agreement between the limbs).

There are a few limitations to our study that deserve mention. First, this study included hospitalized patients only. Although there is no reason to believe that the pathophysiology of cellulitis differs between patients who are hospitalized and those who are not, the association of the various risk factors with the disease may be different. Further studies are needed to elucidate this point. Second, because of the study design, we were unable to establish with certainty whether the bacterial pathogens on case patients' toe webs were the cause or the result of the cellulitis. However, in light of the difficulties in isolating the causative organisms of bacterial cellulitis, and the fact that the infected area is not always contiguous with the toe web, it is unlikely that the presence of pathogens in the toe webs had resulted from the spread of the infection. Finally, although conditional logistic regression was the method of choice for our analysis, it carries the same limitations as other regression analyses, including unknown confounding variables and colinearity of the variables we used. However, the results were consistent across all models and therefore we believe that the findings are valid.

In conclusion, in evaluating the role of toe web intertrigo as a possible site of entry for organisms that cause cellulitis, we found the presence of bacterial pathogens in the toe web to be the strongest microbiological risk factor for lower limb cellulitis.

The potential severity of infection and the frequency of recurrence call for preventive measures on the part of the physician. Predisposing factors are usually difficult to modify, whereas the sites of entry can be controlled. Therefore, in the management of patients with predisposing factors for cellulitis, particular attention should be paid to skin lesions on the legs and to toe web intertrigo. Although uncomplicated tinea pedis may be successfully treated with antifungal drugs, antibacterial agents are needed in the presence of a secondary bacterial infection of the toe web. The pharmacological management of patients who have coexistent onychomycosis, recurrent tinea pedis or bacterial colonization of toe web intertrigo, as opposed to overt infection, may be more challenging. In these instances, improved foot hygiene, notably the prevention of toe web maceration, should be encouraged to reduce the carriage of pathogenic bacteria.

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