Wound Chronicity, Inpatient Care, and Chronic Kidney Disease Predispose to MRSA Infection in Diabetic Foot Ulcers

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OBJECTIVE — To determine the microbiological profile of diabetes-related foot infections (DRFIs) and the impact of wound duration, inpatient treatment, and chronic kidney disease (CKD).

RESEARCH DESIGN AND METHODS — Postdebridement microbiological samples were collected from individuals presenting with DRFIs from 1 January 2005 to 31 December 2007.

RESULTS — A total of 653 specimens were collected from 379 individuals with 36% identifying only one isolate. Of the total isolates, 77% were gram-positive bacteria (staphylococci 43%, streptococci 13%). Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated from 23%; risk factors for MRSA included prolonged wound duration (odds ratio 2.31), inpatient management (2.19), and CKD (OR 1.49). Gram-negative infections were more prevalent with inpatient management ($P = 0.002$) and prolonged wound duration ($P < 0.001$). Pseudomonal isolates were more common in chronic wounds ($P < 0.001$).

CONCLUSIONS — DRFIs are predominantly due to gram-positive aerobes but are usually polymicrobial and increase in complexity with inpatient care and ulcer duration. In the presence of prolonged duration, inpatient management, or CKD, empiric MRSA antibiotic cover should be considered.

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This study was undertaken to evaluate microbiological specimens collected from patients with diabetes-related foot infections (DRFIs) and managed by a multidisciplinary diabetic foot unit (DFU). The primary aim was to determine the prevalence of bacterial isolates including methicillin-resistant *Staphylococcus aureus* (MRSA). The secondary aim was to characterize the effect of wound duration, inpatient treatment, and chronic kidney disease (CKD) on the microbiological profile.

RESEARCH DESIGN AND METHODS

— All individuals managed by a DFU between 1 January 2005 and 31 December 2007 were prospectively recruited. Eligibility criteria required the coexistence of diabetes and an infected pedal wound. Pedal wounds were defined as an epithelial breach distal to the ankle, while clinical infection was defined as the presence of a purulent discharge or two or more of erythema, warmth, tenderness, or induration (1,2). Wounds were deemed acute if present for less than 6 weeks. Consistent with the Kidney Disease Outcomes Quality Initiative guidelines, CKD was diagnosed if the estimated glomerular filtration rate was <60 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-1} (2) for more than 3 months (3).

Baseline data were recorded, including age, sex, diabetes duration, A1C, diabetes treatment, prior inpatient management, and estimated glomerular filtration rate. Inpatient management was defined as at least an overnight stay for any condition during the existence of the pedal wound. Microbiological specimens were collected by a member of the DFU from the base of all clinically infected wounds and consisted of either a postdebridement wound swab or tissue sample (subcutaneous tissue or bone). Bone biopsies were collected by computerized tomography guidance. If an individual had more than one wound, appropriate microbiological samples were collected from each clinically infected wound. Microbiological analyses included Gram staining and aerobic and anaerobic cultures.

Ethics approval was obtained from the Melbourne Health Human Research Ethics Committee. Statistical analysis was undertaken with Stata 10.0 (StataCorp, College Station, TX), with a P value <0.05 considered statistically significant. The Wilcoxon's rank-sum test was used to calculate P values for continuous data, and Fisher's exact test was used for all other univariate statistical analyses. Multivariate analyses were performed using stepwise logistic regression.

RESULTS

— A total of 379 patients were identified as having a DRFI (mean age 67 years [range 22–93], mean A1C 8.0%). Seventy-one percent of the individuals were men, but the percentage of women treated increased significantly during the study period (20% in 2005, 35% in 2007, $P = 0.0071$). Mean diabetes duration was 18 years, and 88% had type 2 diabetes (51% insulin requiring, 31% on oral medication, and 6% on diet alone). Eighty-three percent of the individuals received inpatient management care, but during the study period the proportion of individuals managed exclusively on an outpatient basis increased (13% in 2005, 24% in 2007, $P = 0.0315$). Those with chronic wounds were more likely to be admitted (87 vs. 78%, $P = 0.0256$), and this cohort was also more likely to have coexisting renal impairment (64 vs. 38%, $P = 0.0014$).

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Table 1—*Microbiological isolates for clinical subgroups*

	Total	Outpatients	Inpatients	*P*	Acute	Chronic	*P*	Normal renal function	CKD	*P*
n	379	63 (16.6)	316 (83.4)		166 (43.8)	213 (56.2)		186 (49.1)	193 (50.9)	
Specimens/ wounds	653	86 (13.2)	567 (86.8)		286 (43.8)	367 (56.2)		307 (47)	346 (53)	
Total isolates	1,298	165 (12.7)	1,133 (87.3)		543 (41.8)	755 (58.2)		650 (50.1)	648 (49.9)	
Single isolate	236 (36.1)	35 (40.7)	201 (35.4)	NS	118 (41.3)	118 (32.2)	0.0174	91 (29.6)	145 (41.9)	0.0014
Gram-positive	997	138	859		466	531		508	489	
MSSA	224 (34.3)	46 (53.5)	178 (31.4)	<0.001	144 (50.3)	80 (21.8)	<0.001	105 (34.2)	119 (34.4)	NS
MRSA	147 (22.5)	10 (11.6)	137 (24.2)	0.01	40 (14.0)	107 (29.2)	<0.001	53 (17.3)	94 (27.2)	0.002
Other *Staph*	193 (29.6)	27 (31.4)	166 (29.3)	NS	76 (26.6)	117 (31.9)	NS	106 (34.5)	87 (25.1)	0.024
Streptococcus spp	164 (25.1)	24 (27.9)	140 (24.7)	NS	86 (30.1)	78 (21.3)	0.01	95 (30.9)	69 (19.9)	0.009
B-*haemolytic*	84 (12.9)	15 (17.4)	69 (12.2)	NS	44 (15.4)	40 (10.9)	NS	54 (17.6)	30 (8.7)	<0.001
Enterococcus spp	100 (15.3)	6 (7.0)	94 (16.6)	0.02	37 (12.9)	63 (17.2)	NS	57 (18.6)	43 (12.4)	0.028
Other gram-positive	169 (25.9)	25 (29.1)	144 (25.4)	NS	83 (29.0)	86 (23.4)	NS	92 (30.0)	77 (22.3)	0.025
Gram-negative	282	24	258		70	212		131	151	
Pseudomonas spp	89 (13.6)	7 (8.1)	82 (14.5)	NS	10 (3.5)	79 (21.5)	<0.001	33 (10.7)	56 (16.2)	NS
Other gram-negative	64 (9.8)	7 (8.1)	57 (10.1)	NS	22 (7.7)	42 (11.4)	NS	33 (10.7)	31 (9.0)	NS
Mixed gram-negative	129 (19.8)	10 (11.6)	119 (21.0)	0.042	38 (13.3)	91 (24.8)	<0.001	65 (21.2)	64 (18.5)	NS
Anaerobic	14 (2.1)	3 (3.5)	11 (1.9)	NS	5 (1.7)	9 (2.5)	NS	10 (3.3)	4 (1.2)	NS
Fungal	5 (0.8)	0 (0)	5 (0.9)	NS	2 (0.7)	3 (0.8)	NS	1 (0.3)	4 (1.2)	NS

Data are *n* or *n* (%).

Microbiology of ulcers

From the 379 patients recruited, 653 specimens were analyzed and 1,298 isolates were detected (Table 1). Gram-positive aerobic bacteria accounted for 77% of isolates with staphylococci (43%), streptococci (13%), and enterococci (8%). The remainder of isolates were gram-negative bacteria (22%), anaerobic bacteria (1%), or fungal organisms (0.4%). A greater proportion of gram-positive infections was seen with acute wounds (86 vs. 71%, $P < 0.001$) and those managed exclusively as outpatients (84 vs. 76%, $P = 0.026$). A single bacterial isolate was cultured in 36% of wounds. Acute wounds were more likely to demonstrate monomicrobial growth (41 vs. 32%, $P = 0.0174$).

Methicillin-sensitive *Staphylococcus aureus* (MSSA) was identified in 34% of wounds, while MRSA was isolated in 23%. The frequency of MSSA infection was greater in individuals with acute ulcers (50 vs. 22%, $P < 0.001$) and those exclusively receiving outpatient care (54 vs. 31%, $P < 0.001$). Conversely, individuals receiving inpatient care were twice as likely to have MRSA (24 vs. 12%, $P = 0.01$). A significantly increased frequency of MRSA infection was also demonstrated in those with chronic ulcers (29 vs. 14%, $P < 0.001$) and CKD (27 vs. 17%, $P = 0.002$). Multivariate analyses established that the greatest independent risk factor for MRSA infection was chronic ulceration (odds ratio 2.31, $P < 0.001$), then inpatient care (2.19, $P = 0.027$), and CKD (1.49, $P = 0.042$).

Streptococcal species were isolated from 25% of wounds and were more prevalent among individuals with acute wounds (30 vs. 21%, $P = 0.01$) and normal renal function (31 vs. 20%, $P = 0.009$). However, *Enterococcos* was cultured more frequently in individuals who had received inpatient care (17 vs. 7%, $P = 0.021$) and had normal renal function (19 vs. 12%, $P = 0.03$). One Vancomycin-resistant *Enterococcus* isolate was detected in an inpatient with both a chronic wound and CKD.

Gram-negative infections were more frequent in individuals with chronic wounds (58 vs. 25%, $P < 0.001$) and those managed as an inpatient (46 vs. 28%, $P = 0.002$). Pseudomonas isolates were more common in chronic wounds (22 vs. 3%, $P < 0.001$). Resistant gram-negative "ESCAPPM" organisms (*Enterobacter*, *Serratia*, *Citrobacter freundii*, *Acinetobacter*, *Providencia spp*, *Proteus*, *Morganella*) with chromosomal-inducible β-lactamases were detected in 6% of wound swabs with *Proteus* the most prominent member.

CONCLUSIONS — This study investigated the wound microbiology of 379 DRFI, which were managed by a multidisciplinary diabetic foot service. Gram-positive cocci, especially staphylococci and streptococci, were the predominant pathogens followed by gram-negative and anaerobic infections. MRSA infection, with its associated increased morbidity and mortality, was detected in 23% of wounds (4,5). Wound chronicity, inpatient care, and CKD each independently predisposed patients to MRSA infection. Hospitalization and prolonged wound duration were also associated with increasingly complex polymicrobial infections that often involved resistant gram-negative organisms.

By confirming the microbiological profile of DRFI and identifying risk factors for MRSA infection, we believe this study aids clinicians in the selection of empiric antibiotics. Antibiotic cover for MRSA should be considered in patients with DRFI who have one or more prior hospitalizations with the same ulcer, chronic ulceration, or renal impairment, especially in the acutely unwell who cannot wait for culture and sensitivity results. Furthermore, there is an ongoing need for aggressive strategies to prevent the spread of resistant organisms with emphasis on early detection of at-risk patients, hand hygiene, appropriate multidisciplinary care to facilitate early wound healing, and judicious outpatient management.

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