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ARTICLE

Skin and soft tissue infections in hospitalised patients with diabetes: culture isolates and risk factors associated with mortality, length of stay and cost

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Abstract
Aims/hypothesis Skin and soft tissue infections (SSTIs) cause substantial morbidity in persons with diabetes. There are few data on pathogens or risk factors associated with important outcomes in diabetic patients hospitalised with SSTIs.
Methods Using a clinical research database from CareFusion, we identified 3,030 hospitalised diabetic patients with positive culture isolates and a diagnosis of SSTI in 97 US hospitals between 2003 and 2007. We classified the culture isolates and analysed their association with the anatomic location of infection, mortality, length of stay and hospital costs.
Results The only culture isolate with a significantly increased prevalence was methicillin-resistant *Staphylococcus aureus* (MRSA); prevalence for infection of the foot was increased from 11.6 to 21.9% ($p<0.0001$) and for non-foot locations from 14.0% to 24.6% ($p=0.006$). Patients with non-foot (vs foot) infections were more severely ill at presentation and had higher mortality rates (2.2% vs 1.0%, $p<0.05$). Significant independent risk factors associated with higher mortality rates included having a polymicrobial culture with *Pseudomonas aeruginosa* (OR 3.1), a monomicrobial culture with other gram-negatives (OR 8.9), greater illness severity (OR 1.9) and being transferred from another hospital (OR 5.1). These factors and need for major surgery were also independently associated with longer length of stay and higher costs.
Conclusions/interpretation Among diabetic patients hospitalised with SSTI from 2003 to 2007, only MRSA increased in prevalence. Patients with non-foot (vs foot) infections were more severely ill. Independent risk factors for increased mortality rates, length of stay and costs included more severe illness, transfer from another hospital and wound cultures with *Pseudomonas* or other gram-negatives.

Keywords Diabetes · Foot infections · Hospitalised patients · Length of stay · Mortality · MRSA · Skin and soft tissue infection

Abbreviations

MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
SSTI	Skin and soft tissue infection

Introduction

Skin and soft tissue infections (SSTIs) are leading causes of morbidity and occasionally mortality in persons with

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diabetes mellitus [1–4]. Various complications of diabetes (e.g. sensory neuropathy, vascular insufficiency, immunopathy and metabolic perturbations) can predispose these patients to infections [5, 6]. SSTIs are more common and more severe in diabetic than in non-diabetic patients and constitute a leading cause of hospitalisation [7]. The risk of SSTI-related hospitalisation is more than twice as high in diabetic than in non-diabetic patients [8]. Diabetes is independently associated with increased emergency department visits for SSTIs [9], longer hospital stays [8] and infection-attributable death [10, 11]. The rising prevalence of diabetes [7, 12] is likely to cause increasing numbers of diabetes-related SSTIs in hospitalised patients.

SSTIs occur at all anatomic sites, but the foot is most frequently affected in diabetic patients [7]. In the USA, about 111,000 persons with diabetes are hospitalised annually with foot infections and these precede and contribute to almost 60% of all lower extremity amputations [13]. *Staphylococcus aureus* is the most commonly isolated pathogen in SSTIs, both in ambulatory and hospitalised patients [14–16]. Antimicrobial-resistant pathogens, especially methicillin-resistant *S. aureus* (MRSA), are increasingly isolated in nosocomial infections [17–20]. Several recent reports identified MRSA as the leading pathogen in SSTIs [21–24]; it also causes 20% to 50% of diabetes-associated foot infections in several countries and is associated with worse outcomes than other pathogens [23–29].

The few published multi-centre studies characterising SSTI pathogens have been limited to specific types of organisms [30], with almost all reports on SSTIs in diabetic patients limited to foot infections [31–33]. Few studies have addressed the interaction of specific pathogens with various clinical and economic outcomes [34]. To understand the current characteristics of these common and potentially severe infections better, we investigated the epidemiology and microbiology of wounds diagnosed as SSTI of all anatomic sites in hospitalised diabetic patients. We also assessed the association of infection at various anatomic locations with the organisms isolated from wound cultures, clinical outcomes and hospital costs.

Methods

Data source Data for this study were from one of the clinical research databases of CareFusion (CareFusion Clinical Research Services, Marlborough, MA, USA), which has been used for research for over two decades and been fully described elsewhere [35–39]. Briefly, the database captures selected clinical (e.g. vital signs), laboratory (chemistry, haematology and culture) and administrative (patient demographics, diagnoses, duration of hospitalisation, discharge status, total charges) data. The data for this study were derived from a dataset with all patient-specific information anonymised. It was conducted in compliance with US federal regulations, the Health Insurance Portability and Accountability Act (HIPAA) and the Helsinki Declaration.

Study population We reviewed data on patients admitted to 97 selected hospitals primarily located in the Northeast region of the United States between January 2003 and June 2007 to identify those with a principal diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]) of diabetes and a secondary diagnosis indicating any type of SSTI (including cellulitis, infected ulcer or surgical site infection) involving the foot or any other anatomic site. Included patients had to have a positive result from a culture of an infected skin or soft tissue site (many of which were open wounds) taken within 48 h of hospitalisation.

Definition and classification of type of infection Based on their secondary diagnoses and the culture specimen site, we classified each eligible patient as having: cellulitis, an infected skin ulcer or a surgical site infection. We further identified infections as affecting the foot or another (non-foot) site, classifying infections that involved both sites in the foot group.

Definition and classification of isolated organism(s) Based on wound culture results, we classified patients by the number of isolates (monomicrobial or polymicrobial) and by the specific organism(s) isolated. Because of the implications for selecting appropriate antibiotic therapy for infections caused by MRSA and *Pseudomonas aeruginosa*, we hierarchically classified polymicrobial cultures into one of three mutually exclusive categories: (1) MRSA polymicrobial (MRSA + any other organism); (2) *Pseudomonas* polymicrobial (*P. aeruginosa* + any non-MRSA organism); or (3) other polymicrobial (caused by two or more organisms other than MRSA or *P. aeruginosa*).

Outcome measures For each patient we recorded any in-hospital mortality, length of stay in the hospital and the total costs for the index hospitalisation. We estimated the hospitalisation costs from billed total charges and calculated the hospital-specific cost/charge ratio for each pertinent calendar year using data obtained from the Centers for Medicare and Medicaid Services [40].

Statistical analysis After categorising the micro-organisms isolated from each wound, we analysed the incidence of all isolates over the study period, as well as the types of pathogens found in infections of the foot compared with

non-foot sites. We determined the crude mortality rate, length of stay and hospitalisation costs for infections associated with each organism. We performed statistical analyses in SAS (version 9.01; SAS Institute, Cary, NC, USA) using Fisher's exact test for dichotomous variables due to low mortality events, Wilcoxon non-parametric test for continuous variables and the Cochran–Armitage statistic for trending analysis.

We categorised admission illness severity using an aggregated score, which was generated from the CareFusion multivariable mortality predictive models and adjusts for demographics, physiological presentation and co-morbidities [39]. We also captured other variables that might have had potentially confounding effects on clinical presentation or economic burden, including source of admission (e.g. transfer from another acute care hospital or a skilled nursing facility), any hospitalisation within the previous 30 days or need for a major surgical procedure (i.e. involving spinal or general anaesthesia) at the index hospitalisation. We then conducted forward stepwise logistic regression analyses for mortality and general linear models for log-transformed length of stay and cost to determine the independent contributions of each isolated organism. For the length of stay and cost outcomes, the distributions of which tended to be skewed, we used a log scale. We re-transformed the adjusted log scale length of stay and cost to the natural units of days and US dollars, using the Smearing estimate for correction of bias [41]. We used the median from 1,000 bootstrap reiterations as the retransformed estimate for the attributable length of stay and cost with the 2.5th and 97.5th percentiles for the 95% CI estimates [42].

Results

Baseline patient characteristics A total of 3,030 patients met our inclusion criteria. Since the number with surgical site infections was relatively small (n=114) and the anatomic locations were not available, we lumped these patients into the non-foot infection group, with whom their clinical severity and outcomes were compatible, for aggregated descriptive analyses. The median age (and interquartile range) was similar for patients with a foot infection and a non-foot infection (p=0.50; Table 1). Compared with those with a foot infection, patients in the non-foot infection group were significantly less likely to be male (54.6% vs 64.0%, p<0.0001) and significantly more likely to have had a previous admission at the same hospital within the prior 30 days (11.2% vs 8.7%, p<0.05) or to have come from a skilled nursing facility (5.3% vs 2.8%, p<0.05). They were also more likely to have had a physiological derangement on admission, including hypoglycaemia (7.0% vs 3.5%, p<0.001) and brady- or tachycardia (10.5% vs 3.0%, p<0.0001), as well as altered mental status (12.5% vs 6.3%, p<0.0001), hypoalbuminaemia (30.3% vs 22.0%, p<0.001) and elevated bands on the leucocyte differential (22.3% vs 13.1%, p<0.01). A total of 84% of patients had at least one comorbidity. Those that differed significantly for non-foot compared with foot infection patients were those with: congestive heart failure (27.0% vs 21.4%, p<0.01); chronic lung disease (13.2% vs 10.0%, p<0.05); chronic renal failure (23.1% vs 18.8%, p< 0.05); and a history of amputation (22.0% vs 29%, p<0.001). The highest quartile of aggregated clinical severity contained more patients with non-foot infection than with foot infection (29.5% vs 23.3%, p<0.01).

Pathogens isolated Wound cultures revealed polymicrobial isolates in 53.0% of non-foot and in 58.7% of foot lesions (Table 2). Compared with lesions diagnosed as foot infections, non-foot infections were more likely to have MRSA (9.6% vs 7.4%, p=0.06) or methicillin-susceptible *S. aureus* (MSSA; 16.4% vs 13.2%, p<0.05), but less likely to have isolates of *Streptococcus* spp (4.3% vs 7.2%, p< 0.01) or polymicrobial isolates without MRSA or *P. aeruginosa* (33.7% vs 41.8%, p<0.001).

Over the study period, the proportion of isolates of MRSA increased for non-foot (from 14.0% to 24.6%, p= 0.006 for trend) and foot (from 11.6% to 21.9%, p<0.0001 for trend) sites (Fig. 1). Both monomicrobial and polymicrobial MRSA wound isolates increased significantly, while those with MSSA did not. In addition, the proportion of polymicrobial isolates not involving MRSA or *P. aeruginosa* significantly declined (from 46.4% to 31.7%, p<0.0001 for trend). There were no significant changes in proportion of isolates of any other pathogens.

Mortality, length of stay and cost outcomes in univariate analyses Overall, 41 (1.4%) of the patients in the study population died during hospitalisation (Table 3). Factors significantly associated with increased mortality rate were: severity of illness on admission (p<0.0001); type of infection (cellulitis vs ulcer vs surgical site, p<0.001); and non-foot location (p<0.05). Wounds with polymicrobial isolates that included *P. aeruginosa* and monomicrobial cultures with other (i.e. non-*Pseudomonas*) gram-negatives were each associated with significantly increased mortality rates (p<0.01 and p<0.001, respectively). Factors significantly associated with greater length of stay and higher costs were: increased severity of illness; having been transferred from another acute care hospital or skilled nursing facility; or culture results showing monomicrobial other gram-negative or *P. aeruginosa*, or polymicrobial MRSA.

Independent risk factors for mortality, length of stay and cost in multivariable analyses In multivariable logistic

Table 1 Baseline characteristics of diabetic patients hospitalised for skin and skin structure infections

Variable	Type of infection						
	Cellulitis		Ulcer/other			Overall	
	Foot	Non-foot	Foot	Non-foot	SSI[a]	Foot	Non-foot or SSI[a]
n	1,828	597	392	99	114	2,220	810
Demographics							
Age (years)[b]	60 (50–70)	59 (48–71)	59 (50–72)	64 (47–78)	63 (54–74)	60 (50–70)	61 (49–72)
Death during hospitalisation	16 (0.9)	7 (1.2)	7 (1.8)	4 (4.0)	7 (6.1)	23 (1.0)	18 (2.2) *
Male sex	1,166 (63.8)	328 (54.9)***	254 (64.8)	47 (47.5)**	67 (58.8)	1,420 (64.0)	442 (54.6)****
Hospitalisation and transfer status							
Prior admission to same hospital[c]	143 (7.8)	47 (7.9)	50 (12.8)	22 (22.2)*	22 (19.3)	193 (8.7)	91 (11.2)*
Transfer from other acute-care hospital	13 (0.7)	3 (0.5)	8 (2.0)	1 (1.0)	2 (1.8)	21 (0.9)	6 (0.7)
Transfer from skilled nursing facility	42 (2.3)	19 (3.2)	20 (5.1)	13 (13.1)	11 (9.6)	62 (2.8)	43 (5.3)**
Acute clinical presentation[d]							
Systolic BP <100 mmHg	191 (10.4)	99 (16.6)***	72 (18.4)	26 (26.3)	18 (15.8)	263 (11.8)	143 (17.7)****
Temperature <35.6 or ≥38.0°C	474 (25.9)	154 (25.8)	202 (51.5)	49 (49.5)	46 (40.4)	676 (30.5)	249 (30.7)
Pulse <49 or >125 beats/min	57 (3.1)	61 (10.2)****	26 (6.6)	14 (14.1)*	10 (8.8)	83 (3.7)	85 (10.5)****
Respiration <10 or >29 breaths/min	44 (2.4)	43 (7.2)****	23 (5.9)	5 (5.1)	7 (6.1)	67 (3.0)	55 (6.8)****
Altered mental status	85 (4.6)	50 (8.4)***	54 (13.8)	29 (29.3)***	22 (19.3)	139 (6.3)	101 (12.5)****
Laboratory results							
Albumin ≤27 g/l	151 (19.4)	81 (26.1)*	58 (33.5)	25 (44.6)	19 (41.3)	209 (22)	125 (30.3)**
Blood urea nitrogen >14.3 mmol/l	285 (16.5)	98 (17.6)	82 (22.2)	32 (33.7)*	25 (23.2)	367 (17.5)	155 (20.4)
Creatinine >228.8 μmol/l	118 (6.9)	41 (7.4)	53 (14.4)	10 (10.5)	22 (20.4)	171 (8.2)	73 (9.6)
Sodium ≥146 mmol/l	10 (0.6)	4 (0.7)	8 (2.2)	10 (10.5)***	3 (2.8)	18 (0.9)	17 (2.2)**
Total bilirubin >13.7 μmol/l	152 (20.2)	72 (23.8)	45 (27.4)	13 (23.2)	14 (34.2)	197 (21.5)	99 (24.8)
O_2 pressure /saturation[e]	6 (19.4)	17 (32.7)	6 (26.1)	8 (53.3)	4 (26.7)	12 (22.2)	29 (35.4)
PT INR >1.2 or PT >14 s	140 (17.7)	43 (16.9)	55 (27.8)	13 (27.1)	19 (29.7)	195 (19.7)	75 (20.5)
Leucocyte differential >0.13 bands	51 (14.5)	31 (21.8)	13 (9.4)	9 (28.1)**	6 (18.8)	64 (13.1)	46 (22.3)**
White cell count ≥11×10^9/l	790 (45.6)	247 (43.6)	272 (72.9)	60 (62.5)	70 (66.7)	1,062 (50.5)	377 (49.2)
Physiological derangements ≥1[f]	1,082 (59.2)	360 (60.3)	324 (82.7)	83 (83.8)	86 (75.4)	1,406 (63.3)	529 (65.3)
Glucose on admission (mmol/l)							
≤3.9	54 (3.0)	37 (6.2)**	24 (6.1)	8 (8.1)	12 (10.5)	78 (3.5)	57 (7.0)***
3.94–7.5	288 (15.8)	93 (15.6)	51 (13.0)	9 (9.1)	18 (15.8)	339 (15.3)	120 (14.8)
7.55–13.3	596 (32.6)	169 (28.3)	124 (31.7)	26 (26.3)	41 (36)	720 (32.4)	236 (29.1)
>13.3	890 (48.7)	298 (49.9)	193 (49.2)	56 (56.6)	43 (37.7)	1,083 (48.8)	397 (49.0)
Co-morbidities							
Congestive heart failure	381 (20.8)	152 (25.5)*	95 (24.2)	34 (34.3)	33 (28.9)	476 (21.4)	219 (27.0)**
History MCI	155 (8.5)	42 (7.0)	39 (9.9)	5 (5.1)	16 (14.0)	194 (8.7)	63 (7.8)
Prior coronary artery intervention	350 (19.1)	110 (18.4)	90 (23.0)	10 (10.1)**	32 (28.1)	440 (19.8)	152 (18.8)
Immunosuppressive medication	51 (2.8)	22 (3.7)	22 (5.6)	7 (7.1)	5 (4.4)	73 (3.3)	34 (4.2)
Cancer	33 (1.8)	8 (1.3)	12 (3.1)	3 (3.0)	2 (1.8)	45 (2.0)	13 (1.6)
Peripheral vascular disease	633 (34.6)	181 (30.3)	189 (48.2)	38 (38.4)	62 (54.4)	822 (37.0)	281 (34.7)
Chronic liver disease	21 (1.1)	8 (1.3)	9 (2.3)	2 (2.0)	0 (0.0)	30 (1.4)	10 (1.2)
Chronic lung disease	170 (9.3)	81 (13.6)**	53 (13.5)	11 (11.1)	15 (13.2)	223 (10.0)	107 (13.2)*
Previous stroke	170 (9.3)	62 (10.4)	48 (12.2)	14 (14.1)	16 (14.0)	218 (9.8)	92 (11.4)
Chronic renal disease	325 (17.8)	120 (20.1)	93 (23.7)	25 (25.3)	42 (36.8)	418 (18.8)	187 (23.1)*

Table 1 (continued)

Variable	Type of infection						
	Cellulitis		Ulcer/other			Overall	
	Foot	Non-foot	Foot	Non-foot	SSI[a]	Foot	Non-foot or SSI[a]
History of amputation	526 (28.8)	98 (16.4)****	120 (30.6)	22 (22.2)	58 (50.9)	646 (29.1)	178 (22.0)****
At least one comorbidity	1,510 (82.6)	485 (81.2)	349 (89.0)	85 (85.9)	109 (95.6)	1,859 (83.7)	679 (83.8)
Admission illness severity[g]							
1st quartile	513 (28.1)	163 (27.3)	55 (14.0)	12 (12.1)	15 (13.2)	568 (25.6)	190 (23.5)**
2nd quartile	506 (27.7)	143 (24.0)	77 (19.6)	15 (15.2)	17 (14.9)	583 (26.3)	175 (21.6)
3rd quartile	450 (24.6)	153 (25.6)	101 (25.8)	24 (24.2)	29 (25.4)	551 (24.8)	206 (25.4)
4th quartile	359 (19.6)	138 (23.1)	159 (40.6)	48 (48.5)	53 (46.5)	518 (23.3)	239 (29.5)

Data are shown as *n* (%) unless otherwise specified. For laboratory data, % means % of those with respective laboratory variable measured

[a] SSI, surgical site infection at any anatomic location; [b] median interquartile range (IQR); [c] 30 or fewer days previously; [d] vital signs and altered mental status; [e] partial O_2 pressure <55 or >140 mmHg or O_2 saturation <90%; [f] excluding glucose

[g] Severity was calculated as predicted probability of death on admission based on a multivariable logistic regression model including age, physiological and comorbidity variables listed in this table. For glucose and admission severity, *p* values represent an overall multilevel χ^2 test. For all other dichotomous variables, *p* value represents a pair-wise χ^2 test

For all variables, significance tests were conducted between those with a foot vs those with a non-foot infection, *$p<0.05$, **$p<0.01$, ***$p<0.001$ and ****$p<0.0001$

MCI, myocardial infarction; PT, prothrombin time; PT INR, prothrombin time/international normalised ratio

analyses the significant independent predictors for in-hospital mortality were: increased illness severity; transfer from another acute care hospital; surgical site infection; and cultures yielding other gram-negative or polymicrobial *P. aeruginosa* (Table 4). Factors independently associated with greater length of stay and higher costs were: polymicrobial cultures including *P. aeruginosa* or mono-microbial infection with other gram-negative; greater illness severity; transfer from another hospital; and need for major surgery. The incremental length of stay and costs for polymicrobial *P. aeruginosa* were 1.2 days (95% CI 0.4–1.9) and US$2,403 (95% CI $1,068–3,822); for other gram-negatives, they were 2.2 days (95% CI 0.8–3.9) and $3,256 (95% CI $1,076–5,770). Interestingly, after adjusting for illness severity and other confounders, the differences in mortality rates, length of stay or cost between patients who had a foot infection and those with a non-foot infection were not statistically significant.

Discussion

This analysis of data from a large group of hospitalised diabetic patients with a clinical diagnosis of SSTI and a positive culture from a soft tissue sample enabled us to make several important observations. As expected, the foot was the most frequently involved site, but over a quarter of the diagnosed infections involved other anatomic sites. This is noteworthy because most publications on soft tissue infections in persons with diabetes deal only with foot infections. While we found many similarities between patients diagnosed with an infection of the foot vs another site, there were some significant differences.

As noted in other studies [5, 13], almost two-thirds of our patients with a foot infection were men, but men comprised just over one-half of the patients with non-foot infections. However, patients with a non-foot infection were more likely to have been recently hospitalised or to be residing in a skilled nursing facility, and were more severely ill on admission with higher rates of various physiological derangements. This latter finding may be explained by the fact that, due to concern about risk of lower extremity amputation, patients may be hospitalised with lesser severity foot than non-foot infections. Alternatively, while foot infections are generally a consequence of complications caused by peripheral neuropathy, infection at a non-foot site may be more likely to occur in a patient with impaired immunity or co-morbidities. This possibility is supported by the fact that more patients with a non-foot infection had a history of congestive heart failure, chronic lung disease and chronic renal disease.

Cultures of SSTI showed that staphylococci were the most frequent causative isolates. While MSSA was the most common isolate, 8% of patients had MRSA. Only the prevalence of MRSA isolates increased significantly in patients with a positive culture during the study period, this

Table 2 Microbial isolates from SSTI sites in hospitalised diabetic patients

Variable	Type of infection						
	Cellulitis		Ulcer/other infection			Overall	
	Foot	Non-foot	Foot	Non-foot	SSI[a]	Foot	Non-foot or SSI[a]
Patients (*n*)	1,828	597	392	99	114	2,220	810
Monomicrobial, gram-positive[b]							
MSSA	259 (14.2)	114 (19.1)**	35 (8.9)	8 (8.1)	11 (9.6)	294 (13.2)	133 (16.4)*
MRSA	139 (7.6)	54 (9.0)	26 (6.6)	11 (11.1)	13 (11.4)	165 (7.4)	78 (9.6)
CoN[c] staphylococci	112 (6.1)	40 (6.7)	11 (2.8)	5 (5.1)	3 (2.6)	123 (5.5)	48 (5.9)
Streptococcus spp.	137 (7.5)	27 (4.5)*	23 (5.9)	4 (4.0)	4 (3.5)	160 (7.2)	35 (4.3)**
Enterococcus spp.	37 (2.0)	14 (2.3)	9 (2.3)	0 (0.0)	4 (3.5)	46 (2.1)	18 (2.2)
Other gram-positive	6 (0.3)	5 (0.8)	1 (0.3)	0 (0.0)	0 (0.0)	7 (0.3)	5 (0.6)
Monomicrobial, gram-negative[b]							
Enterobacter	7 (0.4)	2 (0.3)	2 (0.5)	1 (1.0)	1 (0.9)	9 (0.4)	4 (0.5)
P. aeruginosa	22 (1.2)	11 (1.8)	8 (2.0)	1 (1.0)	4 (3.5)	30 (1.4)	16 (2.0)
Other gram-negative	53 (2.9)	21 (3.5)	12 (3.1)	4 (4.0)	5 (4.4)	65 (2.9)	30 (3.7)
Anaerobic bacteria	10 (0.5)	4 (0.7)	1 (0.3)	0 (0.0)	1 (0.9)	11 (0.5)	5 (0.6)
Fungi	6 (0.3)	5 (0.8)	1 (0.3)	1 (1.0)	3 (2.6)	7 (0.3)	9 (1.1)*
Polymicrobial[d]							
Including MRSA	146 (8.0)	57 (9.5)	43 (11.0)	10 (10.1)	9 (7.9)	189 (8.5)	76 (9.4)
With *Pseudomonas* (no MRSA)	145 (7.9)	52 (8.7)	42 (10.7)	13 (13.1)	15 (13.2)	187 (8.4)	80 (9.9)
No MRSA or *Pseudomonas*	749 (41.0)	191 (32.0)****	178 (45.4)	41 (41.4)	41 (36.0)	927 (41.8)	273 (33.7)****
MRSA (mono or poly)	285 (15.6)	111 (18.6)	69 (17.6)	21 (21.2)	22 (19.3)	354 (15.9)	154 (19.0)*

[a] SSI, surgical site infection at any anatomic location; [b] monomicrobial, i.e. only one microbial isolate found on culture; [c] CoN, coagulase-negative; [d] polymicrobial, i.e. two or more microbial isolates found on culture

*$p<0.05$, **$p<0.01$, ***$p<0.001$ and ****$p<0.0001$

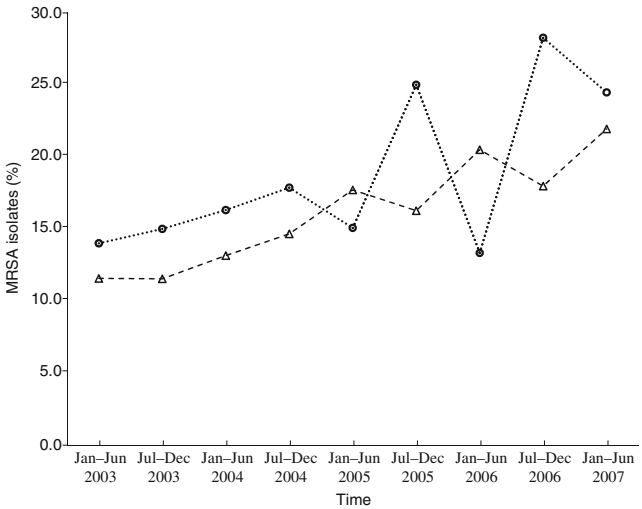

Fig. 1 Percentage of MRSA isolates in monomicrobial or polymicrobial cultures from infections involving the foot vs non-foot (or surgical) sites in hospitalised persons with diabetes during the study period. Dotted line, percentage of admissions with MRSA isolates vs total number of admissions in non-foot (or surgical) site infections group; $p<0.01$ Cochran–Armitage trending test. Dashed line, percentage with MRSA isolates as above, but for foot infections group; $p<0.0001$ Cochran–Armitage trending test

increase being seen for both foot and non-foot infections. Cultures also yielded a variety of aerobic gram-negative isolates, albeit in a relatively small number of cases. The low rate of isolation of obligate anaerobes (0.5%) is compatible with findings in other studies of SSTIs [43], but may also reflect the fact that in non-study situations clinicians often submit suboptimal specimens for anaerobic culture. As expected in these diabetic patients, foot wounds usually had polymicrobial cultures, but over half of non-foot SSTIs were also polymicrobial. About 9% of all polymicrobial cultures included either MRSA or *P. aeruginosa*, organisms that usually require specifically targeted antibiotic therapy, rather than the usually selected empirical regimens.

We identified significant independent risk factors for mortality, including increased severity of illness on admission and having an infection other than cellulitis. A non-foot location of diagnosed infection was associated with greater illness severity than foot infections, but was not an independent predictor of outcomes in multivariable analysis, probably because of various confounding associations. Factors significantly associated with greater hospital length of stay and costs included higher severity of illness or being

Table 3 Relationship of variables to mortality rates, length of stay and hospital cost in univariate analysis

Variable	*n*	Mortality, *n* (%)	Length of stay in days, mean (SD)	Cost per US$, mean (SD)
All patients	3,030	41 (1.4)	8.4 (7.9)	12,065 (18,879)
Live discharge	2,989		8.3 (7.7)****	11,823 (18,479)**
Death during hospitalisation	41		14.2 (14.6)	29,711 (34,005)
Admission illness severity				
Severity 1st quartile	758	0 (0.0)****	5.7 (4.6)****	7,231 (8,020)****
Severity 2nd quartile	758	5 (0.7)	7.0 (5.4)	9,388 (10,159)
Severity 3rd quartile	757	11 (1.5)	9.0 (7.3)	12,591 (13,637)
Severity 4th quartile	757	25 (3.3)	11.9 (11.1)	19,049 (31,507)
Hospitalisation and transfer status				
Prior admission ≤30 days previously	284	5 (1.8)	8.9 (7.4)*	12,729 (12,322)*
Transferred from acute-care hospital	27	2 (7.4)	12.4 (11.0)***	20,922 (21,988)**
Transferred from skilled nursing facility	105	4 (3.8)	11.1 (8.4)***	14,663 (11,559)****
Type of infection				
Cellulitis	2,425	23 (0.9)***	7.8 (6.7)****	10,946 (18,118)****
Ulcer and other infection	491	11 (2.2)	9.6 (8.7)	14,696 (17,080)
Surgical site	114	7 (6.1)	15.7 (17.4)	24,658 (32,226)
Anatomic location of infection				
Foot	2,220	23 (1.0)*	8.1 (6.7)	11,640 (18,202)
Non-foot or any surgical site	810	18 (2.2)	9.2 (10.5)	13,242 (20,605)
Monomicrobial[a]				
MSSA	427	4 (0.9)	7.2 (6.9)***	11,103 (32,419)****
MRSA	243	4 (1.6)	8.1 (7.9)	10,877 (15,345)
Coagulase-negative staphylococci	171	0 (0)	6.9 (5.4)***	8,973 (8,645)**
Streptococcus spp.	195	1 (0.5)	7.9 (6.9)	11,919 (17,627)
Enterococcus spp.	64	1 (1.6)	10.3 (9.8)	12,808 (11,778)
Other gram-positives	12	0 (0)	6.2 (3.5)	8,880 (6,872)
Enterobacter	13	0 (0)	6.3 (4.0)	9,747 (6,575)
P. aeruginosa	46	1 (2.2)	8.3 (6.7)	12,182 (15,778)
Other gram-negatives	95	7 (7.4)***	11.1 (10.1)**	15,778 (18,450)**
Anaerobic bacteria	16	0 (0)	8.8 (7.7)	10,607 (9,616)
Fungi	16	1 (6.3)	6.9 (4.3)	9,425 (8,342)
Polymicrobial[b]				
Including MRSA	265	1 (0.4)	9.9 (12.8)*	14,109 (26,917)**
Including *Pseudomonas* without MRSA	267	9 (3.4)**	9.9 (8.2)****	14,820 (14,089)****
Without MRSA or *Pseudomonas*	1,200	12 (1.0)	8.3 (6.8)	11,817 (12,881)
MRSA (mono or poly)	508	5 (1.0)	9.0 (10.8)	12,564 (22,191)
Major surgery at index hospitalisation	297	7 (2.4)	10.3 (9.1)****	16,834 (17,821)****

[a] Monomicrobial, i.e. only one microbial isolate found on culture; [b] polymicrobial, i.e. two or more microbial isolates found on culture
*$p<0.05$, **$p<0.01$, ***$p<0.001$ and ****$p<0.0001$

transferred from another acute care hospital or skilled nursing facility. These factors have been classified previously as healthcare-associated infections and associated with adverse clinical and economic consequences [37, 38]. We also found that diagnosed infections with monomicrobial isolation of an aerobic gram-negative organism or polymicrobial cultures that included *P. aeruginosa* also increased length of stay and costs. In contrast, neither polymicrobial cultures with MRSA, nor a non-foot location of infection were independently associated with adverse outcomes when controlled for clinical severity and other confounding factors. Because MRSA isolation among these patients was much more common than *P. aeruginosa* or other gram-negatives isolation, anti-MRSA treatment might

Table 4 Variables associated with mortality, length of stay or hospital costs in multivariable analysis

Variable[b]	Mortality[a]		Length of stay		Cost	
	OR (95% CI)	*p* value	Beta[c]	*p* value	Beta[c]	*p* value
Admission illness severity[d]	1.86 (1.53–2.26)	<0.0001	0.210	<0.0001	0.210	<0.0001
Transferred from another acute-care hospital	5.08 (1.01–25.68)	0.0492	0.422	0.0154	0.422	0.005
Major surgery during index hospitalisation	1.26 (0.52–3.01)	0.6096	0.341	0.0002	0.341	<0.0001
Ulcer compared with cellulitis	1.21 (0.56–2.64)	0.6308	0.086	0.9595	0.086	0.0299
Surgical site infection compared with cellulitis	3.54 (1.42–8.85)	0.0067	0.452	<0.0001	0.452	<0.0001
Other (i.e. non-*Pseudomonas*) gram–negative monomicrobial	8.86 (3.56–22.03)	<0.0001	0.244	0.0005	0.244	0.0031
Pseudomonas polymicrobial (no-MRSA)	3.13 (1.40–7.00)	0.0054	0.184	0.0025	0.184	0.0003

[a] C-statistic for logistic mortality rate model was 0.84

[b] Variables with *p* value significant in at least one model

[c] The coefficient generated by multivariable model using log scale of length of stay or cost as an outcome measure. The model fit R^2 was 0.16 and 0.19, respectively

[d] Admission illness severity = the logit transformation of predicted probability of death on admission based on multivariable logistic regression models

have been more prompt and effective. Unfortunately, we were unable to further investigate this issue because our database lacked pharmacy data.

Our literature review uncovered very few previous studies that have compared SSTIs involving the foot vs non-foot sites in diabetic patients. In one prospective study of treatment of complicated skin and skin structure infections, clinical success rates were non-significantly lower in diabetic patients with an infected foot ulcer (~68%) than in those with other types of infections (~85%) [44]. In another prospective treatment study of patients with complicated skin and skin structure infections, the proportion of patients who were clinically cured was similar for those with a diabetic foot infection (~85%) and those with other types of infection (~90%) [31]. Finally, another treatment trial of patients with a complicated SSTI found that the 37% of patients with diabetes were older and more likely to have impaired renal function at enrolment. Complex abscesses were less common in diabetic than in non-diabetic patients, while cellulitis and infected ulcers were more common [45].

Limitations of our study include the fact that analyses were retrospective and our observations constrained by the information available in the database. We were unable to analyse differences between various medical or surgical treatments and their associated outcomes, nor could we determine whether deaths were directly attributable to the SSTI. Moreover, some SSTI patients may have had a negative wound culture and been excluded from our study. In addition, if specimens for culture from an open wound are collected by swab, the results may represent contamination or colonisation, rather than infection. Nevertheless, clinicians rarely culture clinically uninfected wounds, and this study was conducted before culturing to detect MRSA colonisation was common. As all patients had a diagnosis of SSTI that was sufficiently severe to warrant hospitalisation, the possibility that the wounds were uninfected seems remote. Nevertheless, associations between wound isolates and outcomes are not necessarily causal. Another limitation is that we did not investigate nosocomial infections for the index hospitalisation, since we only included cultures collected within 48 h of admission. Hence, our findings may not necessarily be generalisable for hospital-acquired infections. Finally, hospitals included in the study were predominantly in the northeast region of the USA, which may not be representative of other regions in the USA or other countries.

Our data add important observations relating to the sparsely studied but common clinical problem of SSTI in persons with diabetes. The study cohort was large and all patients had positive culture isolates. Perhaps our most noteworthy microbiological finding is that only MRSA increased in prevalence as an isolate; this probably reflects epidemiological trends in the locales of the hospitals included. We identified significant independent risk factors for longer length of stay, higher costs and mortality rates during the admission. Our findings that patients with wounds containing MRSA tended to be more severely ill at clinical presentation may have clinical implications leading to earlier diagnosis and treatment. We would like to see our observations replicated in other populations, especially with prospectively designed studies. Meanwhile, being alert to the risk factors for adverse outcomes, which are easily identified on admission, could allow hospital staff to concentrate efforts on those diabetic patients at high risk of adverse outcomes.

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