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Foot Osteomyelitis Caused by Multidrug- and Extensively Drug-Resistant Gram-Negative Bacteria

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ABSTRACT

There are scarce data regarding foot osteomyelitis (FO) caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria (GNB). This study investigates the causative organisms, the diagnostic and therapeutic approach and the outcome of these infections. All patients with FO caused by MDR and/or XDR GNB who received treatment in the Department of osseous infectious diseases of the "Attikon" University Hospital of Athens, Greece, were recorded and evaluated during a six-year-period. Seventeen patients, of which 64.7% females, with a mean age of 54.06 years were studied. There were nine cases with diabetic (DFO), and 76.5% of patients reported previous use of antimicrobials. Pathogens were isolated from soft-tissue biopsies or intra-operative tissue samples (n=12) and/or affected bone samples (n=5). In most cases, E. coli *and* P. aeruginosa *were isolated (each 29.4%), followed by* P. mirabilis *(11.7%), while polymicrobial infection was detected in nine patients (53%). Most cases were given antimicrobial monotherapy (88.2%) with a mean duration of 90.05 days, while surgery significantly promoted cure of the infection. Foot and DFO cases represent a challenging to treat disease, requiring a multidisciplinary approach. Surgical treatment remains the cornerstone of treatment, while it is of utmost importance to isolate the causative organisms. MDR and XDR GNB represent an emerging threat and more data are needed to better understand these infections.*

Keywords: osteomyelitis, diabetic ulcer, Gram-negative bacteria, foot osteomyelitis, diabetic foot infection.

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INTRODUCTION

Foot osteomyelitis (FO) is a challenging to treat disease, while it poses significant pressure on both the patient and healthcare system (1). Multiple risk factors have been associated with FO, with diabetes mellitus (DM) being the most common one (1, 2). Hematogenous or exogenous spread of bacteria are the main mechanisms of the infection. Hematogenous osteomyelitis involves bacteremia and seeding of the bone with an organism from a remote source, while exogenous spread involves direct inoculation of the bone adjacent tissue, open fractures, penetrating trauma or iatrogenic contamination (1, 2).

Diabetic foot infection (DFI) represents a major complication in patients with DM, causing serious morbidity, discomfort and reduced quality of life, while these infections are the leading cause of non-traumatic lower limb amputations (3, 4). When this infection proceeds into deeper structures, including the underlying bone, diabetic foot osteomyelitis (DFO) develops (3).

Diabetic foot infection and DFO are usually polymicrobial. The most commonly isolated pathogens include *Staphylococcus aureus*, *Proteus* spp. and E*scherichia coli*, while wounds involving deep tissues or in ischemic necrosis cases, obligate anaerobes may also be involved (3-5). Gram-negative bacteria (GNB) are considered less common causative organisms of DFO. Nevertheless, more recent studies have shown that such organisms are involved in 18% to 57% of DFOs (6). Multidrug-resistant (MDR) and extensively drug resistant (XDR) Gram-negative organisms are considered rare causes of FO, while there are scarce data regarding such infections (6, 7).

The aim of the present study was to investigate the MDR and XDR Gram-negative causative organisms of FO cases and to evaluate the proper diagnostic and therapeutic management and, finally, the outcome of these infections. ❑

MATERIALS AND METHODS

Study design

The present research is a retrospective study of a prospectively collected database. During a six-year period, all FO cases caused by MDR and XDR GNB treated in the osseous infectious diseases department of the "Attikon" University hospital of Athens, Greece, were recorded and evaluated.

The present study is a descriptive analysis of clinical characteristics, therapeutic interventions, including surgical and medical treatment and infection outcome at the out-patient reference clinic of the Department.

The study was approved by the Hospital's Ethical Committee.

Data collection

Data regarding patients' age and comorbidities, history of trauma, prior history of bone infection, any orthopaedic device in place, prior use of antimicrobial agents and clinical presentation of the current episode of FO were recorded.

Isolates of GNB from tissue and/or bone and their resistance pattern (MDR or XDR) were identified. At the diagnosis of infection and later on in cases of symptoms of exacerbation, blood cultures were also performed.

Surgical treatment of each patient for the current event of FO was classified as debridement, arthrodesis or amputation.

Antimicrobial treatment – regimen, monotherapy or combination therapy, length of intravenous (IV) administration, total duration of treatment – was assessed. Factors related to lack of eradication of the infection during a 12-month follow-up were evaluated.

Definitions

1. Foot osteomyelitis was identified according to standard clinical, radiological and histological definitions (8). Diabetic foot osteomyelitis (DFO) was defined upon the IWGDF (International working group on the diabetic foot) guidelines: a combination of the probe-to-bone (PTB) test with the erythrocyte sedimentation rate (ESR) C-reactive protein, and plain X-rays being the initial steps for the diagnosis of osteomyelitis (9).

2. Gram-negative bacteria isolates by either bone or tissue specimen relevant to FO were identified by routine conventional biochemical and metabolic tests or Matrix-assisted laser desorption ionization – time of flight (MALDI-TOF). Antimicrobial susceptibility was assessed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations (10). The Vitek 2 (bioMérieux, Durham

NC) automated antimicrobial susceptibility test system was used for microbial sensitivities.

3. An organism was defined as either MDR if non-susceptible to at least one agent in three or more antimicrobial categories (aminoglycosides, anti-pseudomonal cephalosporins, carbapenems, fluoroquinolones, penicillin plus β-lactamase inhibitors, monobactams, phosphonic acids, polymyxins), or XDR if non-susceptible to at least one agent in all but two or fewer antimicrobial categories (*i.e.*, susceptible to only one or two categories) (11).

4. Evaluation of treatment – Antimicrobial treatment was evaluated as either monotherapy by a sole agent or combined antimicrobial treatment (more than one concomitant administration of antimicrobial agents). Surgical treatment included local debridement, arthrodesis or amputation of the infected limb.

5. Outcome was defined as remission if no clinical, laboratory or microbiological signs of infection were detected and relapse if clinical signs or symptoms and laboratory findings of the initially cured infection had reappeared during the 12-month post-treatment follow-up period. Any other condition was considered as lack of eradication and treatment failure.

Statistical analysis

Descriptive statistics were performed to present frequencies. Factors that can influence outcome were included in a univariate analysis model. Chi square and Fischer exact tests were used for categorical variables and independent t-test for continuous variables. Taking into consideration the time to failure of cure in a 12-month follow up, Kaplan-Meier survival analysis was performed. P-values less than 0.05 were considered statistically significant. All analyses were performed using SPSS (22.0 SPSS.Inc IBM). ❑

RESULTS

Seventeen patients with documented FO by MDR or XDR GNB were eligible for evaluation.

All patients were diagnosed with chronic osteomyelitis. No sepsis, septic shock or concomitant bacteremia were recorded. Female patients predominated (n=11, 64.7%) and subjects' mean age was 54.06 years [standard deviation (SD)=16.5].

Time from the current infection onset to treatment ranged from 1-20 months (mean 4.63). Besides DM (9; 52.9%), other comorbidities (13; 76.5%) included renal failure (two; 11.8%) and rheumatoid arthritis (1; 5.9%). Ten patients had post-traumatic FO (58.8%), whilst eight (47.1%) had a history of prior orthopedic surgery at the location of FO; six of them with an embedded orthopedic device. The mean time from orthopedic instrumentation to infection onset ranged from four to 20 months. Nine patients (52.9%) were diagnosed with DFO.

The mean ESR value at the time of FO diagnosis was 61.30 (SD=51.44) mm/hr. Clinical FO presentation included fever (35.3%), local pain (47.1%), foot ulcer (76.5%), local soft tissue infection signs (76.5%) and prone to the bone sinus tract (47.1%). Thirteen patients (76.5%) reported previous use of antimicrobial agents during the previous six months.

TABLE 1. Clinical characteristics, treatment and outcome in MDR *vs* XDR FO cases. MDR=multidrug-resistant; XDR=extensively drug-resistant; FO=foot osteomyelitis

Variables, n (%)	MDR n= 13 (%)	XDR n=4 (%)	OR Lower (CI 95%) Upper	*p*
Age >60 years	6 (46.2)	2 (50)	0.857 (0.091-8.075)	*>0.999*
Male Female	5 (38.5) 8 (61.5)	1 (25) 3 (75)	1.875 (0.150-23.396)	*>0.999*
History of trauma	8 (61.5)	2 (50)	1.600 (0.168-15.273)	*>0.999*
Diabetes mellitus	5 (38.5)	4 (100)	1.800 (1.003-3.229)	*0.082*
Clinical features				
Fever	4 (30.8)	2 (50)	0.444 (0.045-4.374)	*0.584*
Soft tissue infection	9 (69.2)	4 (100)	1.444 (1.005-2.075)	*0.519*
Sinus tract	7 (53.8)	1 (25)	3.500 (0.284-43.161)	*0.576*
Local pain	6 (46.2)	2 (50)	0.857 (0.091-8.075)	*>0.999*
Foot ulcer	10 (76.9)	3 (75)	1.111 (0.082-15.036)	*>0.999*
Polymicrobial infection	7 (53.8)	2 (50)	1.167 (0.124-10.990)	*>0.999*
Treatment				
Use of fluoroquinolones	2 (15.4)	-	0.733 (0.540-0.995)	*>0.999*
Use of carbapenems	5 (38.5)	2 (50)	0.625 (0.065-5.966)	*>0/999*
Use of colistin	-	2 (50)	0.133 (0.037-0.484)	*0.044*
Monotherapy	12 (92.3)	3 (75)	4.000 (0.190-84.199)	*0.426*
Antibiotics > 42 days	9 (69.2)	2 (50)	2.250 (0.229-22.144)	*0.584*
Surgery for FO	9 (69.2)	3 (37.5)	0.750 (0.058-9.618)	***>0.999***
Cure	8 (61.5)	1 (25)	0.208 (0.017-2.600)	*0.294*

TABLE 2. Antimicrobial resistance profile of Gram-negative causative pathogens. MDR=multidrug-resistant; XDR=extensively drug-resistant

Pathogens	MDR	XDR	Total
Gram-negative bacteria (GNB)	n=13 (76.5%)	n=4 (23.5%)	n= 17 (100%)
Escherichia coli	5 (38.5)	-	5 (29.4)
Pseudomonas aeruginosa	3 (23)	2 (50)	5 (29.4)
Proteus mirabilis	2 (15.4)	-	2 (11.7)
Enterobacter cloacae	1 (7.7)	-	1 (5.9)
Klebsiella pneumoniae	-	1(25)	1 (5.9)
Acinetobacter baumannii	-	1 (25)	1 (5.9)
Morganella morganii	1 (7.7)	-	1 (5.9)
Stenotrophomonas maltophilia	1 (7.7)	-	1 (5.9)

All FO cases were radiologically and microbiologically confirmed. No significant differences regarding clinical, microbiological and treatment data of patients with DFO vs those with non-diabetic foot osteomyelitis were observed (Table 1).

Identification and distribution of pathogens characterized as MDR (13; 76.5%) or XDR (4; 23.6%) are highlighted in Table 2. Pathogens were isolated from soft tissue biopsy or intra-operative tissue samples (12; 70.6%) and affected bone samples (5; 29.4%). All blood cultures were negative.

All *Escherichia coli* strains were extended spectrum beta-lactamases (ESBL) producers, with 80% resistance to fluoroquinolones and 100% sensitivity to carbapenems. *Pseudomonas aeruginosa* isolates were XDR (40%) with resistance to fluoroquinolones (80%) and carbapenems (40%). All Proteus mirabilis isolates were ESBL producers. The only *Acinetobacter baumannii* isolate was XDR, resistant to sulbactam, aminoglycosides, fluoroquinolones, cotrimoxazole and carbapenems but susceptible to colistin. Susceptibility test for tigecycline was not provided at the time of the study. The only *Klebsiella pneumoniae* isolate produced *Klebsiella pneumonia* carbapanemase (KPC). Polymicrobial infection was detected in nine cases (53%) and in eight (88.9%) patients a Gram-positive pathogen was identified.

Table 3 highlights the therapeutic management, including antimicrobial treatment and surgical intervention of each case. The mean duration of treatment was 90.05 days (SD= 48.3) and 11 (64.7%) patients received monotherapy. Adverse events (myelotoxicity, rash, gastrointestinal disorders) were reported in three (17.64%) cases. Myelotoxicity and rash were attributed to cotrimoxazole, while gastrointestinal disorders to amoxicillin/ clavulanic acid. In all cases, the side effects were mild and transient.

TABLE 3. Medical and surgical treatment of 17 patients with MDR/XDR GNB foot osteomyelitis. GNB=Gram-negative bacteria; MDR=multidrug-resistant; XDR=extensively drug-resistant; MER=meropenem; ERT=ertapenem; IMI/CL=imipenem/cilastatin; CIPR=ciprofloxacin; AMOX/CLAV=amoxicillin/clavulanate; CEFT=ceftazidime; PIP/TAZ=piperacillin/tazobactam; TYG=tigecycline; AZT=aztreonam; MIN=minocycline; COTR=cotrimoxazole; COL=colistin; antimicrobials linked by "+" correspond to combination treatment; if separated by "," consecutive administration is indicated

Pts	Gender	Age	Prior antimicrobial use	GNB	MDR/XDR	Surgery for infection	Antimicrobials for GNB	Total duration (days)	Cure
1	F	68	Yes	*E. coli*	MDR	Amputation	MER	90	Yes
2	M	63	Yes	*E. coli*	MDR	Debridement	MER	100	Yes
3	M	73	Yes	*P. mirabilis*	MDR	No	AMOX/CLAV	105	No
4	F	29	Yes	*E. coli*	MDR	Debridement	ERT	180	Yes
5	F	62	Yes	*P. aeruginosa*	XDR	Debridement	IMI/CIL, AZT	23	No
6	M	76	Yes	*M. morganii*	MDR	Amputation	ERT	105	Yes
7	F	57	Yes	*P. mirabilis*	MDR	No	PIP/TAZ, TYG	20	No
8	F	57	Yes	*K. pneumoniae*	XDR	No	ERT, MIN	42	No
9	F	39	Yes	*P. aeruginosa*	MDR	Debridement	PIP/TAZ, CEFT	90	Yes
10	M	58	No	*E. coli*	MDR	No	PIP/TAZ	30	No
11	M	61	Yes	*S. maltophilia*	MDR	Debridement	CIPR+ COTR	90	Yes
12	F	51	Yes	*P. aeruginosa*	MDR	No	CIPR	120	No
13	F	52	No	*A. baumannii*	XDR	Debridement	COL	75	No
14	M	61	No	*P. aeruginosa*	XDR	Amputation	COL + AZT	120	Yes
15	F	19	Yes	*P. aeruginosa*	MDR	Debridement	CEFT	120	Yes
16	F	26	Yes	*E. coli*	MDR	Debridement	MIN	180	No
17	F	67	No	*E. cloacae*	MDR	Debridement	MER	41	Yes

TABLE 4. Univariate analysis for factors associated with lack of cure in patients with FO by MDR/XDR GNB.
MDR GNB=multidrug-resistant Gram-negative bacteria; XDR GNB=extensively drug-resistant Gram-negative bacteria; FO=foot osteomyelitis

Variables, n (%)	Cure n=9 (52.9%)	No cure n=8 (47.1%)	OR Lower (CI 95%) Upper	p
Age >60 years	6 (66.7)	2 (25)	0.167 (0.020-1.384)	*0.153*
Male Female	4 (44.4) 5 (55.6)	2 (25) 6 (75)	0.417 (0.053-3.306)	*0.620*
History of trauma	6 (66.7)	4 (50)	0,500 (0.070-3.550)	*0.637*
Diabetes mellitus	3 (33.3)	6 (75)	6.000 (0.722-48.337)	*0.153*
Clinical features				
Fever	3 (33.3)	3 (37.5)	1.200 (0.164-9.799)	*>0.999*
Soft tissue infection	6 (66.7)	7 (87.5)	3.500 (0.284-43.161)	*0.576*
Sinus tract	3 (33.3)	5 (62.5)	3.333 (0.455-24.443)	*0.347*
Local pain	3 (33.3)	5 (62.5)	3.333 (0.455-24.443)	*0.347*
Foot ulcer	9 (100)	4 (50)	3.250 (1.438-7.345)	***0.029***
Pathogens				
MDR GNB XDR GNB	8 (88.9) 1 (11.1)	5 (62.5) 3 (37.5)	0.208 (0.017-2.600)	*0.294*
Pseudomonas aeruginosa	3 (33.3)	2 (25)	0.667 (0.080-5.537)	*>0.999*
Polymicrobial infection	4 (44.4)	5 (62.5)	2.083 (0.209-14.549)	*0.637*
Treatment				
Use of fluoroquinolones	1 (11.1)	1 (12.5)	1.143 (0.060-21.870)	*>0.999*
Use of carbapenems	5 (55.6)	2 (25)	0.267 (0.034-2.116)	*0.335*
Use of colistin	1 (11.1)	1 (12.5)	1.143 (0.060-21.870)	*>0.999*
Antibiotics > 42 days		4 (50)	0.286 (0.035-2.322)	*0.335*
Surgery for FO	9 (100)	3 (37.5)	4.000 (1.501-10.658)	***0.009***

No difference regarding clinical features, history of trauma, diabetes mellitus, surgical treatment, use of carbapenems or fluoroquinolones was found between the MDR and XDR patients' groups. Colistin was exclusively administered in patients with XDR FO (p=0.044) (Table 4).

Surgical intervention as curative treatment for FO by MDR/XDR GNB was performed in 12 patients (70.6%). Surgical procedures included tissue and bone debridement (10; 76.9%) and amputation (3; 25%). The five patients who did not undergo surgery had refused a surgical approach and therefore, treatment efforts had been continued with medical means.

Univariate analysis of factors associated with lack of cure is presented in Table 3. Overall, nine (52.9%) patients were cured. Surgery promoted cure [OR 4.00 (CI 95% 1,501-10.658, p=0.009]. Nine (75%) patients who underwent additional surgical management were cured, whilst in all those who did not undergo a surgical intervention, medical treatment alone had been proven ineffective.

Kaplan-Meier survival analysis showed that surgery was significantly associated with favorable outcome during the 12-month follow-up

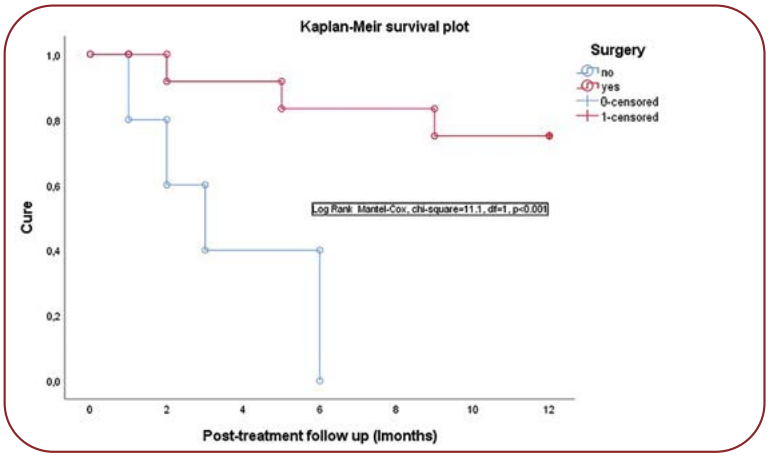

FIGURE 1. Kaplan-Meier survival analysis presenting the impact of surgery on foot osteomyelitis outcome

after the end of treatment (Log Rank test (Mantel-Cox, chi-square=11.1, df=1, p<0.001) and Wilcoxon (Gehan) Statistic=7.842, df=1, p=0.001) (Figure 1). ❑

DISCUSSION

Most FO cases are usually caused by Gram-positive bacteria, mostly deriving from the skin flora, such as *S. aureus* (1-3). However, GNB may also participate in these infections (6). The management of FO, especially through the prism of diabetes mellitus, is extremely challenging. It is of paramount importance to identify the causative microorganism(s) for administration of proper antimicrobial treatment. Although not many series with GNB FO or DFO cases exist, these organisms are not so rarely isolated in such infections (9). Nevertheless, there are scarce data regarding MDR or XDR GNB causing FO or DFO.

During the last decades, bacterial resistance has emerged as a major healthcare issue worldwide (12). It has been estimated that resistant bacteria would be the cause of approximately 10 million deaths worldwide by 2050 (12). Gram-negative bacteria may exhibit intrinsic and acquired mechanisms of resistance to antimicrobial agents, including degradation or modification of such drugs, alternation of drug target, decreased intracellular anti-microbial accumulation, biofilm formation and signaling pathway that mediated antimicrobial resistance (12, 14). Inappropriate overuse of antimicrobials represents a major factor for the development of resistant bacteria. Strict rules of antimicrobial strategies are of the cornerstone for the prevention of such infections (6, 7).

It is already known that infections caused by MDR and XDR GNB contribute to infection's exacerbation due to resistance to last-line antimicrobials (15). Gram-negative bacteria represent a particular issue, since they have a second polar outer membrane and numerous efflux pumps that render these pathogens less susceptible to drug intervention (12, 15, 16). It is of note that the repeated or long-term administration of antimicrobials for treating infections due to MDR or XDR GNB could enhance the development of resistance to newer antimicrobial compounds (16, 17).

There are data suggesting an emerging increase in GNB orthopaedic infections. However, most studies focus on prosthetic joint infections (18, 19). The literature lacks large series of FO cases, their diagnostic approach, treatment and therapeutic interventions (4, 6). There are less published cases due to GNB, especially when it comes to MDR or XDR causative strains (6, 20). Thus, the present study could be considered one of the few single-center series of MDR and XDR GNB FO and DFO.

The present study described the causative organisms of MDR and XDR GNB of FO and DFO cases treated during a six-year period in the Department of osseous infectious diseases of the "Attikon" University hospital of Athens, Greece. Furthermore, the antimicrobial sensitivities of the causative pathogens were identified, while the diagnostic approaches, including clinical symptomatology, laboratory examination and imaging techniques, were evaluated. Additionally, the therapeutic management, including antimicrobial treatment and surgical intervention, as well as outcome of these infections were also evaluated and presented.

Gram-negative bacteria in foot or DFO are most commonly reported in mixed infections with Gram-positive pathogens in patients with chronic or previously treated infections (6, 20, 21). In many cases, early empirical treatment may be initiated covering mainly Gram-positive organisms. Nevertheless, it is absolutely necessary to isolate the causative pathogens from deep bone cultures, since GNB may also represent colonizers or contaminants (22, 23). In the present series, polymicrobial infection was detected in nine cases (53%) and in eight (88.9%) patients a Gram-positive pathogen was identified.

It has been reported that in DFO cases, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp (12, 13) were the GNB that caused most nosocomial infections. In the present study, as depicted in Table 1, in most cases *E. coli* and *P. aeruginosa* were isolated (five cases each; 29.4%), followed by *P. mirabilis* (2; 11.7%) and *E. cloacae*, *K. pneumoniae*, *A. baumannii*, *M. morganii* and *Stenotrophomonas maltophiia* in one case (5.9%) each. It should be noted that the causative pathogens of foot or DFO may depend on many factors such as the geographic location (affected by the climate and socio-economic variables),

the chronicity of the wound, the location where the infection was acquired (including community or hospital and specific exposures or previous surgical interventions) (12, 16).

Regarding the surgical treatment of foot or DFO, it is of note that this study revealed that surgical intervention significantly promoted the eradication of the infection. Most cases were treated with radical soft tissue and bone debridement (76.9%), followed by amputation (25%). Surgical removal of all infected and necrotic bone and tissue has been reported as the most common approach to treating foot and DFO (4, 24-27).

In the present series, *E. coli* and *P. aeruginosa* were the most commonly isolated MDR and/or XDR GNB. Regarding the treatment of *E. coli* cases, in two (40%) of them meropenem was used, followed by ertapenem, piperacillin/tazobactam and minocycline in one case each (20%). For the treatment of patients with *P. aeruginosa* infection, the following antimicrobial agents were used: imipenem/cilastatin and aztreonam in one case (20%), piperacillin/tazobactam and ceftazidime in another one (20%), ciprofloxacin and ceftazidime in one case each, and the combination of colistin + aztreonam in another one.

Surgery alone in osteomyelitis cases is not an adequate treatment. These infections require systemic proper antimicrobial treatment as well (3, 7, 28). It should be kept in mind that antimicrobial-related adverse events are frequent in all types of infections. In studies with DFO, this incidence ranges between 15% and 30%, while they mostly occur during the first three weeks of therapy (4, 28). In the present series, adverse events included myelotoxicity, rash and gastrointestinal disorders, which occurred in 17.64% of all cases.

Regarding the duration of antimicrobial treatment for DFO, 4-6 weeks are usually recommended, but it varies vastly in the published series (28, 29). Laboratory markers such as C-reactive protein (CRP) and the clinical severity of infection should be routinely evaluated during treatment (4, 29). In this series, the mean antimicrobial treatment duration was 90.05 days.

Facing the threat and the increasingly serious problem of GNB drug-resistance, there are three main tactics for future solutions, including discovery of novel antimicrobial agents, developing new antimicrobial adjuvants and screening alternatives to antimicrobials (12). Continuous development of novel antimicrobials or extending the lifespan of the current ones, such as development of antimicrobial adjuvants, remains the focus in the treatment of bacterial infections (13, 14). However, the discovery of new agents against GNB is becoming difficult, since none of the novel agents specifically targeting GNB has been approved by the FDA in decades (12). It is of note that various combinations of antimicrobials have been recently suggested for difficult to treat GNB infections, including ceftazidime/avibactam, ceftolozane/tazobactam, cefiderocol, imipenem/relebactam and meropenem/vaborbactam (30-33).

Limitations of the present study include the relatively small number of patients coming from a single center. Moreover, details on surgical procedures (peri-operative conditions, antimicrobial prophylaxis, the extension of concomitant tissue damage, the need for plastic surgery) were not available. Furthermore, data on previous prolonged antimicrobial treatment, including time before the current infection, type of agent and correlation with current resistance and data on empirical antimicrobial treatment are not available as well due to the retrospective nature of the study. Nevertheless, taking into account the rarity of MDR or XDR osteomyelitis reports especially on the foot area, the present information may be useful for the management of such cases. ❑

CONCLUSION

Foot and DFO cases represent challenging to treat disease, requiring a multidisciplinary approach. It is of paramount importance to isolate the causative microorganism(s) for the administration of proper antimicrobial treatment, while treatment duration seems that should be defined upon the clinical characteristics and the inflammation laboratory markers. Multidrug-resistant and/or XDR GNB causing foot and DFO are a dangerous reality. Surgical management seems to remain the cornerstone of treatment, since removal of all necrotic tissues is a major factor in the eradication of the infection. Further experience is required to elucidate the steps of medical and surgical management. ❑

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editing; EG and AP were responsible for data collection. All authors have read and agreed to the published version of the manuscript.

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