The Impact of Gram-Negative Bacilli in Bacteremic Skin and Soft Tissue Infections Among Patients With Diabetes

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Skin and soft tissue infections (SSTIs) are common and may be more severe in patients with diabetes. In particular, the development of diabetic foot ulcers facilitates diabetic foot infections (DFIs), which are generally not included in SSTI classifications (1). In these situations, Gram-negative bacilli (GNB) may have an impact on the etiology of severe SSTIs.

We aimed to analyze the GNB etiology, epidemiologic trends, and risk factors for mortality among a large cohort of adult patients with diabetes attended in our hospital (1996–2016) with bloodstream infections from an SSTI source (1). Cases with nosocomial acquisition or due to a sacral decubitus ulcer were excluded.

Out of 30,363 episodes of bacteremia, 7,202 (23.7%) occurred in patients with diabetes; this proportion increased over time from 17.7% in 1996–2000 to 28.3% in 2011–2016 ($P < 0.001$). Among bacteremic episodes in patients with diabetes, 247 (3.4%) were secondary to SSTIs, of which 223 were analyzed (Table 1). The most common clinical form was cellulitis ($n = 184$, 82.5%). DFI represented 25% of cases (with abscesses in 23%), of which 41.8% required surgery (amputation, 43.5%).

Regarding the microbiology, 138 (61.9%) cases were caused exclusively by Gram-positive cocci (GPC) (mainly *Streptococcus* spp. [63.8%] and *Staphylococcus aureus* [29%]) and 68 (30.5%) by GNB (*Escherichia coli* [26.5%] and *Pseudomonas* spp. [26.5%]). Seventeen cases (7.6%) were polymicrobial mixed infections (combining GPC and GNB); those were excluded for specific comparison of patients with GNB SSTIs vs. GPC SSTIs (Table 1). The former were older, had higher rates of diabetic complications and health care–related infections, had received prior antibiotics more often, and had infections that were mostly located on the lower extremities.

Comparison of the 1996–2000 and 2011–2016 time periods revealed an upward trend in the prevalence of GNB SSTIs (14.3% vs. 40.6%; $P = 0.020$), in the previous use of antibiotics (14.3% vs. 44.9%; $P = 0.003$), and in the proportion of GNB resistant to frequently used antibiotics (amoxicillin-clavulanate and fluoroquinolones) (0% vs. 20.3%; $P = 0.100$).

The 30-day mortality rate was 21.5%, ranging from 57.9% in necrotizing fasciitis to 17.2%, 14.3%, and 10.5% in cellulitis, pyomyositis, and abscesses, respectively ($P < 0.001$). Mortality from DFIs was 16%. Patients with GNB SSTIs had higher mortality rates (32.4%) compared with patients with GPC SSTIs (13.8%) ($P = 0.002$) in all types of SSTIs but necrotizing fasciitis, which had an intrinsic high mortality independent of the etiology. In multivariate analysis after adjusting for age, sex, presence of coronary disease, type of SSTI (excluding necrotizing fasciitis), and site of acquisition, infection due to GNB was the only statistically significant risk factor for mortality (adjusted odds ratio 2.73 [95% CI 1.11–6.70]; $P = 0.028$).

Our study shows an increasing trend in GNB SSTIs among patients with diabetes, with consequent greater mortality. The results may be inherently limited by the retrospective review and conditioned not only by diabetes but also by other comorbidities of the patients or the presence of bacteremia itself.

The most common SSTI was cellulitis, but DFI represented 25% and had higher rates of abscesses and need for amputation. This supports the previous opinion about considering DFIs in further classifications of SSTIs because of their frequency and particular characteristics (1).

Despite the dominance of GPC etiology, we observed a greater proportion of GNB (30.5%) than is classically reported (2). This fact seems not only related to the presence of ulcers but also the location of SSTIs on the lower extremities and the

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Table 1—Clinical characteristics of the studied cohort and differences between patients with an infection due to GNB, GPC, or mixed polymicrobial infection

	Total (N = 223)	Mixed polymicrobial infections (n = 17; 7.6%)	GNB (n = 68; 30.5%)	GPC (n = 138; 61.9%)	P value[a]
Demographic characteristics					
Age, mean (years)	67.1	70.1	72.1	64.7	<0.001
Women	92 (41.3)	7 (41.2)	29 (42.7)	56 (40.6)	0.777
Characteristics of diabetes and secondary complications[b]					
Insulin-dependent	126 (58.9)	10 (58.8)	43 (65.2)	73 (55.7)	0.204
Diabetic complications	129 (57.9)	14 (82.4)	46 (67.7)	69 (50)	0.016
Coronary disease	44 (19.9)	4 (23.5)	13 (19.1)	27 (19.9)	0.901
Cerebrovascular disease	20 (9.1)	6 (35.3)	9 (13.2)	5 (3.7)	0.011
Diabetic nephropathy[c]	51 (23.1)	3 (17.7)	25 (36.8)	23 (16.9)	0.002
Peripheral arterial disease	75 (33.9)	10 (58.8)	25 (36.8)	40 (29.4)	0.288
Type of infection					
Cellulitis	184 (82.5)	11 (64.7)	58 (85.3)	115 (83.3)	0.718
Abscesses	33 (14.8)	2 (11.8)	8 (11.8)	23 (16.7)	0.355
Necrotizing fasciitis	23 (10.3)	4 (23.5)	8 (11.8)	11 (8)	0.376
Pyomyositis	10 (4.5)	0 (0)	4 (5.9)	6 (4.4)	0.630
DFIs	56 (25.1)	11 (64.7)	13 (19.1)	32 (23.2)	0.506
Characteristics of the infection					
Presence of ulcer as portal of entry	104 (47.1)	15 (88.2)	32 (47.1)	57 (41.9)	0.485
Location of infection on the lower extremity	183 (82.1)	16 (94.1)	63 (92.7)	104 (75.4)	0.003
Presence of SIRS on admission[d]	52 (23.3)	9 (52.9)	23 (33.8)	20 (14.5)	0.001
Received antibiotics previously	81 (36.3)	6 (35.3)	38 (55.9)	37 (26.8)	<0.001
Health care–related infection[e]	73 (32.7)	5 (29.4)	36 (52.9)	32 (23.2)	<0.001
Surgical treatment	67 (30.32)	7 (41.2)	18 (26.9)	42 (30.7)	0.577
Overall mortality (at 30 days)	48 (21.5)	7 (41.2)	22 (32.4)	19 (13.8)	0.002

[a]Comparison between GNB and GPC cases. [b]Glycated hemoglobin was available only in almost one-third of the cases (median 8.2% (interquartile range 6.9–10.2); thus, these data are not presented in the table. [c]Among patients with diabetic nephropathy, 21 (41.2%) had a glomerular filtration rate (GFR) between 30–59 mL/min/1.73 m^2, 10 (19.6%) had severe impairment of renal function (GFR 15–29 mL/min/1.73 m^2), and 20 (39.2%) were on hemodialysis. [d]SIRS (systemic inflammatory response syndrome) according to definition in ref. 6. [e]In accordance with definitions by Friedman et al. (7).

specific immunosuppressive conditions that patients with diabetes may present. Also, we recognized a significant increase in the proportion of GNB bacteremia over time, as has been noted worldwide in similar settings (3). Finally, we noticed an increase in the SSTIs caused by GNB resistant to the most commonly used antibiotics but without a specific increment in those GNB defined as multidrug resistant, thus leading us only to hypothesize about their lower virulence or a possible emergence of multidrug resistance in the future.

In our study, the mortality rates varied according to the type of SSTI and were high considering overall mortality from SSTIs but comparable to other studies with the same type of patients or with bloodstream infections (4). Notably, infections due to GNB were associated with twofold increased odds of mortality, after adjusting for other causes. These differences were detected in all types of SSTIs except necrotizing fasciitis. To our knowledge, scarce reference has been made previously to GNB etiology as an independent risk factor for mortality in SSTIs (5).

In conclusion, because of the increase in GNB infections, including those resistant to the most commonly used antibiotics, and their greater mortality, appropriate empirical coverage is mandatory, whether in patients with SSTIs and severe systemic manifestations or suspicion of bacteremia.

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