RESEARCH

DIFFERENCES IN CLINICAL FEATURES, ETIOLOGY, TYPES, AND RISK FACTORS FOR COMPLICATIONS BETWEEN YOUNG AND OLDER PATIENTS WITH SKIN AND SOFT TISSUE INFECTIONS

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Abstract

Introduction: This study investigated differences in clinical features, types, etiology, and risk factors for complications between young and older patients with skin and soft tissue infections. Futhermore, age-related differences in healthcare-associated and complicated infections were identified.

Materials and Method: This retrospective study included 206 skin and soft tissue infection patients hospitalized during an 8-year period. Data were collected using a form: patients' characteristics, clinical features, laboratory values, prior antibiotic use, causative microorganisms, and antibiotic treatment. For cases with clinically diagnosed, samples were taken from the suspected infection sites. Gram staining, deep swab, deep tissue and blood culture results were evaluated.

Results: The incidence of diabetes mellitus was significantly higher among patients aged ≥65 years. Among these old patients, Escherichia coli (11/31, 35.5%) and Pseudomonas aeruginosa (8/31, 25.8%) were the most frequently isolated pathogens. Approximately half of the Staphylococcus aureus and Staphylococcus epidermidis strains isolated from patients with health care-associated infection were resistant to methicillin (8/15, 53.3%), and these patients produced higher levels of extended-spectrum beta-lactamase. Venous insufficiency (p=0.008) and prior hospitalization (p=0.001) were identified as risk factors for complication in patients aged ≥65. The median time- to -clinical response was 7 days in older patients with non-complicated infection (p=0.007).

Conclusion: Diabetes mellitus was the most common co-morbid factor in older patients. Risk factors for complication may differ by age. Gram-negative pathogens were more commonly isolated in older patients. The time- to -clinical response was significantly longer in older patients with non-complicated infection than young patients.

Keywords: Cellulitis; Diabetic foot; Aged; Cross Infection; Risk factors

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ARAŞTIRMA

DERİ VE YUMUŞAK DOKU ENFEKSİYONLU GENÇ VE YAŞLI HASTALAR ARASINDA KLİNİK ÖZELLİKLER, TİP, ETİYOLOİ VE KOMPLİKE EDİCİ RİSK FAKTÖRLERİ AÇISINDAN FARKLILIKLAR

Öz

Giriş: Bu çalışmada, deri ve yumuşak doku enfeksiyonu tanısı alan genç ve yaşlı hastalar arasında klinik özellikler, tip, etiyoloji ve komplike edici risk faktörleri açısından farklılıklar araştırıldı. Ayrıca sağlık bakımı ilişkili ve komplike deri ve yumuşak doku enfeksiyonlu hastalarda yaşla ilişkili farklılıklar belirlendi.

Gereç ve Yöntem: Bu retrospektif çalışmaya sekiz yıllık süre içinde deri ve yumuşak doku enfeksiyonu tanısı alıp yatırılan 206 hasta alındı. Hastaların karakteristik ve klinik özelliklerini, laboratuvar değerlerini, öncesinde antibiyotik kullanımlarını, izole edilen etken mikroorganizmaları ve antibiyotik tedavilerini içeren veriler bir forma kaydedildi. Klinik olarak deri ve yumuşak doku enfeksiyonu tanısı koyulanların şüpheli enfeksiyon bölgelerinden örnekler alındı. Gram boyama, derin sürüntü, doku ve kan kültürleri değerlendirildi.

Bulgular: Diabetes mellitus, 65 yaş ve üzerindeki hastalarda yüksekti. Bu yaşlı hastalar arasında Escherichia coli (11/31, %35,5) ve Pseudomonas aeruginosa (8/31, %25,8), en sık izole edilen patojenlerdi. Sağlık bakımı ilişkili hastalardan izole edilen Staphylococcus aureus ve Staphylococcus epidermidis suşlarının yaklaşık yarısı (8/15, %53,3) metisiline dirençliydi ve bu hastalarda genişlemiş spektrumlu beta laktamaz üretimi de yüksekti. Venöz yetmezlik (p=0.008) ve önceden hastanede yatış (p=0.001), 65 yaş ve üzerindeki hastalarda komplike edici risk faktörleri olarak belirlendi. Ortalama klinik yanıt alma zamanı, komplike olmayan yaşlı hastalarda ortalama 7 gündü (p=0.007).

Sonuç: Diabetes mellitus, yaşlı hastalar arasında en yaygın komorbid faktördü. Komplike edici risk faktörlerinin yaşla ilişkili değişebildiği gözlendi. Yaşlı, deri ve yumuşak doku enfeksiyonlu hastalardan en sık izole edilen etkenler Gram-negatif patojenlerdi. Ortalama klinik yanıt alma zamanı, komplike olmayan yaşlı hastalarda gençlere göre anlamlı olarak yüksekti.

Anahtar sözcükler: Selülit; Diyabetik ayak; Yaşlı hastalar; Çapraz enfeksiyon; Risk faktörleri

INTRODUCTION

Skin and soft tissue infections (SSTIs) are among the most common infections, and are characterized by induration, erythema, warmth, and pain. These infections range from mild and self-limiting to life-threatening necrotizing fasciitis. These cases may be complicated by deep soft tissue involvement; severe conditions such as ulcers, burns, or major abscesses requiring significant surgical intervention; and co-morbid host factors such as diabetes mellitus (DM), obesity, and immunodeficiency (1). Elderly patients exhibit changes in skin consistency and are more likely to have underlying skin disorders and co-morbid factors, and are therefore have a high risk of SSTIs. Healthcare-associated (HCA) SSTIs such as pressure ulcers and surgical site infections are more common in elderly populations (2). Although community-acquired (CA) SSTIs are generally diagnosed and treated easily, complicated SSTIs (CSSTIs) can cause serious morbidity and even mortality, especially in the elderly and immunosuppressed patients. This study investigated differences in clinical features, types of SSTIs, isolated the causative microorganisms, and complicated risk factors between young and older patients. Currently, the microbial spectra of SSTIs in older patients and those with HCA infections are largely unknown. Although short-duration treatment regimens are generally suggested for CA-SSTIs, to our knowledge, no study has clearly investigated the time-to-clinical response to the antibiotic therapy in the older patients with complicated SSTI and in those with HCA-SSTI. In this study, we also investigated the times to clinical response in these two groups.

MATERIALS AND METHOD

Hospital setting and study design

Bulent Ecevit University Teaching and Research Hospital is a 600-bed tertiary care hospital in Zonguldak, Turkey. The hospital contains all major departments, including those associated with medical and surgical subspecialties, as well as medical and surgical intensive care units. This retrospective study enrolled 206 patients with CA- and HCA-SSTIs who were aged ≥18 years and had been hospitalized between January 2005 and December 2012. The patients were hospitalized in the Department of Infectious Diseases and Clinical Microbiology or another department that consulted with an Infectious Diseases (ID) specialist. Patients were monitored by the ID team during daily rounds. The study protocol was approved by the Ethics Committee of Bulent Ecevit University Teaching and Research Hospital, and written informed consent was obtained from the patients' legal representatives.

Data collection

This study included all patients with CA- and HCA-SSTIs who were hospitalized during the study period and for whom an ID consultation was requested. A form was used to collect the following data: name, age, sex, hospital ward, type of SSTI, antibiotic use before the consultation, empirical antibiotic treatment, clinical features of the SSTI (e.g., complicated or non-complicated), co-morbid factors, results of a complete blood count analysis (e.g., total white blood cell count, hemoglobin level, platelet count), sedimentation rate, C-reactive protein level, biochemical parameters (serum sodium, potassium, urea, creatine, and glucose levels), presence of fever, and signs of SSTI (e.g., induration, erythema, warmth, and tenderness). For cases with clinically suspected SSTI, samples were taken from the suspected infection sites. Also blood cultures were taken from all of the study patients. If an abscess or a bullous lesion was present, microbiological samples were obtained from aspirated exudates, bullous liquid and deep tissues after debridement and cleansing of superficial tissue. Swabs of pus or deep tissue samples were obtained from the open wounds. When an ulcer was present, deep swab and tissue samples were cultured. Gram stain, deep swab, tissue and blood culture results were evaluated together for the final decision of antibiotic regimen. Only blood cultures were taken from the patients with non-complicated SSTIs such as simple, nonpurulent, nonbullous selulitis. *Staphylococcus epidermidis* is generally

considered as a part of skin flora. In this study it was thought as a causative microorganism when it grew from an abscess material, deep tissue sample or ≥2 blood cultures from the patients with SSTIs. Patients were excluded from the study if they had been treated with intravenous antibiotics for >24 h prior to enrollment, were expected to undergo amputation or complete resection of the infected site, and had any diagnosis of nosocomial SSTI.

Definitions

Skin and soft tissue infections are defined as infections characterized by induration, erythema, warmth, and pain or tenderness (3). Complicated skin and soft tissue infections are defined as infections involving deep soft tissue or requiring significant surgical intervention, or those in patients with a significant underlying condition such as DM, obesity, immunodeficiency, or venous or arterial insufficiency (1). A HCA-SSTI was defined as any SSTI in a patient who had been recently hospitalized (i.e., within the previous 30 days), had used antibiotics in the 30 days prior to admission, had been transferred from a nursing home, or required dialysis (4, 5). A CA-SSTI was defined as an episode that developed in an outpatient setting or within 48 h after hospital admission in patients who did not fit the criteria for a HCA-SSTI (5). The empirical antibiotic treatment choice was made according to the pathogens suspected to be responsible for the SSTI.

Appropriate antimicrobial treatment was defined as the use of antibiotics with in vitro activity against the isolated pathogens or the presence of a clinically proven response when administered at an adequate dosage and time interval. Antimicrobial treatment was defined as inappropriate when the prescribed agent was not effective against the infecting microorganism(s) isolated from the infection sites or blood; if clinical deterioration, such as a lack of response, recurrence or worsening of fever, worsening of the infection site, increased purulence, erythema, induration, or local warmth, was observed within 72 hours of the initiation of treatment; or if the patients exhibited ≥2 systemic inflammatory reaction symptoms such as hypotension, tachycardia, a body temperature of <35°C or >38°C, and confusion or reduced consciousness. Broadening of antibiotic treatment was considered if no clinical or microbiological response was observed, the patient's clinical status worsened, and/or the isolated causative bacteria was resistant to the initial antibiotic therapy according to in vitro antibiotic susceptibility testing. The following criteria were considered indicative of a clinical response: 1) resolution of fever or hypothermia, with a body temperature between 36°C and 38°C; 2) disappearance of the induration, erythema, warmth and tenderness, and/or pain; and 3) the absence of purulence and exudation in the infection site (6,7).

The treatment duration was 10–14 days for patients with non-complicated SSTI and ≥21 days for patients with CSSTI. Surgeons were also consulted for drainage and debridement in cases involving complicating factors such as necrotizing infection, abscesses, arthritis, and osteomyelitis.

Prior antibiotic use was defined as treatment for at least 24 h within 30 days prior to the beginning of the SSTI. Previous hospitalization was defined as hospitalization within the previous 30 days. If a suspicion of an abscess or an osteomyelitis was present, magnetic resonance imaging was also used. Isolation and Identification of Microorganisms from Cultures

Isolates were identified using conventional methods; when required, the results were confirmed using semi-automated API systems (bioMérieux, Marcy l'Etoile, France). Antibiotic susceptibility tests were performed according to the Kirby–Bauer disk diffusion method and the guidelines of the Clinical and Laboratory Standards Institute (CLSI) (8).

Statistical analysis

Statistical analyses were performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). The Shapiro–Wilk test was used to determine the distribution of data. Continuous variables are expressed as means±standard deviations, whereas categorical variables are expressed as frequencies and percentages. Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using Pearson's chi-square test for two groups. A binary

logistic regression analysis with a forward stepwise method was performed to identify significant risk factors. A p value of <0.05 was considered statistically significant for all tests.

RESULTS

A total of 206 patients with SSTIs were recorded during the study period, including 132 male (64%) and 74 female patients (36%). The mean patient age was 57.17±15.17 years (range: 20–83 years). Sixty-nine patients were aged ≥65 years. Most patients were hospitalized in the Departments of Infectious Diseases and Clinical Microbiology (38.3%), Plastic and Reconstructive Surgery (15.5%), and Orthopedic Surgery (14.1%). Demographic features, co-morbid factors, and clinical characteristics were compared between patients aged <65 years and those aged ≥65 years (Table 1). Of the co-morbid factors, the incidence of DM was significantly higher among older patients. Similarly, leukocytosis was significantly more frequent among patients aged ≥65 years, whereas erythema was significantly more common among younger patients (Table 1).

Table 1. Demographic and clinical variables of patients with SSTIs by age.

Variable	All Patients N=206 n (%)	18–65 years N=137 n (%)	≥65 years N=69 n (%)	p
Sex (male)	132 (64)	88 (64)	44 (64)	1.000
DM	104 (50.5)	57 (41.6)	47 (68.1)	<0.001
Essential hypertension	36 (17.5)	20 (14.6)	16 (23.2)	0.348
CRF	20 (9.7)	11 (8.0)	9 (13.0)	0.316
Malignancy	19 (9.2)	10 (7.3)	9 (13.0)	0.276
COPD	12 (5.8)	5 (3.6)	7 (10.1)	0.110
CHF	6 (2.9)	2 (1.5)	4 (5.8)	0.098
Fever on admission	66 (32.0)	46 (33.6)	20 (29)	0.611
Erythema	110 (53.7)	82 (60.3)	28 (40.6)	0.007
Induration	63 (30.7)	43 (31.6)	20 (29.0)	0.821
Tenderness/pain	35 (17.1)	24 (17.6)	11 (15.9)	0.912
Exudation	27 (13.1)	17 (12.5)	10 (14.5)	0.857
Leukocytosis	86 (41.7)	50 (36.5)	36 (52.2)	0.031
Prior antibiotic use	131 (63.6)	86 (62.8)	45 (65.2)	0.731
Prior hospitalization	93 (45.1)	57 (41.6)	36 (52.2)	0.725
Operation	58 (28.2)	37 (27.0)	21 (30.4)	0.150
Trauma	27 (13.1)	21 (15.3)	6 (8.7)	0.266
Obesity	44 (21.4)	27 (19.7)	17 (24.6)	0.526
Toe-web intertrigo	35 (17.0)	22 (16.1)	13 (18.8)	0.760
Venous insufficiency	38 (18.4)	22 (16.1)	16 (23.2)	0.291
HCA-SSTI	87 (42.2)	52 (38)	35 (50.7)	0.080
CSSTI	117 (56.8)	74 (54)	43 (62.3)	0.256
	median (min–max)	median (min–max)	median (min–max)	
Time to resolution of fever (days)	3 (2–10)	3 (2–10)	3 (2–10)	0.596
Time to clinical response (days)	5 (2–14)	5 (2–14)	7 (3–12)	0.179

SSTI, skin and soft tissue infection; HCA, healthcare-associated; CSSTI, complicated SSTI; DM, diabetes mellitus; CRF, chronic renal failure; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure.

Table 2. Types of SSTI.

Type	All Patients N=206 n (%)	18–65 years N=137 n (%)	≥65 years N=69 n (%)	p	CA-SSTI patients N=119 n (%)	HCA-SSTI patients N=87 n (%)	P
Cellulitis	94 (45.6)	68 (49.6)	26 (37.7)	0.104	66 (55.5)	28 (32.2)	0.001
Diabetic foot	54 (26.2)	25 (18.2)	29 (42.0)	<0.001	29 (24.4)	25 (28.7)	0.587
Erysipelas	24 (11.7)	15 (10.9)	9 (13.0)	0.832	9 (7.6)	15 (17.2)	0.055
Fournier gangrene	12 (5.8)	9 (6.6)	3 (4.3)	0.754	5 (4.2)	7 (8.0)	0.388
Abscess	8 (3.9)	7 (5.1)	1 (1.4)	0.272	5 (4.2)	3 (3.4)	1.000
Ulcer	4 (1.9)	4 (2.9)	0 (0.0)	0.303	2 (1.7)	2 (2.3)	1.000
Burn	4 (1.9)	4 (2.9)	0 (0.0)	0.303	0 (0.0)	4 (4.6)	0.031
NF	3 (1.5)	2 (1.5)	1 (1.4)	1.000	1 (0.8)	2 (2.3)	0.575
Other	3 (1.5)	3 (2.2)	0 (0.0)	0.552	2 (1.7)	1 (1.1)	1.000

SSTI, skin and soft tissue infection; CA, community-acquired; HCA, healthcare-associated ; NF, necrotizing fasciitis,

Cellulitis and diabetic foot infections were the most frequent SSTI infections in all patients (Table 2). Cellulitis was significantly more common in patients with CA-SSTI (p=0.001), whereas burn infections were more common in patients with HCA-SSTI (p=0.031). Patients aged ≥65 years were significantly more likely to have a diabetic foot infection, compared to younger patients (p=0.001).

Pathogenic microorganism(s) were isolated from 96 (46.6%) of the 206 patients (19 cases were polymicrobial). Causative microorganism isolation rate from blood cultures was 4.9%. Gram negative bacteria isolation rate was higher in patients aged ≥65 years (25/31, 80.6%), than the patients aged <65 years (35/65, 53.8%) (p<0.001).

In patients aged <65 years, methicillin-sensitive *Staphylococcus aureus* (MSSA)/*epidermidis* (MSSE) (21/65, 32.3%) and *Escherichia coli* (18/65, 27.6%) were the most common pathogens responsible for SSTIs. In patients aged ≥65 years, *E. coli* (11/31, 35.5%) and *Pseudomonas aeruginosa* (8/31, 25.8%) were the most frequently isolated pathogens. Among patients with complications, *P. aeruginosa* was the most commonly isolated pathogen (25/83, 30.1%). MSSA was the most frequently isolated pathogen from patients with CA-SSTI (18/40, 45.0%), whereas *P. aeruginosa* was most frequently from patients with HCA-SSTI (19/56, 33.9%). Methicillin resistance was detected in only one of 22 *S. epidermidis/aureus* isolates (4.5%), and three of nine *E. coli* and *K. pneumoniae* isolates (33.3%) from patients with CA-SSTI produced extended-spectrum beta-lactamase (ESBL). In patients with HCA-SSTI, approximately half of the *S. aureus* and *S. epidermidis* isolates were methicillin-resistant (8/15, 53.3%). Patients with HCA-SSTI were more likely to produce ESBL (9/21, 42.8%) than were patients with CA-SSTI. Table 3 compares patients with CSSTI and non-complicated SSTI in terms of

the study variables. Furthermore the differences in variables between young and older patients with CSSTI and non-complicated SSTI are shown in this table. Of the evaluated co-morbid factors, DM was significantly more common in patients with CSSTI ($p<0.001$). Malignancy was significantly more common in non-complicated patients ($p=0.002$), and erythema ($p<0.001$) and induration ($p=0.001$) were more frequently seen in this population. By contrast, patients with CSSTI were significantly more likely to exhibit leukocytosis ($p=0.005$), exudation ($p<0.001$) prior antibiotic use ($p<0.001$), prior hospitalization ($p<0.001$), toe-web intertrigo ($p=0.013$), and venous insufficiency ($p<0.001$) or to have undergone surgery ($p<0.001$). Furthermore, the time- to -resolution of fever ($p< 0.001$) and time-to -clinical response ($p=0.016$) were significantly longer in patients with CSSTI. Patients with CSSTI were also significantly more likely to have HCA-SSTI ($p<0.001$). DM was significantly a more common co-morbid factor in both patients with complicated SSTI ($p=0.025$) and those with non-complicated SSTI patients ($p=0.030$) aged ≥65 years. Among co-morbid factors, chronic renal failure was also significantly more common in older patients with non-complicated SSTIs ($p=0.013$). Erythema was significantly a more common sign in non-complicated SSTI aged <65 years ($p=0.024$). Time- to -clinical response was significantly found to be longer in older patients with non-complicated SSTI ($p=0.007$).

Table 4 presents a comparison of patients with CA-SSTI and HCA-SSTI in terms of co-morbid factors and some clinical features. This table also presents differences in variables between young and the older patients with CA-SSTI and HCA- SSTI. Prior antibiotic use ($p< 0.001$), prior hospitalization ($p<0.001$), and operation ($p<0.001$) were significantly more common among patients with HCA-SSTI, and these patients were also more likely to have CSSTI ($p<0.001$). However, patients with CA-SSTI and HCA-SSTIs did not differ significantly in terms of the time to resolution of fever and time to clinical response. Erythema ($p<0.001$) and induration ($p=0.032$) were more common in patients with CA-SSTI. Exudation was significantly more common in patients with HCA-SSTI ($p=0.006$). DM was found to be significantly more common in older patients with both CA ($p=0.019$) and HCA-SSTI ($p=0.014$). Erythema was a more common sign in young patients with HCA-SSTI ($p=0.047$).

Risk factors for CSSTI are shown in Table 5. Male sex ($p=0.000$), venous insufficiency ($p=0.028$), DM ($p=0.001$) prior hospitalization ($p=0.005$) and operation ($p=0.019$) were identified as risk factors for CSSTI in patients aged <65 years, whereas venous insufficiency ($p=0.008$) and prior hospitalization ($p=0.001$) were identified as risk factors for CSSTI in patients aged ≥65 years. Inappropriate antibiotic use was identified in 34 patients. Complicated cellulitis and diabetic foot infections were the most common SSTIs in these patients. The most commonly reported reasons for switching antibiotic treatment regimens were the resistance of causative bacteria (18/34, 52.9%) and lack of a clinical response (15/34, 44.1%). Half of these patients had HCA-SSTI. Twenty-three of were aged <65 years, and 11 were aged ≥65 years old.

Table 3. The differences in variables between young and older patients with complicated SSTI and non-complicated SSTI.

Variable	Complicated SSTI				Non-complicated				
	All N=117 n (%)	<65 N=74 n (%)	≥65 N=43 n (%)	P	All N=89 n (%)	<65 N=63 n (%)	≥65 N=26 n (%)	p	p (for all patients of CSSTI and non-complicated SSTI)
Sex (male)	86 (73.5)	56 (75.7)	30 (69.8)	0.631	46 (51.7)	32 (50.8)	14 (53.8)	0.977	0.001
DM	73 (62.4)	40 (54.1)	33 (76.7)	0.025	31 (34.8)	17 (27.0)	14 (53.8)	0.030	<0.001
Essential hypertension	20 (17.1)	12 (16.2)	8 (18.6)	0.939	16 (17.9)	8 (12.7)	8 (30.8)	0.067	1.000
CRF	9 (7.7)	7 (9.5)	2 (4.7)	0.482	11 (12.4)	4 (6.3)	7 (26.9)	0.013	0.377
Malignancy	4 (3.4)	1 (1.4)	3 (7.0)	0.140	15 (16.9)	9 (14.3)	6 (23.1)	0.357	0.002
COPD	9 (7.7)	3 (4.1)	6 (14.0)	0.073	3 (3.4)	2 (3.2)	1 (3.8)	1.000	0.312
CHF	2 ((1.7)	1 (1.4)	1 (2.3)	1.000	4 (4.5)	1 (1.6)	3 (11.5)	0.073	0.406
Obesity	27 (23.1)	16 (21.6)	11 (25.6)	0.793	17 (19.1)	11 (17.5)	6 (23.1)	0.562	0.604
Toe-web intertrigo	27 (23.1)	17 (23.0)	10 (23.0)	1.000	8 (9.0)	5 (7.9)	3 (11.5)	0.687	0.013
Venous insufficiency	33 (28.2)	19 (25.7)	14 (32.6)	0.559	5 (5.6)	3 (4.8)	2 (7.7)	0.627	<0.001
Fever on admission	42 (35.9)	28 (37.8)	14 (32.6)	0.708	24 (27.0)	18 (28.6)	6 (23.1)	0.788	0.174
Erythema	26 (22.2)	20 (27.4)	6 (14.0)	0.148	84 (94.4)	62 (98.4)	22 (84.6)	0.024	<0.001
Induration	24 (20.5)	15 (20.5)	9 (20.9)	1.000	39 (43.8)	28 (44.4)	11 (42.3)	1.000	0.001
Tenderness/ pain	18 (15.4)	13 (17.8)	5 (11.6)	0.534	17 (19.1)	11 (17.5)	6 (23.1)	0.562	0.726
Exudation	26 (22.2)	17 (23.3)	9 (20.9)	0.949	1 (1.1)	0 (0.0)	1 (3.8)	0.292	<0.001
Ulcer	4 (3.4)	3 (4.1)	1 (2.3)	1.000	0 (0.0)	-	-		0.071
Bullous skin lesion	2 (1.7)	1 (1.4)	1 (2.3)	1.000	0 (0.0)	-	-		0.260
Leukocytosis	78 (66.7)	52 (70.3)	26 (60.5)	0.378	42 (47.2)	35 (55.6)	7 (26.9)	0.026	0.005
Prior antibiotic use	88 (75.2)	56 (75.7)	32 (74.4)	1.000	43 (48.3)	30 (47.6)	13 (50.0)	1.000	<0.001
Prior hospitalization	72 (61.5)	43 (58.1)	29 (67.4)	0.422	21 (23.6)	14 (22.2)	7 (26.9)	0.841	<0.001
Operation	45 (38.5)	28 (37.8)	17 (39.5)	1.000	13 (14.6)	9 (14.3)	4 (15.4)	1.000	<0.001
Trauma	14 (12)	10 (13.5)	4 (9.3)	0.703	13 (14.7)	11 (17.5)	2 (7.7)	0.331	0.728
HCA-SSTI	63 (53.8)	36 (48.6)	27 (62.8)	0.198	24 (27.0)	16 (25.4)	8 (30.8)	0.797	<0.001
			median (min–max)				median (min–max)		
Time to resolution of fever (days)	3 (2–10)	8 3-12	6 3-10	0.074	2 (2–8)	2 (2-6)	2 (2-8)	0.687	<0.001
Time to clinical response (days)	6.5 (3–12)	4 (2-10)	3 (2-10)	0.254	5 (2–14)	5 (2-14)	7 (3-12)	0.007	0.016

SSTI, skin and soft tissue infection; HCA, healthcare-associated; DM, diabetes mellitus; CRF, chronic renal failure; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure.

Table 4. The differences in variables between young and older patients with CA-SSTI and HCA-SSTI.

Variable	CA-SSTI				HCA-SSTI				
	N=119 n (%	<65 N=85 n %	≥65 N=34 n %	p	N=87 n %	<65 N=52 n %	≥65 N=35 n %	p	p (for all patients of CA-SSTI and HCA-SSTI)
Sex (male)	75 (63.0)	54 (63.5)	21 (61.8)	1.000	57 (65.5)	34 (65.4)	23 (65.7)	1.000	0.713
DM	62 (52.1)	38 (44.7)	24 (70.6)	0.019	42 (48.3)	19 (36.5)	23 (65.7)	0.014	0.588
Essential hypertension	22 (18.5)	13 (15.3)	9 (26.5)	0.247	14 (16.1)	7 (13.5)	7 (20.0)	0.606	0.794
CRF	10 (8.4)	5 (5.9)	5 (14.7)	0.146	10 (11.5)	6 (11.5)	4 (11.4)	1.000	0.616
Malignancy	10 (8.4)	6 (7.1)	4 (11.8)	0.469	9 (10.3)	4 (7.7)	5 (14.3)	0.475	0.817
COPD	4 (3.4)	3 (3.5)	1 (2.9)	1.000	8 (9.2)	2 (3.8)	6 17.1	0.056	0.143
CHF	3 (2.5)	1 (1.2)	2 (5.9)	0.196	3 (3.4)	1 (1.9)	2 (5.7)	0.562	0.690
Obesity	24 (20.2)	15 (17.6)	9 (26.5)	0.406	20 (23.0)	12 (23.1)	8 (22.9)	1.000	0.752
Toe-web intertrigo	16 (13.4)	13 (15.3)	3 (8.8)	0.553	19 (21.8)	9 (17.3)	10 (28.6)	0.326	0.163
Venous insufficiency	26 (21.8)	15 (17.6)	11 (32.4)	0.131	12 (13.8)	7 (13.5)	5 (14.3)	1.000	0.197
Fever on admission	37 (31.6)	27 (31.8)	10 (29.4)	0.975	29 (33.3)	19 (36.5)	10 (28.6)	0.588	0.134
Erythema	78 (65.5)	58 (69.0)	20 (58.8)	0.396	32 (36.8)	24 (46.2)	8 (22.9)	0.047	<0.001
Induration	43 (36.1)	30 (35.7)	13 (38.2)	0.963	20 (23.0)	13 (25.0)	7 (20.0)	0.777	0.032
Tenderness /pain	20 (16.8)	13 (15.5)	7 (20.6)	0.690	15 (17.2)	11 21.2	4 11.4	0.374	1.000
Exudation	8 (6.7)	8 (9.5)	0 (0.0)	0.103	19 (21.8)	9 (17.3)	10 (28.6)	0.326	0.006
Ulcer	2 (1.6)	2 (2.4)	0 (0.0)	1.000	2 (2.3)	1 (1.9)	1 (2.9)	1.000	1.000
Bullous skin lesion	2 (1.6)	1 (1.2)	1 (2.9)	0.495	0 (0.0)	0 (0.0)	0 (0.0)	-	0.265
Leukocytosis	71 (59.7)	55 (64.7)	16 (47.1)	0.117	49 (56.3)	32 (61.5)	17 (48.6)	0.329	0.631
Prior antibiotic use	49 (41.2)	37 (43.5)	12 (35.3)	0.536	82 (94.3)	49 94.2	33 94.4	1.000	<0.001
Prior hospitalization	20 (16.8)	15 (17.6)	5 (14.7)	0.907	73 (83.9)	42 (80.8)	31 (88.6)	0.501	<0.001
Operation	17 (14.3)	14 (16.5)	3 (8.8)	0.389	41 (47.1)	23 (44.2)	18 (51.4)	0.660	<0.001
Trauma	17 (14.3)	15 (17.6)	2 (5.9)	0.146	10 (11.5)	6 (11.5)	4 (11.4)	1.000	0.706
CSSTI	54 (45.4)	38 (44.7)	16 (47.1)	0.977	63 (72.4)	36 (69.2)	27 (77.1)	0.572	<0.001
			median (min–max)				median (min–max)		
Time to resolution of fever (days)	3 (2–8)	3 (2-8)	2 (2-8)	0.590	3 (2–10)	3 (2-10)	4 (2-10)	0.675	0.096
Time to clinical response (days)	5 (2–14)	5 (2-14)	7 (4-12)	0.265	5 (3–10)	6 (3-10)	7 (3-10)	0.467	0.836

SSTI, skin and soft tissue infection; CA, community-acquired; HCA, healthcare-associated; CSSTI, complicated SSTI; DM, diabetes mellitus; CRF, chronic renal failure; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure.

Table 5. Age related risk factors for CSSTI.

Risk factor	OR	95% CI	p
For patients aged ≥65 years			
Venous insufficiency	10.160	1.823–56.641	0.008
Prior hospitalization	8.273	2.505–27.329	0.001
For all patients			
DM	2.952	1.541–5.656	0.001
Prior hospitalization	5.730	2.934–11.190	<0.001
Venous insufficiency	6.526	2.253–18.898	0.001
For patients aged <65			
Sex (male)	5.199	2.062-13.109	0.000
Venous insufficiency	6.066	1.210-30.408	0.028
DM	4.930	1.980-12.400	0.001
Prior hospitalization	3.972	1.524-10.348	0.005
Operation	3.908	1.251-12.198	0.019

SSTI, skin and soft tissue infection; CSSTI, complicated SSTI; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus

DISCUSSION

SSTIs are common both in the general population and among older patients. The latter are particularly at risk of developing SSTIs because of changes in skin consistency, co-morbid conditions that affect immunity, skin disorders such as edema, and trauma (2, 9).

A previous report identified cellulitis as a frequent occurrence in long-term care facilities, where it affected 1–9% of residents (10). In our study, cellulitis was the most common SSTI among all patients, whereas diabetic foot infection was more common in older patients. In our study, DM was the most common comorbid disease in patients with CSSTIs and in older patients among all sub-groups of SSTIs such as complicated, non-complicated, community acquired and healthcare-associated. The authors of a previously reported study also found DM to be the most common of the active co-morbid factors at the time of enrollment in each complicated infection type. That study also reported peripheral vascular disease, renal insufficiency, chronic renal failure, immunosuppression, and advanced age as risk factors (11). By contrast, we did not identify advanced age as a risk factor for CSSTI. However, we identified venous insufficiency and prior hospitalization as risk factors for complications in all patients and in older patients.

In older patients, cellulitis often presented with atypical symptoms. Systemic symptoms, such as fever, tachycardia, hypotension, and leukocytosis occur infrequently. Some conditions associated with skin fragility, such as edema and skin tears, are known to predispose a patient to cellulitis (2). In our study, erythema, a main clinical sign of SSTI, was significantly more common among young patients with non-complicated SSTI. However, we observed that an elevated leucocyte count was more common

in the older group. Exudation was a more common clinical sign in patients with CSSTIs, and these patients also had a longer time- to -clinical response and time- to -resolution of fever. These results were independent of age. Although an antibiotic therapy duration of approximately 5 days was recently recommended (12), in our study, the median time-to -clinical response was approximately 7 days in patients with CSSTIs. Also this time was significantly longer in older patients with non-complicated SSTI than the younger patients. Therefore, our treatment duration was longer that recommended in the current guideline.

Per the literature, the main etiological agents of SSTIs are Gram-positive organisms such as *S. aureus* and beta-hemolytic streptococci (13). Current IDSA guideline described positive blood culture rates of only 2%–4% and positive punch biopsy culture 20%-30% in patients with CA-SSTIs. Furthermore, blood, aspirate and other biopsy material cultures are no longer routinely recommended for simple, nonpurulent CA-SSTIs because of low isolation of causative microorganism rates (12). In another domestic guideline recently reported by the Korean authors, routine blood, aspiration, or punch biopsy culture was recommended only in immunosuppressive patients, similar to that reported in the IDSA guideline (14) In our study, causative microorganisms were isolated from 47% of included patients; in other words, our bacteria isolation rate was higher than that reported previously (12). We attribute this high rate to the facts that patients with CSSTI comprised 57% of our study population and that most cultures were grown from deep swab and tissue samples. Our study population was hospitalized before the reporting date of these guidelines, so the patients' blood cultures were taken routinely even from patients with simple cellulitis. Our causative microorganism isolation rate from blood cultures was 4.9%, similar to that reported previously (12). In a recently published study of 158 elderly patients with cellulitis, positive bacterial cultures were grown from the superficial samples of 15% of the patients, and *S. aureus* was the most commonly isolated pathogen (15). Similarly, in our study, Gram-positive microorganisms were most frequently isolated from patients with CA-SSTI and those aged <65 years. By contrast, Gram-negative pathogen isolation rate was significantly higher in older patients. Although DM was significantly more common in older patients, it was not found as a significant risk factor for CSSTI for this population. So we think this high isolation rate may be due to the advanced age. In patients with HCA-SSTI, approximately half of the staphylococcal strains were methicillin-resistant, and ESBL production by gram-negative bacteria was more frequently observed. Accordingly, we think that initial antibiotic regimens administered to older patients and those with HCA-SSTI should target Gram-negative pathogens. Additionally, the high frequency of resistant pathogens was unsurprising, as many patients had a history of prior antibiotic use. The identification of a resistant organism should prompt a change in the initial antibiotic regimen. We believe that culture and antibiotic sensitivity tests should be performed for older patients and those with HCA-SSTIs. Penicillinase-resistant penicillin was suggested for the patients in whom the clinical findings could not accurately distinguish between streptococcal and staphylococcal infection. The initial regimen was suggested in combination with clindamycin, linezolid, or vancomycin if MRSA is suspected as a causative agent (13). Generally, SSTIs are considered as complicated if they require surgical procedures or involve deeper subcutaneous tissues. In our study, more than half of the patients had CSSTI, and more than half these cases were HCA. The treatment of a CSSTI may be challenging because of the complex spectrum of causative microorganisms. A previous report noted that the prevalence of antibiotic-resistant microorganisms had increased among CSSTI cases (11). In our study, Gram-negative pathogens were more common among patients

with CSSTIs. Although infection management depends on many factors, including the local prevalence, previous antibiotic use, and previous hospitalization, we recommend that patients with CSSTI receive an initial treatment regimen that targets Gram-negative microorganisms, especially *P. aeruginosa*.

Although it was suggested that empirical initial antibiotic therapy for elderly patients should target Gram-positive agents, we also suggest Gram-negative pathogens, and even *P. aeruginosa*, should be targeted in this group, as well as in patients with CSSTIs and HCA-SSTIs (9).

Previous studies have defined many risk factors for SSTIs, including obesity, venous or lymph stasis, tinea pedis, recent trauma, and underlying skin disorders (9, 16); however, overweight and lymphedema were identified as the prominent risk factors (16). In our study, we compared the risk factors for complications between young and older patients with SSTI. In young patients, male sex, DM, operation, venous insufficiency, and prior hospitalization were identified as significant risk factors for CSSTI, whereas the latter two remained risk factors for CSSTI in patients aged ≥65 years. Although toe-web intertrigo, which is mostly caused by fungal infection, was also reported as a major risk factor, we did not identify this condition as a risk factor for complications in age related sub-groups of patients with SSTI.

In conclusion, DM was the most common co-morbid factor in older patients with SSTI in each sub-group. We did not find advanced age as a risk factor for CSSTI, but found that risk factors for complicated SSTI may differ by age. Time- to-resolution of fever and time- to- clinical response were significantly longer in patients with CSSTI and time- to- clinical response was longer in older patients with non-complicated SSTI. Furthermore isolation rate of Gram-negative bacteria is more common among in older patients. Although current guidelines and reviews suggest providing coverage for beta-hemolytic streptococcal and methicillin-sensitive staphylococcal strains when treating CA-SSTIs, we should not overlook the likelihood that Gram-negative pathogens are the etiologic agents of SSTIs, especially in elderly patients.

Conflict of interest

The authors have no potential conflicts of interest.

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