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Original Article

Empiric Treatment of Foot Infection in Patients with Severe Diabetes

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ABSTRACT

Background: Despite being treated with antibiotics of broad spectrum recommended by International Consensus, severe diabetic patients with lower limb infection do not present a positive clinical evolution during empirical treatment. This study's bacterial profile was analysed and compared with other worldwide hospital centers.

Objective: To confirm the need of an individualized empirical treatment for severe diabetic patients with foot infection.

Methods: Retrospective analysis of cultures and antibiograms of severe diabetic patients admitted by foot infection.

Results: The results were consistent with the socioeconomic realities of developing countries. Gram-negative bacteria (52,11%) were present in most bone cultures. Results presented a high incidence of *Enterococcus faecalis* in both gram-positive (21,2%) and polymicrobial (34,7%) samples. Bacterial resistance with the use of ordinary antibiotics in the statistical analysis was high.

Conclusion: The community infections should undergo broad spectrum empirical therapy combining amikacin (80,43%) or meropenem (72,00%) with gram-negative and vancomycin (100%) or teicoplanin (90,00%) or linezolid (74,19%) with gram-positive.

Introduction

Diabetes Mellitus (DM) is a chronic disease that has been growing rapidly worldwide. It is believed that there will be more than 550 million people with DM by 2030 [1-3]. It is widely known for many years that this population needs a specific multidisciplinary approach in order to control glycemic, neurological and infectious parameters, among others [4, 5]. The inefficient therapy approach gets worse morbidity and mortality dramatically. Per year, more than one million lower limb amputation are performed due to complications related to this disease [1, 4].

In 1996, the International Working Group on Diabetic Foot (IWGDF) was created and published its first International Consensus in 1999 [1, 2, 6]. Since then, the methodology for collecting and performing culture and antibiogram as well as therapeutic antibiotics use became part of the published Consensus [6-10]. Despite of the meticulous rigor, an empirical antibiotic therapy currently recommended in the guidelines of the American Society of Infectious Diseases (IDSA) for the treatment of severe diabetic patients does not present satisfactory clinical results. It is important to emphasize that these negative results refer only to empirical therapy, in other words, to treatment performed until individualized treatment based on the culture is possible.

Objective

The objective of the present study is to corroborate the need of an individualized empirical treatment for severe diabetic patients with foot infection in developing countries and to identify the antibiotics that should be used in our health service.

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Methods

Retrospective study of bone cultures and antibiograms of severe diabetic patients admitted to the Centro Hospitalar Municipal Universitário de Santo André (Faculdade de Medicina do ABC) in 2018 by foot infection and therapeutic surgery. Patients come from a single community managed by a single integrated health system. As recommended in the 2012 and 2019 Consensus (IWGDF / IDSA), in this studies, serious infection are considered the ones that occur in patients with metabolic changes or with signs of systemic toxicity. In the presence of critical lower limb ischaemia, any infection is considered severe and the patient must be hospitalized [1, 2, 6, 9]. The collected data was analyse according to the international CLSI protocol, following the standards and norms assumed by ANVISA NBR ISO/IEC 17025 (Collegiate Board Resolution - RDC 302, of October 13, 2005). Therefore, it is evident that no swab sample was considered, and all intra operative bone biopsies were done under appropriate conditions [6, 7, 11].

Statistical Analysis

The analyses were performed using the programme IBM SPSS Statistics version. The characterization of cultures and antibiograms was presented as percentage and frequency. The Binomial test compared the percentages of the number of cultures and the number of bacteria between gram-positive, gram-negative and both simultaneously. When the test presented significance between the results of antibiotics, the percentages of the results in each bacterium were compared (Table 1). The level of significance used was 5%.

Table 1: Number of the cultures and bacteria.

Bacteria	Number of cultures		Number of bacteria	
	n	%	n	%
Gram-positive	24a	33,80	33a	30,84
Gram-negative	37b	52,11	51b	47,66
Gram-positive and Gram-negative	10c	14,08	23c	21,50
	P-value*		P-value*	
a x b	0,100		0,049	
a x c	0,015		0,183	
b x c	< 0,001		0,001	

(*) Poisson test (statistically significant if $p < 0,05$).

Results

Among the 129 severe diabetic patients operated in 2018, 100 patients were included in this sample and 118 bone cultures were collected. Unfortunately, the data reported in medical records did not present albumin excretion rate (macroalbuminuria and microalbuminuria), patient weight, circumference waist measurement and glycosylated haemoglobin at the time of admission.

The linear analysis of the data presents a majority of males diagnosed with recent diabetes (Table 2). There was no growth of bacteria in 47 cultures (negative cultures) and there was growth in 71 cultures (positive cultures). A total of 107 bacteria were isolated. Among the 118 bone cultures, there was growth of only gram-positive bacteria in 24 cultures with 33 isolated bacteria, with the highest incidence being *Staphylococcus aureus* (27,2%) and *Enterococcus faecalis* (21,2%). There was a growth of only gram-negative bacteria in 37 cultures with 51 isolated bacteria, where *Pseudomonas aeruginosa* (13,7 %), *Proteus mirabilis* (11,7%), *Escherichia coli* (11.6%) and *Morganella morganii* (9,8%) had the highest incidence.

Table 2: Sample clinical characteristics.

Clinical characteristics	Percentage of patients
Age 18-44	23
Age 45-64	52
Age > 64	25
Patients who take aspirin	21
Patients who take statins	38
White patients not hispanics	54
Black patients not hispanics	38
Hispanics	7
Other	1
Male gender	62
Diagnosis of diabetes	
< 01 year	42
1-2 years	31
>2 years	27
Patients who take dapagliflozin	1
Patients who take metformin	42
Patients who take insulin	31

Stroke	7
Arrhythmia	4
Rheumatoid arthritis	3
Chronic pulmonary disease	9
Scleroderma	1
High blood pressure	61
Hypothyroidism	12
Cardiac insufficiency	26
Neoplasia	1
Venous thrombosis	2

In 10 cultures there was growth of both gram-positive and gram-negative bacteria with a total of 23 isolated bacteria, where *Enterococcus faecalis* (34.7%) and *Pseudomonas aeruginosa* (17.3%) had the highest incidence. The number of cultures presented statistical significance among bacteria, where gram-positive (33.80%) obtained a percentage similar to gram-negative (52.11%) and both were higher in percentage than the gram-positive and negative (14,08%). In addition, (Table 1) presents that the number of bacteria was also significant, gram-negative had the highest percentage (47.66%) compared to gram-positive (30.84%) and both simultaneously (21,50%). Table 3 illustrates that there was a significant difference between the results of sensitivity and resistance of gram-negative bacteria to some antibiotics.

Table 3: Characterization and comparison of the gram-negative bacteria and antibiotics.

Antibiotics	Results	N	%	P-value*
Ampicillin	Resistant	28	93,33	< 0,001
	Sensitive	2	6,67	
Ampicillin/Sulbactam	Resistant	23	76,67	0,005
	Sensitive	7	23,33	
Amikacin	Resistant	9	19,57	< 0,001
	Sensitive	37	80,43	
Amoxicillin/Clavulanic acid	Resistant	22	68,75	0,051
	Sensitive	10	31,25	
Aztreonam	Resistant	34	87,18	< 0,001
	Sensitive	5	12,82	
Cefazolin	Resistant	7	70,00	0,344
	Sensitive	3	30,00	
Cefotaxime	Resistant	15	88,24	0,002
	Sensitive	2	11,76	
Cefoxitin	Resistant	16	48,48	0,999
	Sensitive	17	51,52	
Cefuroxime	Resistant	15	93,75	0,001
	Sensitive	1	6,25	
Ceftazidime	Resistant	39	78,00	< 0,001
	Sensitive	11	22,00	
Cefepime	Resistant	37	75,51	< 0,001
	Sensitive	12	24,49	
Ceftriaxone	Resistant	11	68,75	0,210
	Sensitive	5	31,25	
Ciprofloxacin	Resistant	32	65,31	0,044
	Sensitive	17	34,69	
Colistin	Resistant	6	54,55	0,999
	Sensitive	5	45,45	
Ertapenem	Resistant	12	30,77	0,024
	Sensitive	27	69,23	
Fosfomycin	Resistant	6	100,00	0,031
	Sensitive	0	0,00	
Gentamicin	Resistant	24	48,98	0,999
	Sensitive	25	51,02	
Imipenem	Resistant	14	32,56	0,032
	Sensitive	29	67,44	

Levofloxacin	Resistant	24	68,57	0,041
	Sensitive	11	31,43	
Meropenem	Resistant	14	28,00	0,003
	Sensitive	36	72,00	
Piperacillin/tazobactam	Resistant	21	45,65	0,659
	Sensitive	25	54,35	
Polymyxin B	Resistant	2	16,67	0,039
	Sensitive	10	83,33	
Trimethoprim/sulfamethoxazole	Resistant	24	72,73	0,014
	Sensitive	9	27,27	
Sulfazotrim	Resistant	7	43,75	0,804
	Sensitive	9	56,25	
Tetracycline	Resistant	7	100,00	0,016
	Sensitive	0	0,00	
Tobramycin	Resistant	17	51,52	0,999
	Sensitive	16	48,48	
Tigecycline	Resistant	7	53,85	0,999
	Sensitive	6	46,15	
Ticarcillin/clavulanic acid	Resistant	5	62,50	0,727
	Sensitive	3	37,50	

(*) Binomial test (statistically significant if $p < 0,05$).

Gram-negative bacteria presented high resistance to cefepime (75,51%), ceftriaxone (68,75%), levofloxacin (68,57%) and ciprofloxacin (65,31%). They were sensitive to polymyxin B (83,33%), amikacin (80.43%), meropenem (72,00%), ertapenem (69.23%) and imipenem (67.44%). The analyse presented in (Table 3), that presented significance, were studied in (Table 4) in order to measure resistant gram-negative bacteria.

Table 4: Characterization and comparison of the gram-negative bacteria individual's results.

Bacteria	Resistant		Sensitive		P value*
	n	%	n	%	
Acinetobacter baumannii/haemolyticus	41	75,93	13	24,07	< 0,001
Burkholderia P. cepacia	4	50,00	4	50,00	0,273
Citrobacter freundii	6	35,29	11	64,71	0,094
E. coli	47	61,84	29	38,16	0,049
Enterobacter cloacae	15	68,18	7	31,82	0,041
Klebsiella pneumoniae	60	85,71	10	14,29	< 0,001
Morganella morganii	30	54,55	25	45,45	0,590
Proteus mirabilis	32	44,44	40	55,56	0,410
Proteus sp	5	62,50	3	37,50	0,219
Proteus vulgaris	22	53,66	19	46,34	0,755
Providencia stuartii	4	44,44	5	55,56	0,245
Pseudomonas aeruginosa	56	65,12	30	34,88	0,007
Serratia marcescens	7	38,89	11	61,11	0,121
Serratia marcescens (First sample)	3	37,50	5	62,50	0,219
Serratia marcescens (Second sample)	3	42,86	4	57,14	0,273

(*) Binomial test (statistically significant if $p < 0,05$).

Klebsiella pneumoniae (85.71%), *Acinetobacter baumannii/haemolyticus* (75,93%), *Enterobacter cloacae* (68,18%), *Pseudomonas aeruginosa* (65,12%) and *E. coli* (61,84%) were the bacteria with highest resistance to the tested antibiotics. Table 5 demonstrates that there was a significant difference between the results of sensitivity and resistance of gram-positive bacteria to some antibiotics. Gram-positive bacteria showed high resistance to ceftriaxone (78.95%), erythromycin (77.42%) and amoxicillin + clavulanic acid (76,47%). They were sensitive to daptomycin (100.00%), vancomycin (100.00%), teicoplanin (90.00%) and linezolid (74.19%). The analyse presented in (Table 5), that showed significance, was studied in (Table 6) in order to measure resistant gram-positive bacteria. *Staphylococcus lugdunensis* (100.00%), *Streptococcus agalactiae* (Group B) (100.00%), *Streptococcus pyogenes* (100.00%) and *Enterococcus faecalis* (76.47%) were the gram-positive bacteria with the greatest sensitivity to the tested antibiotics.

Table 5: Characterization and comparison of the gram-positive bacteria and antibiotics.

Antibiotics	Results	N	%	P-value*
Ampicillin	Resistant	16	59,26	0,442
	Sensitive	11	40,74	
Ampicillin/Sulbactam	Resistant	12	70,59	0,143
	Sensitive	5	29,41	
Amoxicillin/ Clavulanic acid	Resistant	13	76,47	0,049
	Sensitive	4	23,53	
Cefoxitin	Resistant	0	0,00	0,250
	Sensitive	3	100,00	
Ceftriaxone	Resistant	15	78,95	0,019
	Sensitive	4	21,05	
Ciprofloxacin	Resistant	13	43,33	0,585
	Sensitive	17	56,67	
Clindamycin	Resistant	15	60,00	0,424
	Sensitive	10	40,00	
Daptomycin	Resistant	0	0,00	< 0,001
	Sensitive	22	100,00	
Erythromycin	Resistant	24	77,42	0,003
	Sensitive	7	22,58	
Streptomycin	Resistant	3	100,00	0,250
	Sensitive	0	0,00	
Streptomycin of high-level	Resistant	2	28,57	0,453
	Sensitive	5	71,43	
Gentamicin	Resistant	12	48,00	0,999
	Sensitive	13	52,00	
Gentamicin of high-level	Resistant	1	14,29	0,125
	Sensitive	6	85,71	
Levofloxacin	Resistant	12	40,00	0,362
	Sensitive	18	60,00	
Linezolid	Resistant	8	25,81	0,011
	Sensitive	23	74,19	
Nitrofurantoin	Resistant	2	33,33	0,688
	Sensitive	4	66,67	
Norfloxacin	Resistant	2	33,33	0,688
	Sensitive	4	66,67	
Oxacillin	Resistant	12	70,59	0,143
	Sensitive	5	29,41	
Penicillin	Resistant	19	57,58	0,487
	Sensitive	14	42,42	
Rifampicin	Resistant	7	29,17	0,064
	Sensitive	17	70,83	
Sulfamethoxazole- trimethoprim	Resistant	7	36,84	0,359
	Sensitive	12	63,16	
Sulfazotrim	Resistant	2	66,67	0,999
	Sensitive	1	33,33	
Synercid	Resistant	10	38,46	0,327
	Sensitive	16	61,54	
Tetracycline	Resistant	12	37,50	0,215
	Sensitive	20	62,50	
Teicoplanin	Resistant	3	10,00	< 0,001
	Sensitive	27	90,00	
Vancomycin	Resistant	0	0,00	< 0,001
	Sensitive	33	100,00	

(*) Binomial test (statistically significant if $p < 0,05$).

Table 6: Characterization and comparison of the gram-positive bacteria individual's results.

Bacteria	Resistant		Sensitive		P value*
	n	%	n	%	
Enterococcus avium	4	26,67	11	73,33	0,118
Enterococcus faecalis	8	23,53	26	76,47	0,003
Staphylococcus aureus	24	40,68	35	59,32	0,193
Staphylococcus auricularis	3	42,86	4	57,14	0,999
Staphylococcus epidermidis	6	42,86	8	57,14	0,791
Staphylococcus hyicus	4	66,67	2	33,33	0,688
Staphylococcus lugdunensis	0	0,00	7	100,00	0,016
Staphylococcus sciuri	8	42,11	11	57,89	0,648
Staphylococcus spp	1	33,33	2	66,67	0,999
Staphylococcus spp coagulase negativa	2	50,00	2	50,00	0,999
Staphylococcus xylosus	3	50,00	3	50,00	0,999
Streptococcus agalactiae (Group B)	0	0,00	6	100,00	0,031
Streptococcus pyogenes	0	0,00	3	100,00	0,031

(*) Binomial test (statistically significant if $p < 0,05$).

Discussion

Despite of the number of cultures presenting significance between different types of bacteria with a similar percentage between gram-positive and gram-negative bacteria as presented in (Table 1); this study differs from the literature, with higher incidence of gram-negative bacteria. Hatipoglu and contributors found, in a sample of 2,097 patients, that Western medical centers comprehending Europe and the USA have a higher prevalence of gram-positive bacteria, while Asian and African countries tend to have a higher number of gram-negative bacteria. Within this geographical context, this study should have identified a higher percentage of positives. The socio-economic conditions of Brazil can explain this difference. It is impossible to make an efficient comparison without taking into account cultural similarity to developing countries. Our country financial situation is coherent with a higher percentage of gram-negative bacteria probably due to adverse health policy conditions that involve from the basic sanitation to the primary level of the health care. The patients contemplated in this study have a socioeconomic discrepancy that is exemplified in the incidence of *Enterococus faecalis* (21.2%) and with cultures of gram-positive bacteria and in polymicrobial (34.7%) [12, 13].

In (Table 1), despite of the differences already explained, the results showed a reduced expression of polymicrobial and anaerobic cultures. Only 10 (14.08%) cultures had gram-positive and gram-negative bacteria. Unlike this study, Ramakant and contributors published a retrospective study involving 447 hospitalized patients with a majority of 66% polymicrobials. Zubair and colleagues found 31.4% of anaerobes in their study. The unmonitored use of antibiotics in an extra-hospital environment prior to hospitalization, as well as repeated hospitalizations in different medical services without standardization between hospitals may justify this differences [13, 14].

Our sample presents the peculiarity of 39.83% of negative cultures, in other words, without the growth of bacteria. This peculiarity relates to the fact that all procedures were performed by vascular surgeons in an operating room under general anaesthesia or spinal sympathetic block. None of the collected fragments were acquired under local anaesthesia or simple sedation by nurses or doctors of another specialty. The guidelines of the literature in which the effective surgical procedure allows a more efficient, broad, definitive and less morbid therapeutic approach was followed by this study. In a study of 819 patients, Chen and contributors showed that clinical treatment without a surgical approach promotes slow healing of ulcers with a predisposition to worsening morbidity and mortality. Johani and collaborators recommended performing a surgical procedure after analysing a sample of 20 patients in which 80% had changes in bacterial biofilm [15-17].

In addition to the peculiar spectrum discussed above, the relation between sensitivity and resistance to antibiotics is particularly important. The sample of gram-negative has alarming resistance rates that includes ciprofloxacin ($p = 0.04$), amoxicillin (68.75%) and other drugs recommended by international Consensus. Similarly, gram-positive bacteria also exhibit atypical behaviour with high resistance to recommended antibiotics such as clindamycin (60%) [1, 3, 6]. For many decades, the Consensuses have recommended broad-spectrum empirical therapy such as ciprofloxacin associated with clindamycin or ceftriaxone together with clindamycin, among others. In 1986, Wheat and collaborators documented this in a two-year prospective study of 54 patients. Unfortunately, the broad spectrum coverage suggested earlier do not cover some hospital centers with a profile similar to Brazilian hospital centers [6, 14, 18].

Currently, it is possible to observe a change in the patterns found in cultures and antibiograms. Like this study, numerous academic groups suggest that empirical therapy should accompany these changes and be modified. Although they seem paradoxical, these considerations are not contradictory since they refer to vastly different institutions with different patients. While Young and contributors do not recommend treating empirically Pseudomonas sp., Ramakant and contributors request that the empirical antimicrobial therapy policy in tertiary level care be changed [4, 14, 19].

Within this apparent antagonism, many hospitals already use markers such as Procalcitonin (PCT) associated with Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) curves in an attempt to make possible discoveries. Despite of the need of further studies, it is believed that the PCT composed of 116 amino acids, in addition to stratifying soft tissue infections from true osteomyelitis, can help to differentiate patients with infection from the sick without infection or even

distinguish between sepsis and local infections. Like ESR and CRP, PCT can also denote and guide possible therapeutic success with the reduction of its serum curve [20, 21]. In the future, there will probably be serum markers that, in addition to being predictive of prognosis, will help in the empirical therapy of severe diabetic patients.

Conclusion

The recommendation of broad-spectrum antibiotic therapy with drugs used in multidrug-resistant bacteria for all patients with severe infection regardless of their origin, comorbidities or previous use of antibiotics can trigger the abuse of antibiotics that goes global policies to reduce antimicrobial resistance but in severe diabetic patients with gram-negative bacteria flora present better results if treated empirically with amikacin (80.43%) or meropenem (72.00%), after the mandatory assessment of the clinical condition of each patient using parameters such as creatinine clearance among many others. Similarly, the flora of gram-positive bacteria should receive vancomycin (100.00%) or teicoplanin (90.00%) or linezolid (74.19%) until individualized treatment based on the antibiograms is possible.

Conflicts of Interest

None.

Author Contributions

Alexandre Sacchetti Bezerra: Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published; Flávia Altheman Loureiro: Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work; Carla Maria Pasquareli Vázquez: Final approval of the version to be published; Afonso César Polimanti: Drafting the work or revising it critically for important intellectual content; Rafi Felicio Bauab Dauar: Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, final approval of the version to be published.

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