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Microbiological Etiology and Treatment of Complicated Skin and Skin Structure Infections in Diabetic and Nondiabetic Patients in a Population-Based Study

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Background. Diabetes is a major risk factor for skin and skin structure infection (SSSI), and the global burden of diabetics with SSSI is enormous. The more complex microbiology of diabetic foot infection (DFI) is well established, but it is not known whether microbiological etiology differs between diabetics and nondiabetics in other disease entities under the umbrella of complicated SSSI (cSSSI).

Methods. This retrospective, population-based study included patients with cSSSI, and it was conducted in 2 Nordic cities with a low prevalence of antimicrobial resistance. In analyses, patients ($N = 460$) were separated into 3 groups: diabetics ($n = 119$), nondiabetics ($n = 271$), and patients with DFI ($n = 70$).

Results. After exclusion of patients with DFI, there was no difference in the microbiological etiology or initial antimicrobial treatment of cSSSI between diabetics and nondiabetics. Gram-positive bacteria encountered 70% of isolations in diabetics and 69% in nondiabetics, and the empirical treatment covered initial pathogens in 81% and 86% of patients, respectively. However, diabetes was the only background characteristic in the propensity score-adjusted analysis associated with broad-spectrum antimicrobial use and longer antibiotic treatment duration. Patients with DFI had Gram-negative and polymicrobial infection more often than nondiabetics.

Conclusions. These observations suggest that diabetics without DFI are not different in the causative agents of cSSSI, although they are more exposed to antimicrobial therapy of inappropriate extended spectrum and long duration. Broad-spectrum coverage was clearly needed only in DFI. A clear opportunity for antimicrobial stewardship was detected in the rapidly growing population of diabetic patients with cSSSI.

Keywords. antimicrobial treatment; complicated skin and skin structure infection; diabetes; microbiological etiology.

The estimated prevalence of diabetes was 8.5% in the global adult population in 2014 [1]. In comparison to general population, diabetics are more susceptible to a variety of infectious diseases, have more community-based antibiotic prescriptions, and also increased rate of hospitalization due to infection, including skin infections [2–4]. Skin and skin structure infection (SSSI) is generally regarded as complicated if it involves deep subcutaneous tissues, needs surgery in addition to antimicrobial therapy, or affects a patient with severe comorbidities such as diabetes [5–8].

Gram-positive cocci, particularly streptococci and *Staphylococcus aureus*, are the major causative organisms of SSSI, but Gram-negative rods and anaerobic bacteria are frequently detected in patients with diabetic foot infection (DFI) [8–10]. Therefore, broad-spectrum antimicrobial therapy that also covers Gram-negative infections is recommended by Infectious Diseases Society of America (IDSA) guidelines only in the treatment of moderate-to-severe DFI [11]. On the other hand, IDSA guidelines recommend antimicrobial therapy targeted only to Gram-positive cocci in the treatment of (mild-to-moderate) cellulitis or abscess irrespective of the presence of diabetes [12].

Studies evaluating the microbiological etiology of SSSI (excluding DFI) separately among diabetics and nondiabetics are scarce. In a study including mostly patients with uncomplicated cellulitis or abscess, Gram-negative pathogens were not more common among diabetics than among nondiabetics [13]. Yet, the authors reported higher overall use of antibiotics with broad Gram-negative activity and also longer antimicrobial treatment duration in diabetics compared with nondiabetics [13]. To the best of our knowledge, no population-based

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comparative studies have been done between diabetics and nondiabetics with complicated SSSI (cSSSI).

In a population-based survey, we observed that diabetic patients with cSSSI had longer total duration of antimicrobial treatment than nondiabetics [14]. We wanted to further analyze the factors beyond this phenomenon, ie, possible differences in microbiological etiology and treatment practices between diabetics and nondiabetics in our population-based material collected in 2 areas with low antimicrobial resistance.

MATERIALS AND METHODS

This was an observational retrospective cohort study, and inclusion and exclusion criteria are described in more detail in the primary publication of this study [14]. The study population consisted of all adult residents from cities with nearly equal population (Helsinki, Finland population of 588 000 and the Gothenburg area, Sweden population 600 000) who were treated because of cSSSI during 2008–2011 in Helsinki University Central Hospital or Helsinki City Hospital in Finland and in Sahlgrenska University Hospital in Gothenburg, Sweden. These hospitals have the only emergency departments on their catchment area and are thus responsible for treatment of almost all patients hospitalized with SSSIs. First selection was made by certain *International Classification of Diseases, Tenth Revision* diagnostic codes, and, to be included in the final analysis population ($N = 460$), patients were required to have an infection affecting deeper soft tissue, infection that required significant surgical intervention, developed on a lower extremity in a subject with diabetes mellitus or peripheral vascular disease, or to have a major abscess or infected ulcer. In addition to local signs of cSSSI, the patient also had to have at least 1 systemic sign of infection (temperature >38 or <36°C, white blood cell count >10 000/mm^3 or <4000/mm^3).

In the analyses, patients were divided into 3 separate groups: diabetics, nondiabetics, and patients with DFI. In our study, the definition of DFI was based on typical clinical presentation with infected (neuropathic) ulceration or (traumatic) wound, and due to requirement of systemic signs of infection, the DFIs in our study were classified as severe based on IDSA classification [11]. Presence of diabetes mellitus was based on medical records. Cellulitis or fasciitis was determined as lack of abscess, diabetic foot or leg ulcer, or peripheral vascular disease ulcer. The evaluation of clinical stability was based on improvement of vital signs and decreased fever, and treatment failure was defined as follows: need for unplanned surgery, no improvement in clinical situation after 5 days of treatment, or treatment failure registered in patient records by treating physician. Carbapenems and piperacillin-tazobactam were considered as broad-spectrum antimicrobial therapy in this analysis. Microbiological diagnosis was obtained by a bacterial culture of blood, tissue specimens, or superficial swabs in routine cultures. In this analysis, coagulase-negative staphylococci and candida were not regarded as true pathogens. Data for evaluation of recurrences and mortality were collected until 1-year post-cSSSI diagnosis.

Statistical Analysis

Results are presented as absolute values and percentages unless otherwise specified. Pearson's χ^2 test was applied to compare categorical variables, whereas Mann-Whitney *U* test was used for non-parametric data. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated. Univariate factors with $P \leq .1$ were accepted for binary logistic regression multivariate analysis.

To verify the stability of the main results, a propensity score (PS) was calculated by logistic regression for the assignment of either (1) broad-spectrum or nonbroad-spectrum or (2) short (<17 days) or long (≥17 days) definitive antimicrobial treatment. Variables interpreted as relevant for this assignment were age >60, chronic renal failure, respiratory disease, and injection drug abuse. Next, a PS-adjusted binary logistic regression multivariate analysis was performed to estimate treatment characteristics specific for patients with a diagnosis of diabetes. All tests were 2-tailed and $P < .05$ was considered as significant. Analyses were done using SPSS version 21.0 (SPSS Inc., Chicago, IL).

RESULTS

In total, there were 460 patients with cSSSI, and the main comparison was performed between patients with diabetes ($n = 119$) and without it ($n = 271$), after the exclusion of 70 patients with DFI as a separate group. Diabetics were found to be significantly older (mean age 71 [standard deviation {SD} = 15] vs 64 [SD = 20] years; $P = .001$), and they more often had chronically elevated serum creatinine levels (13% vs 2%, median 182 vs 333 μmol/L) or a respiratory disease (13% vs 6%), but they were less likely to be an injection drug abuser (1% vs 24%), compared with nondiabetics (Table 1). Diabetics were also found to have significantly more infection localized in the lower extremity (68% vs 49%, $P = .001$), classified as cellulitis (65% vs 43%), and they were likely to seek treatment earlier from the onset of symptoms (Table 1). Otherwise, diabetics did not differ from nondiabetics in their background or disease characteristics (Table 1).

Statistically significant differences were not found in initial microbiological etiology or initial antimicrobial therapy of cSSSI between diabetics and nondiabetics (Tables 2 and 3). However, broad-spectrum antimicrobial treatment was used more often in diabetics than in nondiabetics when the total period of antimicrobial treatment was analyzed: 42% vs 28%, respectively (OR 1.83, $P = .008$). Other factors associated with use of broad-spectrum therapy at any time during the course of treatment in multivariate analysis were as follows: invasive surgery within the previous 3 months (OR 2.79, $P = .001$), admission to intensive care unit ([ICU] OR 2.65, $P = .001$),

Table 1. Background and Disease Characteristics of Complicated Skin and Skin Structure Infections Among Diabetics, Nondiabetics, and Patients With Diabetic Foot Infection (*N* = 460)[a]

Patient or Disease Characteristic	Patients With Diabetes (*n* = 119)	Patients Without Diabetes (*n* = 271)	Diabetics vs Nondiabetics		Diabetic Foot Infection (*n* = 70)	Diabetic Foot Infection vs Nondiabetics	
			OR (95% CI)	*P*[b]		OR (95% CI)	*P*[b]
Male gender	70 (59)	157 (58)	1.04 (0.67–1.61)	.870	53 (76)	2.26 (1.25–4.11)	.006
Age >60 years	93 (78)	149 (55)	2.93 (1.78–4.81)	<.001	58 (83)	3.96 (2.03–7.70)	<.001
HIV infection	3 (3)	4 (1)	1.73 (0.38–7.84)	.474	0 (0)	0.99 (0.97–1.00)	.307
Any disease with immune system impairment	3 (3)	10 (4)	0.68 (0.18–2.50)	.554	1 (1)	0.38 (0.05–3.01)	.340
Cancer/malignancy	10 (8)	22 (8)	1.04 (0.48–2.27)	.925	4 (6)	0.69 (0.23–2.06)	.499
Chronic renal failure	15 (13)	6 (2)	6.37 (2.41–16.9)	<.001	11 (16)	8.23 (2.93–23.2)	<.001
Congestive heart disease	10 (8)	25 (21)	0.90 (0.42–1.94)	.794	8 (11)	1.27 (0.55–2.95)	.578
Liver disease	4 (3)	16 (6)	0.55 (0.18–1.70)	.295	3 (4)	0.71 (0.20–2.52)	.599
Peripheral vascular disease	32 (27)	67 (25)	1.12 (0.69–1.83)	.651	36 (51)	3.22 (1.87–5.55)	<.001
Respiratory disease	16 (13)	17 (6)	2.32 (1.13–4.77)	.019	1 (1)	0.22 (0.03–1.66)	.106
Alcohol abuse	6 (5)	25 (21)	0.52 (0.21–1.31)	.160	9 (13)	1.45 (0.65–3.27)	.366
Injection drug abuse	1 (1)	29 (24)	0.07 (0.01–0.53)	.001	2 (3)	0.25 (0.06–1.06)	.042
Hospitalization within previous 3 months	30 (25)	50 (42)	1.49 (0.89–2.49)	.128	4 (6)	0.27 (0.09–0.77)	.009
Invasive surgery within previous 3 months	23 (19)	47 (17)	1.14 (0.66–1.99)	.638	1 (1)	0.07 (0.01–0.51)	.001
Treatment with antibiotics before diagnosis of cSSSI	25 (21)	72 (27)	0.74 (0.44–1.23)	.242	31 (44)	2.20 (1.28–3.78)	.004
Abscess	42 (35)	124 (46)	0.65 (0.41–1.01)	.054	17 (24)	0.38 (0.21–0.69)	.001
Cellulitis/fascitis	77 (65)	116 (43)	2.45 (1.57–3.83)	<.001	0 (0)	0.57 (0.52–0.63)	<.001
Postsurgical wound	29 (24)	48 (18)	1.50 (0.89–2.52)	.128	2 (3)	0.14 (0.03–0.58)	.002
Posttraumatic wound	10 (8)	37 (14)	0.58 (0.28–1.21)	.143	3 (4)	0.28 (0.09–0.95)	.030
Number of Days Between Symptoms Start and Diagnosis							
<2 days	50 (42)	74 (27)	1.93 (1.23–3.03)	.004	6 (9)	0.25 (0.10–0.60)	.001
2–7 days	53 (45)	139 (51)	0.76 (0.50–1.18)	.219	38 (54)	1.13 (0.67–1.91)	.655
>7 days	16 (13)	50 (18)	0.69 (0.37–1.26)	.225	24 (34)	2.31 (1.29–4.12)	.004
Unknown	0 (0)	8 (3)	0.97 (0.95–0.99)	.058	2 (3)	0.97 (0.20–4.66)	.967
Highest C-reactive protein level (*n* = 451, mean [SD])	240 (116)	222 (140)		.056[c]	192 (97)		.291[c]
Bacteremia	18 (15)	34 (13)	1.24 (0.67–2.30)	.490	9 (13)	1.03 (0.47–2.26)	.944
Septic shock	2 (2)	6 (5)	0.76 (0.15–3.80)	.732	0 (0)	0.98 (0.96–1.00)	.209
Admitted to ICU	15 (13)	52 (19)	0.61 (0.33–1.13)	.113	6 (9)	0.40 (0.16–0.96)	.035

Abbreviations: CI, confidence interval; cSSSI, complicated skin and skin structure infection; HIV, human immunodeficiency virus; ICU intensive care unit; OR, odds ratio; SD, standard deviation.

[a]Data are no. (%) of patients unless otherwise specified.

[b]Pearson's χ^2 test.

[c]Mann-Whitney *U* test.

bacteremia (OR 2.55, *P* = .002), and polymicrobial etiology of infection (OR 3.76, *P* < .001). In contrast, staphylococcal infection was found to be inversely associated with broad-spectrum therapy in multivariate analysis (OR 0.37, *P* = .001). Diabetes was the only background characteristic that was a risk factor for broad-spectrum therapy after PS-adjusted analysis (OR 1.75, *P* = .022). The initial bacterial pathogen was covered by the empirical antibiotic treatment in the vast majority of patients, and no significant difference was found between diabetics (81%) and nondiabetics (86%, *P* = .250). Gram-positive aerobic bacteria accounted for 70% and 69% of positive microbiological diagnoses, and methicillin-resistant *S aureus* (MRSA) was detected in only 2% and 1% of patients with diabetes and without diabetes, respectively. Antimicrobial treatment with an agent covering MRSA was uncommon in our study; however, it was used in 0.4% and 4% of patients in initial and subsequent antibiotic treatment, respectively.

Patients without diabetes stabilized faster than diabetics (mean 3.9 vs 4.1 days) (Table 4) and were more likely to have surgical intervention conducted after diagnosis of cSSSI (57% vs 44%; OR 1.31, *P* = .014). Total duration of antimicrobial treatment differed significantly between diabetics and nondiabetics: the median of treatment duration was 21 days among diabetics and 14 days among nondiabetics (Table 4). Factors associated with longer (≥17 days) antibiotic treatment in multivariate analysis were as follows: diabetes (OR 1.71, *P* = .014), admission

Table 2. Microbiological Diagnosis of Complicated Skin and Skin Structure Infections Among Diabetics, Nondiabetics, and Patients With Diabetic Foot Infection (*N* = 460)[a]

Microbiological Diagnosis	Patients With Diabetes (*n* = 119)	Patients Without Diabetes (*n* = 271)	Diabetics vs Nondiabetics		Diabetic Foot Infection (*n* = 70)	Diabetic Foot Infection vs Nondiabetics	
			OR (95% CI)	*P*[b]		OR (95% CI)	*P*[b]
Staphylococci	27 (23)	77 (28)	0.74 (0.45–1.22)	.239	9 (13)	0.37 (0.18–0.79)	.008
Methicillin-sensitive *Staphylococcus* aureus	26 (22)	75 (28)			8 (11)		
Methicillin-resistant *S aureus*	1 (1)	2 (1)			1 (1)		
Streptococci	27 (23)	67 (25)	0.89 (0.54–1.49)	.665	11 (16)	0.57 (0.28–1.14)	.110
Streptococcus pyogenes	8 (7)	46 (17)			0 (0)		
Streptococcus agalactiae	4 (3)	2 (1)			2 (3)		
β-hemolytic streptococci	14 (12)	8 (3)			9 (13)		
Streptococcus pneumoniae	1 (1)	2 (1)			0 (0)		
α-hemolytic streptococci	0 (0)	9 (3)			0 (0)		
Gram-negative bacteria	8 (7)	13 (5)	1.43 (0.58–3.55)	.438	9 (13)	2.93 (1.20–7.16)	.014
Enterobacteriacae	5 (4)	8 (3)			6 (9)		
Pseudomonas	3 (3)	2 (1)			0 (0)		
Other Gram-negative bacteria	0 (0)	3 (1)			3 (4)		
Other microorganism	3 (3)	10 (4)	0.68 (0.18–2.50)	.554	1 (1)	0.38 (0.05–3.01)	.340
Anaerobic bacteria	2 (2)	8 (3)			0 (0)		
Enterococci	1 (1)	2 (1)			1 (1)		
Polymicrobial infections	19 (16)	45 (17)	0.95 (0.53–1.71)	.875	22 (31)	2.30 (1.27–4.18)	.005
Only Gram-positive bacteria	4 (3)	19 (7)			8 (11)		
Only Gram-negative bacteria	0 (0)	1 (0)			2 (3)		
Mixed	15 (13)	25 (9)			12 (17)		
Negative/unknown	35 (29)	59 (22)	1.50 (0.92–2.44)	.104	18 (26)	1.24 (0.68–2.29)	.482

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Data are no. (%) of patients unless otherwise specified.

[b]Pearson's β^2 test.

to ICU (OR 2.96, $P < .001$), chronic renal failure (OR 2.85, $P = .024$), polymicrobial infection etiology (OR 2.27, $P = .003$), infection localized to lower extremity (OR 2.11, $P = .001$), and short (<2 days) duration of symptoms before diagnosis of cSSSI (OR 1.86, $P = .006$). Background characteristics that differed significantly in univariate analysis were included in the PS-adjusted analysis, in which only diabetes (OR 1.99, $P = .004$) was detected to be statistically significantly associated with longer (≥17 days) antimicrobial treatment duration. There was no difference in 30-day mortality, clinical failure rate,

Table 3. Initial Antimicrobial Agents in the Treatment of Complicated Skin and Skin Structure Infections Among Diabetics, Nondiabetics, and Patients With Diabetic Foot Infection (*N* = 458)[a]

Antimicrobial Agent	Patients With Diabetes (*n* = 118)	Patients Without Diabetes (*n* = 270)	Diabetics vs Nondiabetics		Diabetic Foot Infection (*n* = 70)	Diabetic Foot Infection vs Nondiabetics	
			OR (95% CI)	*P*[b]		OR (95% CI)	*P*[b]
Broad-spectrum[c]	26 (22)	39 (14)	1.67 (0.96–2.91)	.066	21 (30)	2.54 (1.37–4.69)	.002
Cephalosporins[d]	60 (51)	133 (49)	1.07 (0.69–1.64)	.773	31 (44)	0.82 (0.48–1.39)	.458
Other[e]	11 (9)	31 (11)	0.79 (0.38–1.64)	.529	2 (3)	0.23 (0.05–0.97)	.030
Penicillins[f]	12 (10)	29 (11)	0.94 (0.46–1.91)	.866	11 (16)	1.55 (0.73–3.28)	.250
Penicillins with staphylococcal effect[g]	9 (8)	38 (14)	0.50 (0.24–1.08)	.073	5 (7)	0.47 (0.18–1.24)	.120

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Data are no. (%) of patients unless otherwise specified.

[b]Pearson's χ^2 test.

[c]Carbapenem and piperacillin-tazobactam.

[d]Cefadroxil, cefotaxim, ceftriaxone, cefuroxime, and cephalexin.

[e]Clindamycin, doxycyclin, fluoroquinolone, fusidic acid, linezolid, metronidazole, cotrimoxazole, tobramycin, and vancomycin.

[f]Amoxicillin, benzylpenicillin, and phenoxymethylpenicillin.

[g]Cloxacillin, flucloxacillin, and other β-lactamase-stable penicillins.

Table 4. Clinical Outcomes and the Use of Resources of Complicated Skin and Skin Structure Infections Among Diabetics, Nondiabetics, and Patients With Diabetic Foot Infection[a]

Outcome	Patients With Diabetes	Patients Without Diabetes	Diabetics vs Nondiabetics		Diabetic Foot Infection	Diabetic Foot Infection vs Nondiabetics	
			OR (95% CI)	*P*		OR (95% CI)	*P*
Clinical failure due to cSSSI (*n* = 457)	31 (26)	56 (21)	1.33 (0.81–2.21)	.262[b]	19 (27)	1.41 (0.77–2.58)	.263[b]
Hospitalized again due to cSSSI (*n* = 439)	16 (13)	38 (14)	0.93 (0.50–1.75)	.825[b]	18 (26)	2.12 (1.12–4.02)	.020[b]
Mortality 30 days (*n* = 460)	6 (5)	11 (4)	1.26 (0.45–3.48)	.662[b]	2 (3)	0.70 (0.15–3.21)	.640[b]
Mortality 12 months (*n* = 451)	23 (19)	25 (9)	2.35 (1.27–4.34)	.005[b]	5 (7)	0.75 (0.28–2.04)	.571[b]
Time to clinical stability, days (*n* = 402, mean [SD])	4.1 (3.5)	3.9 (4.2)		.038[c]	4.1 (4.3)		.133[c]
Total duration of antibiotic treatment, days (*n* = 448, median [IQR25, IQR75])	21 (12–38)	14 (8–28)		<.001[c]	21 (10–40)		.005[c]
Number of different antibiotic therapy courses (*n* = 457, mean [SD])	3.6 (2.2)	3.3 (1.9)		.560[c]	3.8 (2.7)		.368[c]
Length of hospital stay, days (*n* = 416, median [IQR25, IQR75])	13 (6–21)	10 (5–20)		.090[c]	14 (8–26)		.006[c]
Number of clinics during hospital stay (*n* = 460, mean [SD])	1.7 (1.0)	1.5 (1.0)		.022[c]	1.9 (1.5)		.078[c]

Abbreviations: CI, confidence interval; cSSSI, complicated skin and skin structure infection; IQR, interquartile range; OR, odds ratio; SD, standard deviation.

[a]Data are no. (%) of patients unless otherwise specified.

[b]Pearson's χ^2 test.

[c]Mann-Whitney *U* test.

or rehospitalization rate between diabetics and nondiabetics (Table 4).

Patients with DFI were compared separately with nondiabetic patients, and they had staphylococcal infection less often and Gram-negative or polymicrobial infections more often than nondiabetics (Table 2). Accordingly, patients with DFI had broad-spectrum antimicrobial as initial therapy more often than patients without diabetes (Table 3). The median duration of antimicrobial treatment and hospital stay was longer among patients with DFI than nondiabetics, 21 vs 14 days and 14 vs 10 days, respectively (Table 4). However, patients with DFI had more recurrences than nondiabetics: 26% of patients with DFI and 14% of patients without diabetes were hospitalized again due to cSSSI (Table 4).

DISCUSSION

In our population-based study, a statistically significant difference was not detected between nondiabetics and diabetics without DFI in the microbiological etiology of cSSSI. However, compared with nondiabetics, diabetics without DFI were treated more often with broad-spectrum antimicrobial therapy, and their antimicrobial treatment also continued for a longer time period.

Diabetics constituted 37% of our patient population and 35% of patients hospitalized due to cSSSI in an American study, indicating that diabetes is clearly one of the main risk factors for cSSSI [7]. Diabetic patients have differed from nondiabetics in many aspects both in our cSSSI population and previous studies with less severe SSSI [13, 15–17]. Diabetics have been older, more likely to have infection classified as cellulitis or infection localized into a lower extremity, and had chronic renal failure more often but less injection drug abuse [13, 15–17]. However, in our study, no statistically significant differences were detected between diabetics and nondiabetics in the objective markers of disease severity (C-reactive protein [CRP] level or rate of bacteremia, septic shock, or admission to ICU). It is possible that diabetic patients had been educated to seek treatment earlier or had easier access to their primary care physician and were also send more often to hospital evaluation than nondiabetics.

More importantly, statistically significant differences in the microbiological etiology between diabetics and nondiabetics were not found in cSSSI in our study nor in SSSI in the study by Jenkins et al [13]. In our study, Gram-positive aerobic bacteria accounted for the vast majority of microbiological diagnosis (diabetics 70% and nondiabetics 69%), which is consistent with the study by Jenkins et al [13] and also to other studies in patients with cSSSI [7, 8, 18, 19]. In light of this finding, the observation of more frequent use of broad-spectrum antibiotics among diabetics in our study and in the study by Jenkins et al [13] is remarkable. More frequent broad-spectrum use was not observed in either study in the empirical antibiotic choice, but the antibiotics were changed to broad-spectrum more often among diabetics than in nondiabetics. We found that diabetics have later treatment response than nondiabetics, which can also explain why diabetics had their antibiotic treatment escalated to broad-spectrum therapy more often than nondiabetics. Many

newer broad-spectrum antibiotics are officially indicated for the treatment of cSSSI, and these are actively studied and marketed [16]. The extent to which this might have affected the treatment choices in our study cannot be answered.

Our results in cSSSI and those of Jenkins et al [13] in SSSI support the current treatment recommendations. In the treatment of cellulitis or an abscess, IDSA guidelines recommend antimicrobial treatment that covers staphylococci and streptococci, irrespective of the presence of diabetes. Broad-spectrum empirical antimicrobial therapy is only recommended for the most severe forms of SSSI (Figure 1) [12]. Our findings suggests that empirical broad-spectrum therapy could also be streamlined to narrow-spectrum therapy in cSSSI in diabetics, although it has been noticed that streamlining rarely happens in real life [8, 14].

The third main observation of this study also correlates with the results by Jenkins et al [13] that antimicrobial treatment lasts longer in diabetics than in nondiabetics. In our study, the median total duration of antimicrobial treatment was 21 days in diabetics and 14 days in nondiabetics, compared to 13 and 12 days detected by Jenkins et al [13], respectively. Because the severity of infection was not similar in these studies, the total treatment durations cannot be compared between them. The slightly longer time (0.2 days) to clinical stability among diabetics might partially explain the longer antibiotic treatment. However, no difference was not found in the length of hospital stay between diabetics and nondiabetics. This means that the difference in the duration of antimicrobial treatment mainly reflects antibiotics prescribed at the time of discharge from hospital. In comparison with nondiabetics, diabetics were more often transferred between departments during their hospital stay, a factor that may also have an impact on their longer duration of antimicrobial treatment.

Diabetic foot infection comprised only 15% of our patients. Diabetic foot infection was separated from other cSSSIs among diabetics in the analyses, and DFI seems to differ substantially from cSSSI among nondiabetics. Patients with DFI had less staphylococci and more Gram-negative or polymicrobial infections than nondiabetics with cSSSI, and their treatment was started more often with a broad-spectrum antibiotic. Moreover, our data support the IDSA guidelines, which recommend the use of broad-spectrum antibiotic in empirical therapy only in moderate-to-severe DFI (Figure 1) [11]. Our patients with DFI would be classified as severe because signs of systemic infection were required. In addition, patients with DFI had more recurrences, longer median time of hospital stay, and longer total antimicrobial treatment duration than nondiabetics. The definition of DFI in our study can be questioned, yet the classification of infection was made by 2 experienced clinicians who collected the data and ended up with similar proportions of DFI between the study centers (Helsinki, 32 of 219; Gothenburg, 37 of 241). Minority of infections in the lower extremities of diabetics were classified as DFI in our study. In theory, the inclusion criteria of our study may have allowed patients with diabetes (or peripheral arterial disease) with less severe infections of lower extremities to be included; however, no statistically significant difference

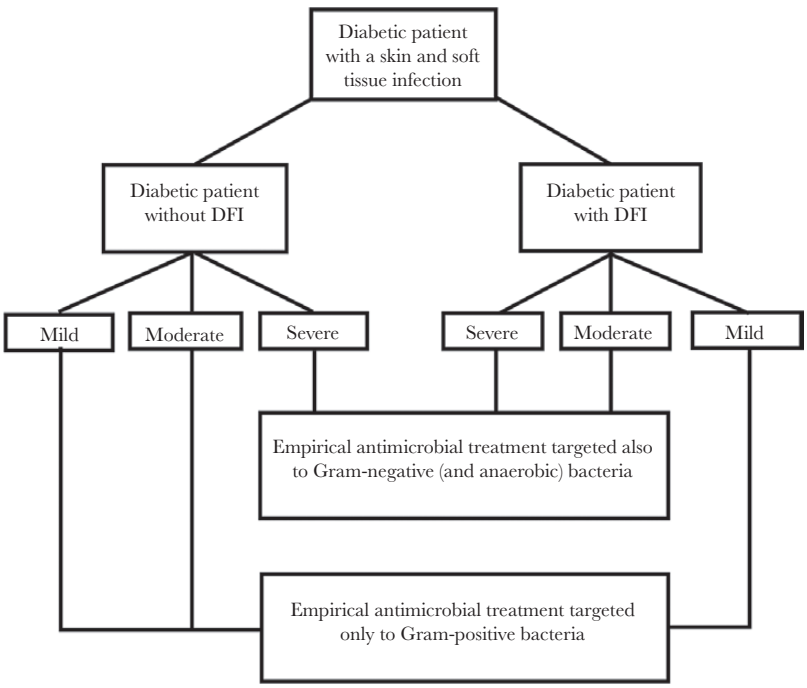

Figure 1. Suggested algorithm for empirical treatment of a skin and soft tissue infection in diabetic patients. Modified from Infectious Diseases Society of America guidelines [11, 12] and supported by our study data. DFI, diabetic foot infection.

was detected in the level of highest CRP value between patients with DFI and nondiabetics with cSSSI. On the basis of above facts, it can be stated that the patients with DFI in our study shared similarities with the DFI patients in general [10, 20–22] and, on the other hand, differed from the diabetics without DFI in our study.

The high affinity of people to public healthcare in Nordic countries enabled the population-based approach used in this study. We also considered the low prevalence of MRSA in Nordic countries (2011: 2.8% in Finland and 0.8% in Sweden) to be a strength of the study by eliminating 1 possible confounding factor [23, 24]. The data were collected in 2 countries, which makes it more generalizable. The weaknesses of our retrospective study included its complete dependence on clinical patient records, which were not initially made for research purposes, and lack of evaluation of glycemic control. Furthermore, microbiological diagnosis was mainly based on superficial swabs, which may also detect bacterial colonization in addition to causative microbiological agents. It is possible that this did not lead to bias in intergroup analyses; however, prospective studies with invasive microbiological sampling in diabetics with cSSSI are needed. Furthermore, patients with severe conditions, compared with patients with an optimistic prognosis, were probably more likely receive broad-spectrum antimicrobial treatment. This phenomena of "confounding by indication" is a further source for bias in our retrospective cohort analyses [25]. Propensity score-adjusted analyses may reduce the potential bias associated with retrospective analyses [26]. The main results of the present study were observed in PS-adjusted analysis, correcting for significant differences between diabetics and nondiabetics.

CONCLUSIONS

In conclusion, after exclusion of patients with diabetic foot infection, no statistically significant differences in the microbiological etiology of cSSSI were found between diabetics and nondiabetics. However, diabetics were treated significantly more often than nondiabetics with broad-spectrum antibiotics covering Gram-negative and anaerobic bacteria, and their antibiotic treatment lasted longer than the treatment for patients without diabetes. These observations offer a clear opportunity for antimicrobial stewardship in the vulnerable, ever-growing population of diabetic patients.

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