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Diabetic Foot Infection: Exploratory Analysis of Its Clinical Profile, Microbiology, and Outcomes

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Pie diabético infectado. Análisis exploratorio de su perfil clínico, microbiología y desenlaces

ABSTRACT

Diabetic foot infections (DFI) lead to severe complications, including amputation and hospitalizations. Despite frequent antibiotic use, local microbiological data remain scarce in Chile. ***Aim:*** *To assess the microbiological profile, resistance patterns, and clinical outcomes of DFI patients in a single Center in Chile.* ***Methodology:*** *A retrospective analytical study was conducted on hospitalized adult with DFI who underwent surgical debridement or amputation with positive intraoperative cultures between 2017 and 2022. Data were collected from medical records.* ***Results:*** *Among 516 patients, 272 had positive intraoperative cultures, with 126 randomly selected for analysis. Mean age was 61.8 years. Most presented with localized infections and Wagner stage ≥3. Patients presented with localized infections, with minimal inflammatory or systemic repercussion. Only one patient required ICU admission. Microbiological analysis revealed Gram-positive cocci (GPC; 93.4%) predominating in patients without prior amputation, whereas Gram-negative bacilli (GNB; 52%) were significantly higher in those with prior amputations (p= 0.03). For previously amputated patients, higher resistance values for third-generation cephalosporins (OR 17.6), piperacillin-tazobactam (OR 8.8), and sulbactam-ampicillin (OR 6) were detected. 85.7% of patients underwent amputations and median hospital stay was 14 days. Within the first year, 54% (n= 68) of patients required at least one rehospitalization. Patients were followed for a median of 33 months and during this period, 47 patients (37.3%) died. Only 5 out of 47 deaths (10.6%) were directly or indirectly caused by DFI. Multivariate logistic regression analysis found*

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amaurosis, heart failure, and age as independent mortality predictors. Median overall survival was 60 months. Microbiological follow-up in new admissions, indicated an increasing proportion of GNB with a higher proportion of antimicrobial resistance to first- or second-line compounds. ***Conclusion:*** *DFI in Chile exhibits high morbidity, recurrent hospitalizations and progressive antibiotic resistance. Mortality is not significantly associated to infection but to other factors linked to DM.*
Keywords: *Amputation, Surgical; Diabetic Foot; Drug Resistance, Bacterial; Mortality.*

RESUMEN

Las infecciones del pie diabético (IPD) pueden provocar complicaciones graves, incluidas amputaciones y hospitalizaciones. A pesar del uso frecuente de antibióticos, los datos microbiológicos locales en Chile siguen siendo escasos. ***Objetivo:*** *Evaluar el perfil microbiológico, los patrones de resistencia y los resultados clínicos de los pacientes con IPD en un centro único en Chile.* ***Metodología:*** *Se realizó un estudio analítico retrospectivo en adultos hospitalizados con IPD que fueron sometidos a desbridamiento quirúrgico o amputación con cultivos intraoperatorios positivos entre 2017 y 2022. Los datos fueron recopilados de los registros médicos.* ***Resultados:*** *De 516 pacientes, 272 tuvieron cultivos intraoperatorios positivos, de los cuales se seleccionaron aleatoriamente 126 para el análisis. La edad media de los pacientes fue de 61.8 años. La mayoría presentaba infecciones localizadas y estadio Wagner ≥3, con mínima repercusión inflamatoria o sistémica. Solo un paciente requirió ingreso en la UCI. El análisis microbiológico mostró un predominio de cocos Gram positivos (CGP; 93,4%) en pacientes sin amputaciones anteriores, mientras que los bacilos Gram negativos (BGN; 52%) fueron significativamente más frecuentes en aquellos con amputaciones previas (p= 0,03). En pacientes con amputaciones anteriores, se observaron mayores valores de resistencia para cefalosporinas de tercera generación (OR 17,6), piperacilina-tazobactam (OR 8,8) y sulbactam-ampicilina (OR 6). El 85,7% de los pacientes fueron sometidos a amputaciones y la mediana de estancia hospitalaria fue de 14 días. Dentro del primer año, el 54% (n= 68) de los pacientes requirió al menos una rehospitalización. El seguimiento tuvo una mediana de 33 meses, durante las cuales fallecieron 47 pacientes (37,3%). Solo 5 de las 47 muertes (10,6%) fueron directa o indirectamente causadas por IPD. La mediana de sobrevida fue de 60 meses. El análisis de regresión logística multivariante identificó la amaurosis, la insuficiencia cardíaca y la edad como predictores independientes de mortalidad. El seguimiento microbiológico en nuevas hospitalizaciones indicó un aumento en la proporción de BGN, con una mayor resistencia antimicrobiana para compuestos de primera y segunda línea.* ***Conclusión:*** *La IPD en Chile presenta una alta morbilidad, hospitalizaciones recurrentes y resistencia antibiótica progresiva. La mortalidad no se asocia significativamente*

a la infección, sino que a otros factores ligados a la DM.
Palabras clave: *Amputación quirúrgica; Infección del pie diabético; Mortalidad; Resistencia bacteriana a fármacos.*

According to 2017 estimates, 14% of the Chilean population has diabetes mellitus (DM). Patients with DM suffer from ulcers in their lower limbs due to neuropathic, autonomic, and ischemic complications, which in many cases progress to major and minor amputations, frequent hospitalizations, and serve as a marker of reduced overall survival[1,2,3,4]. The management of these ulcers, with or without associated osteomyelitis, is multidisciplinary and requires microbiological information, especially in severe cases, to improve wound or amputation site healing and prevent recurrence[2,5,6,7].

Despite the high prevalence and frequent antibiotic prescriptions in patients with diabetic foot infection (DFI), microbiological information in Chile is virtually nonexistent. Only a seminal study conducted in the Metropolitan Region over 25 years ago and another more recent study carried out in Antofagasta, in the northern part of the country, are available. The first study demonstrated the polymicrobial nature of these infections in a high percentage of cases, the involvement of anaerobes, and the inability to predict antimicrobial susceptibility empirically[8]. The second study, which is part of a broader Latin American investigation in recent years, confirmed a similar microbial profile but did not include anaerobes in a systematic manner. In the latter study, microbiological findings were associated to time of evolution and ischemia but none of these reports, explore the contribution of the DFI on the overall survival[8,9]. Therefore, it is urgent to obtain more local data to determine the prevalence of different microorganisms, their resistance patterns, and their association with prior antibiotic exposure, hospitalizations and amputations. The collected information may be useful for designing appropriate therapeutic regimens. Additionally, it is necessary to assess whether microbiological variables and their treatment influence patient prognosis.

Methodology

This was a retrospective descriptive-analytical study. Cases were identified using the list of consultations maintained by the Infectious Diseases department, based on visits generated by the Antimicrobial Stewardship Program (ASP) since mid-2016. Only hospitalized adult patients with DM were included, in whom the culture sample was obtained in the operating room (bone/tissue sample transported in a sterile container) and yielded a positive result. The microbiological study did not include anaerobic bacteria and was conducted using routine practices at the local laboratory, with bacterial identification performed using MALDI-TOF and the VITEK 2 Compact automated system (bioMérieux), which analyzes biochemical reactions on test cards. Bacterial susceptibility was determined using the same system, which conducts automated broth microdilution to establish the minimum inhibitory concentration (MIC) of antimicrobials. All susceptibility interpretations were performed according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (M100). Demographic data (age, sex) were extracted from medical records, along with relevant clinical variables such as diabetes mellitus duration, peripheral pulses, vascular studies, prior amputations, glycosylated hemoglobin levels, erythrocyte sedimentation rate, renal function, target organ damage (kidney, heart, retina, and CNS), characteristics of the lesion leading to hospitalization, prior antibiotic exposure, procedures, previous hospitalizations, smoking habits, and

histological findings if available.

Patient outcomes were analyzed based on in-hospital mortality or mortality during follow-up, whether related to the infectious event or other causes, along with associated risk factors, through univariate analysis, followed by multivariate analysis using binary logistic regression. Results are presented descriptively for continuous and categorical variables, using parametric or non-parametric tests as appropriate based on available data. Statistical analyses were conducted using SPSS software.

Various factors potentially affecting microorganism distribution during the first hospitalization in the study period were examined. Odds ratios (OR) and significance levels were calculated for this purpose. Changes in antimicrobial resistance percentages between the first hospitalization (H1) and a second hospitalization (H2) within the first-year post-discharge were analyzed using tetrachoric tables, applying the Chi-square test or Fisher's exact test depending on the expected number of cases per cell. A significance level of $p<0.05$ was used.

Ethical Considerations

This study was approved by the Scientific Ethics Committee of the Los Ríos Health Service.

Results

At the Regional Hospital of Valdivia (Los Ríos Region, Chile), between September 2017 and September 2022, a total of 516 patients were hospitalized one or more times for DFI and underwent surgical debridement or amputation in the operating room. Of these, 272 had at least one intervention with a positive intraoperative culture (47.2%). A randomly selected subset of 126 patients (using random numbers) was analyzed, representing 46.3% of the total patients with at least one positive culture.

The positivity rate of cultures increased progressively from 2017 onwards due to the implementation of the ASP, which incorporated culture requests into the management of patients with this condition. The proportion of positive cases increased from 15% in 2017 to 48% in 2021.

The age distribution was normal (skewness 0.16), with a mean age of 61.8 years (standard deviation 10.87 years; range 33 to 92 years). The mean duration of diabetes mellitus was 15.8 years (SD ± 8.9 years). General features of the study group are presented in Table 1, highlighting the high prevalence of hypertension, dyslipidemia, obesity, active smoking, retinopathy, and previous hospitalizations due to DFI.

Table 1. General features of patients admitted by diabetic foot infection, Valdivia, Chile 2017-2022.

Variable	n	%
Male gender	101	71.1%
Hipertension	98	69%
Dyslipidemia	49	34.5%
Obesity	33	23.2%
Current smoking	27	19%
Chronic renal failure without dialysis	20	14.1%
Chronic renal failure in dialysis	10	7%
Coronary cardiopathy	10	7%
Heart failure (any stage)	11	7.7%
Myocardial infarction	7	4.9%
Coronary revascularization	4	2.8%
Stroke	15	10.6%
Chronic liver failure	4	2.8%
Minor amputations in lower limbs	48	3.8%
Major amputation in lower limbs	7	4.9%
Diabetic retinopathy (any stage)	68	47.9%
Amaurosis (uni or bilateral)	10	7%
Revascularization lower limbs	7	4.9%
Previous admissions by DFI	52	36.6%
Admissions last year any cause	50	35.2%
Current insulin user	78	54.9%

Admission Data

Patients presented with localized infections, with minimal inflammatory impact or systemic repercussions, as indicated by the low frequency of either leukocytosis, significantly elevated C-reactive protein (CRP) levels, systolic hypotension, tachycardia, or fever (Table 2). Only one patient required admission to the intensive care unit (ICU). Most patients had localized necrosis and Wagner stage ≥3 lesions (n= 69; 54.8%, Table 2). Only a few patients had exposed bone on physical examination. On plain radiographs, the most prevalent finding was vascular calcifications. The presence of gas or bone erosion was detected in about one-third of the patients (Table 2).

Peripheral pulse examination, performed in 93 cases, revealed an ischemic limb in 90% of patients (Table 2). However, plethysmogram were conducted in only 57 patients, demonstrating ischemia in 63% of cases. The ankle-brachial index was measured in only 56% of patients, with normal values observed in 33% of the group (data not shown).

Table 2. Clinical features at admission among patients admitted for DFI, Valdivia, Chile 2017-2022.

Variable	n	%
Fever (Temperature ≥ 37.5ºC)	17	12%
Tachycardia > 100 bpm	20	14.1%
Systolic hypotension	4	2.8%
ICU Admission	1	0.7%
Wagner Grade 2 lesion	6	4.2%
Wagner Grade 3 lesion	51	35.9%
Wagner Grade 4 lesion	64	45.1%
Wagner Grade 5 lesion	5	3.5%
Leukocytosis ≥ 12,000/uL	56	39.4%
C reactive protein > 100 mg/dL	0	0%
Necrosis	104	73.2%
Exposed bone	18	12.7%
Plain radiographs performed	114	80.3%
Subcutaneous gas	34	29.8%*
Lytic bone lesions	39	34.2%*
Vascular calcifications	61	53.5%*
Osteomyelitis	69	48.6%
Ischemic limbs according to peripheral pulses	84	90.3%*
Plethysmograph performed	57	40.1%
Non-ischemic plethysmograhic curves		
> 20 mmHg, dicrotic pulse +	7	12.3%*
> 20 mmHg, dicrotic pulse -	14	24.6%*
Subtotal non-ischemic	21	36.8%*
Ischemic plethysmograhic curves		
5-20 mmHg	33	57.9%*
<5 mmHg	2	3.5%*
Plain curve	1	1.8%*
Subtotal ischemic	36	63.2%*

*: percentage calculated among available studies.

The average duration of symptoms before admission was 46 days (range 0 to 734 days), with a median of 21 days (IQR 7–41 days). The longest duration before admission was observed in a patient with Charcot arthropathy. HbA1c levels were available for only 11 admissions, with a median of 10.9% (IQR 9.4–10.9%). Similarly, erythrocyte sedimentation rate (ESR) data were available for only 19 cases, with a median of 76 mm/h (IQR 52–76). Approximately half of the cases (Table 2) presented with osteomyelitis (OM), which in this study was defined as the presence of visible bone, lytic lesions on radiography, a positive bone tissue culture, or a biopsy showing acute or chronic inflammation. Only 56% of OM cases (39 out 69) were detected by plain radiographs. Cases classified as osteomyelitis were not associated with ESR>70 mm/h or a symptom duration exceeding 21 days.

Microbiological Analysis

All included cases had positive cultures obtained aseptically in the operating room. Due to local limitations, anaerobic studies were not conducted. For clinical convenience and a practical approach, a separate analysis was performed for patients with and without a history of amputation. There was a trend toward a higher frequency of monomicrobial cultures (excluding anaerobes) in patients without a history of amputation (60% vs. 44%, p= 0.07). The presence of three or more bacterial strains was uncommon in patients without prior amputation (7.4%) but prevalent in those with a history of amputation (26%). The prevalence of Gram-positive cocci (GPC) in patients without prior amputation was 93.4%, decreasing to 88% in those with a history of amputation (not significant) (Table 3). However, the prevalence of Gram-negative bacilli (GNB) was significantly higher in patients with a history of amputation (52% vs. 26.3%) (p= 0.03; OR 3.0, 95% CI 1.42–6.44) (Table 3).

In patients without prior amputation, the three predominant GPC species were *E. faecalis, S. aureus*, and *S. agalactiae* (Table 3). This same profile remained unchanged in patients with prior amputation. The acquired resistance profile in these strains was low, with quinolone resistance being the most common. Methicillin-resistant *S. aureus* (MRSA) strains were observed in patients without prior amputation, with three cases showing a pattern consistent with community-acquired resistance (Table 3). The overall prevalence of MRSA strains was higher in the group with prior amputation (p<0.05).

The identified GNB species included various *Enterobacteraciae* and *P. aeruginosa*, without a clear predominance (Table 3). The distribution remained stable regardless of amputation history, with a slight trend toward an increase in *P. aeruginosa* strains in previously amputated patients. The acquired antimicrobial resistance profile in GNB increased for all analyzed agents in previously amputated patients, with significant resistance observed for third-generation cephalosporins (OR 17.6; 95% CI 2.1–145), piperacillin-tazobactam (OR 8.8; 95% CI 1.04–74), and sulbactam-ampicillin (OR 6; 95% CI 1.4–25) (Table 3). A complementary analysis was conducted to identify additional risk factors associated with resistance to third-generation cephalosporins or beta-lactam/beta-lactamase inhibitors in the subgroup of patients with GNB infections, but no other associated factors were found (data not shown).

In 18 of the 126 cases (14.3%), a bone culture was performed in parallel with a soft tissue culture, and the microbiological findings were concordant in all cases. Additionally, bacterial species of interest were identified, including three cases with a profile compatible with community-acquired MRSA, although the strains were not further characterized. Other notable cases included infections with *Raoultella ornithinolytica* and *Providencia rettgerii*, as well as potential zoonotic transmission cases involving, *Staphylococcus caprae*, *S. simulans*, and *S. pseudintermedius*. Furthermore, an infection by *S. lugdunensis* was detected, a coagulase-negative *Staphylococcus* known for its higher virulence.

Based on the microbiological data, we compared the theoretical empirical coverage of different antimicrobial agents. In patients without prior amputation, coverage rates exceeded 80% for ampicillin-sulbactam, piperacillin-tazobactam,

Table 3. Bacterial species distribution and antimicrobial resistance pattern of intraoperative cultures (excluding anaerobes) observed in patients admitted by DFI, Valdivia, Chile 2017-2022.

	No previous amputation		Previous amputation	
	n	%	n	%
Gram positive cocci*	71	93%	44	88%
Staphylococcus aureus	29	38%	21	42%
Coagulase negative Staphylococci	5	7%	7	14%
Enterococcus faecalis	31	41%	18	36%
Enterococcus faecium	1	1%	2	4%
Streptococcus agalactiae	16	21%	4	8%
Other Gram positive cocci	5	7%	8	16%
Resistance **	n	%		%
Quinolones	10	11%	15	28%
Cotrimoxazole	2	6%	3	11%
MRSA	3	11%	7	33%***
VRE	0	0%	2	100%
Gram negative bacilli*	20	26.3%	26	52%
Escherichia coli	8	10.5%	3	6%
Proteus mirabilis	5	6.6%	6	12%
Klebsiella pneumoniae	2	2.6%	5	10%
Citrobacter freundii	2	2.6%	3	6%
Enterobacter cloacae	0	0%	3	6%
Pseudomonas aeruginosa	2	2.6%	8	16%
Other Gram negative bacilli	4	5.3%	7	14%
Resistance**	n	%**	n	%**
3rd Gen. Ceph.	1	5%	16	44****
Quinolones	6	26%	13	36%
Cotrimoxazole	3	14%	8	30%
Pip/Tazo	1	4%	10	29%***
Ampi/Sulbactam	7	37%	14	78%***
Meropenem	0	0%	3	8%
Tigecycline	0	0%	0	0%

*: Percentage calculated by number of patients; ** Percentage calculated by available bacterial isolates, excluding compound without activity due to intrinsic resistance; ***:p<0,05; ****:p<0,001. MRSA: methicillin resistant S. aureus; VRE: vancomycin-resistant Enterococci; 3rd Gen Ceph: Third generation cephalosporins; Pip/Tazo: piperacillin-tazobactam; Ampi/Sulbactam: ampicillin-sulbactam.

and quinolones, in the latter associated with metronidazole for anaerobic coverage (Figure 1). In patients with prior amputation, these theoretical coverage rates decreased across all agents, with the highest relative coverage observed for piperacillin-tazobactam and quinolones (with metronidazole).

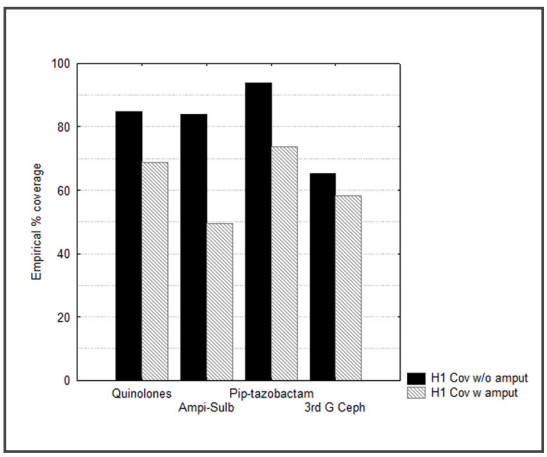

Figure 1: *Empirical coverage over Gram negative and Gram-positive bacterial isolates during the first admission among patients with or without a preceding amputation. Ampi-Sulb: ampicillin-sulbactam; Pip-Tazobactam: Piperacillin-tazobactam; 3rd G Ceph: Third generation cephalosporins. Metronidazole is added in case of cephalosporin or quinolones use (except for moxifloxacin). H1 Cov w/o amput: Theoretical antimicrobial empirical coverage for patients without amputation in the first hospitalization; H1 Cov w amput: Theoretical antimicrobial empirical coverage for patients with amputation in the first hospitalization.*

Initial Management and Evolution

A total of 85.7% of the patients underwent single or sequential amputation, while the remaining 14.3% were treated with surgical debridement only. Among the amputations, 96 patients (67.6%) had minor amputations, 7 (4.9%) had major amputations, and 5 (3.5%) had both major and minor amputations. Most patients required only one surgical intervention (n= 96; 74.6%), while others needed two (n= 24; 19%) or three (n= 8; 6.3%) procedures, including debridement or amputations. Additionally, 8 patients (6.3%) underwent angioplasty, and 1 patient (0.8%) received a revascularization procedure.

The median length of hospital stay was 14 days (IQR 8–22 days; range 1 to 72 days). 98.4% of patients received effective antibiotic therapy either from the start or after adjustments based on culture results. The median duration of effective treatment was 18 days (IQR 13–29 days; range 1 to 64 days). Nearly half of the patients (n= 61; 49.2%) received effective therapy with both lipophilic (quinolones, cotrimoxazole, or linezolid) and hydrophilic (beta-lactams, vancomycin, and amikacin) antimicrobials, either in combination or sequentially. This was followed by hydrophilic-only therapy (n= 35; 24.6%) and lipophilic-only therapy (n= 28; 22.6%).

Only one patient (0.7%) died, presenting with a foot abscess that did not require amputation, but with advanced liver cirrhosis. The cause of death was hepatorenal syndrome. Only two patients (1.6%) developed nosocomial complications, both due to *Clostridioides difficile*-associated diarrhea.

Follow-up and Outcome

Within the first-year post-discharge, 54% (n= 68) of patients required at least one rehospitalization: 23.8% with one admission, 16.7% with two, and 14.3% with three. From another perspective, only 54.5% (n= 69) of patients achieved either complete healing (n= 65) or improvement (n= 4) of the original infection site after one year.

Patients were followed for a median of 33 months (IQR 16–45 months; range 0 to 95 months). During this period, 67 patients suffered new amputations (53%). Of the total series, 47 patients (37.3%) died, while 23 patients (18.2%) did not require any readmissions. The rest (n= 56), were rehospitalized but survived, and the majority (n= 48) were readmitted due to DFI.

Mortality analysis showed that only 5 out of 47 deaths (10.6%) were directly or indirectly caused by complications of DFI. In 24 cases (51.1%), death was unrelated to this condition, while in 18 cases (38.3%), there was insufficient data to determine a cause. Univariate analysis

identified chronic kidney disease (without dialysis), heart failure, amaurosis, prior hospitalizations for DFI, and an ischemic plethysmographic curve as risk factors for mortality (Table 4).

Multivariate logistic regression analysis found amaurosis, heart failure, and age as independent mortality predictors, with a 7% increase in risk per additional year of age. The overall median survival was 62.5 months. Patients with heart failure had a significantly lower median survival (11.8 months) compared to those without (63.8 months) (Figure 2A). Patients with amaurosis had a median survival of 40.8 months, versus 62.5 months in those without (Figure 2B).

Microbiological Follow-up During the First Year Post-Discharge

Among patients who had no prior amputations before their first recorded hospitalization (H1), 24 patients had positive intraoperative cultures during a second hospitalization (H2) within the first year of follow-up. This subgroup was analyzed to assess changes in microbial species and antibiotic resistance patterns. The proportion of GPC significantly decreased between H1 and H2 (94% to 33.3%, p<0.001). Conversely, non-fermenting Gram-negative bacilli (NFGNB) and mixed cultures (GPC + GNB/NFGNB) significantly increased between H1 and H2 (2.6% to 41.7%,

Table 4. Univariate and multivariate analysis of factors associated with mortality during hospitalization and follow-up among patients admitted for DFI, Valdivia, Chile 2017-2022.

	Deceased				
Univariate analysis **Factor**	**Yes/total with Factor**	**No/total with factor**	**OR**	**IC95**	**p**
Chronic renal failure without dialysis	12/20	35/106	3.04	1.14-8.12	0.04
Heart failure	10/11	37/115	21.08	2.6-170	0.000
Amaurosis	7/10	40/115	4.37	1.07-17	0.04
Previous admission by DFI	27/52	20/73	2.86	1.35-6.05	0.008
Ischemic plethysmograhic curve	13/36	2/21	5.37	1.07-26	0.033
Multivariate analysis					
Factor			**aOR**	**IC95**	**p**
Amaurosis			23.4	2.3-242	0.008
Heart failure			16.01	1.11-230	0.04
Age (every additional year)			1.07	1.01-1.13	0.02

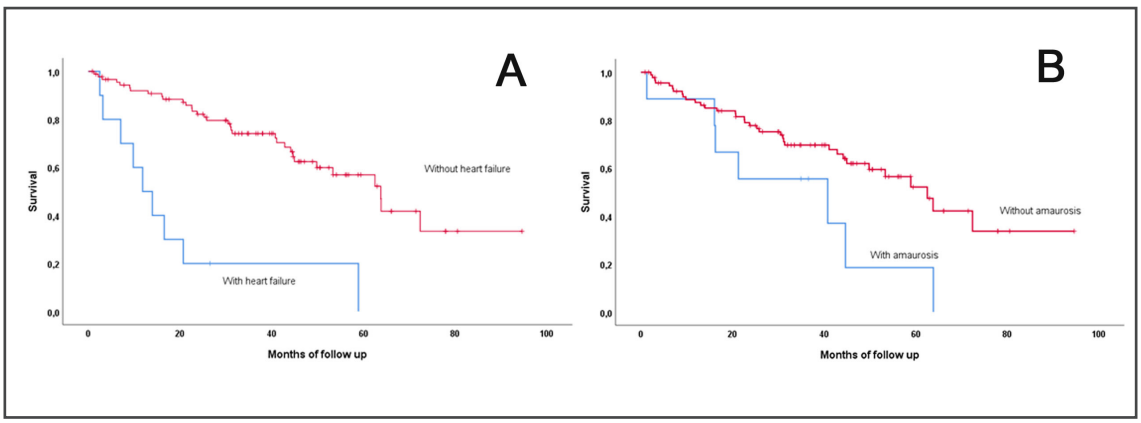

Figure 2: *A. Kaplan Meier Survival analysis according to the presence or not of heart failure among patients admitted by DFI. B. Same analysis for patients with or without amaurosis. Valdivia, Chile 2017-2022. Differences were calculated by the Cox proportional hazards model. For heart failure an OR of 6.17 was obtained (IC95 2.88-13.2; p<0,001); for amaurosis an OR of 2.7 was calculated (IC95 1.18-6.2; p<0.05).*

p<0.001 and 19.7% to 41.7%, p<0.05, respectively). Although there was a non-significant increase in enteric GNB cases (23.7% to 33.3%), the trend suggested a growing presence of these pathogens. No analysis was conducted for H3 cultures due to an insufficient number of isolates for comparison.

Among enteric GNB, there was a significant increase in resistance between H1 and H2 for the following antibiotics: Third-generation cephalosporins: 4.8% to 44% (p<0.05); piperacillin-tazobactam: 0% to 36.4% (p<0.01); quinolones: 19% to 77.8% (p<0.01) and trimethoprim-sulfamethoxazole: 14.3% to 55.6% (p<0.05; Figure 3). There was no change in resistance to ampicillin-sulbactam (19% to 7%) or carbapenems (no resistance in H1 or H2).

For NFGNB, despite a lower number of isolates, notable changes included a significant increase in meropenem resistance: 0% to 27.3% (p<0.05) and trends toward increased resistance to imipenem (0% to 27.3%) and third-generation cephalosporins active against NFGNB (0% to 45.5%).

For Gram-positive bacteria, key resistance changes between H1 and H2 included a significant increase in quinolone resistance: 12.5% to 43.5% (p<0.01) and a trend toward increased MRSA isolates: 11.1% to 42.9%. Due to the low number of isolates, comparisons for vancomycin-resistant enterococci (VRE) were limited, but 2 cases of VRE emerged in H2 (none in H1). Notably, no isolates resistant to tigecycline or trimethoprim-sulfamethoxazole-resistant *S. aureus* were detected in H1 or H2.

Discussion

The results of this study indicate that DFI is a late-stage complication in diabetic patients, occurring after several years of disease progression, in the presence of extensive tissue damage, comorbidities, and previous amputations. Moreover, hospitalized patients with DFI present a predominantly localized clinical picture, with minimal systemic inflammatory response and a primarily ischemic origin. Patients had a subacute evolution and near half of the had OM barely recognized by plain radiographs[10]. Unlike other studies, we could not establish a relationship between the presence of osteomyelitis and an elevated ESR[11]. The presence of patients with high glycosylated hemoglobin levels, active smoking, obesity and no treatment for hypertension, emphasize the need for enhancing preventive strategies[6]. In addition, interventions to reduce mortality require to add

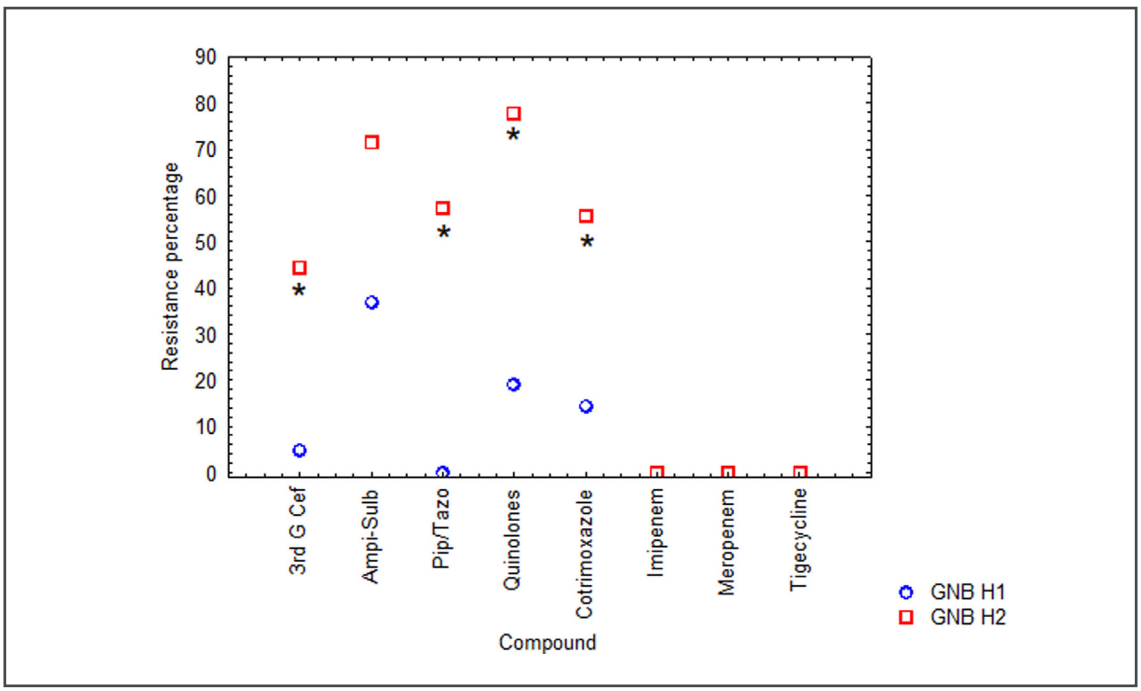

Figure 3: *Changes in antimicrobial resistance among enteric Gram-negative bacilli isolates (GNB) at the first (H1, circles) and second hospitalization (H2, squares) during the first 12 months of follow up. 3rd G Ceph: Third generation cephalosporins; Ampi-Sulb: ampicillin-sulbactam; Pip-Tazo: Piperacillin-tazobactam. An asterix indicates a significative increase.*

other strategies such as exercise and drug therapy with aspirin and statins[6,12].

The overall survival of these patients was limited (median of 5 years), consistent with previous reports[3,4,13]. Heart failure and amaurosis were independently associated with a short-term prognosis, findings that have been reported in other studies[13]. However, we found no significant role of previous amputations, reamputations or of infection in overall prognosis, except in a few cases. In another national series, DFI contributed to 5 out of 21 patient deaths[4]. Although DFI is rarely the direct cause of death, these infections represent a high burden of morbidity, with frequent readmissions and reamputations.

Our results show that the bacterial composition and antimicrobial resistance profile in DFI are dynamic, influenced by previous healthcare exposure and antimicrobial treatments. Patients with prior amputations showed greater bacterial species diversity and a higher prevalence of MRSA and GNB resistant to third-generation cephalosporins and β-lactam/β-lactamase inhibitor combinations. A similar trend was observed in the follow-up subgroup, where bacterial strains evolved toward increased antimicrobial resistance in readmissions within the first year. These findings suggest that empirical antimicrobial regimens should consider these changes and that bacterial cultures are essential at every new event.

The predominant microbial composition in DFI varies between studies and resistance increases after previous hospitalization and antimicrobial exposure[9,14,15]. In our analysis, *E. faecalis* was highly prevalent, which limits the use of cephalosporins as an initial empirical option. *E. faecalis* has a great diversity of pathogenic/virulence factors that enable this bacterial species to adhere, invade, and evade the immune response[16]. These factors include microbial surface components able to recognize

adhesive matrix molecules, pili, cytolysin, and gelatinase, among others[16].

DFI is a progressive disease requiring new hospitalizations and amputations in a high percentage of the patients even if the original lesion is healed. Antimicrobials are useful only to ensure healing of the surgical wound and rarely to avoid death due to the localized nature of the DFI in most patients. Avoiding excessive use of antimicrobial is essential and, in our series, the median duration of effective treatment was 18 days. Recent randomized controlled studies have demonstrated that antimicrobial therapy for OM is without benefit beyond 3 weeks and for those without OM, 10 days are adequate[17,18].

Our study has several limitations, including its single-center design, which may affect the generalizability of the findings, the lack of anaerobic pathogen analysis, despite their significant role in DFI[19], its small sample size, which may have limited the detection of statistically significant differences in some variables, and the exclusion of patients with negative cultures. Despite these limitations, this study is one of the few national reports providing detailed insights into a prevalent issue in the diabetic population.

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