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Brief report

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Exploring therapeutic options for mild diabetic-related foot infections: a comparative *in vitro* study of cefditoren versus amoxicillin/clavulanic acid

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ABSTRACT

Skin and soft tissue infections (SSTIs), and particularly diabetic-related foot infections (DFI), present diagnostic and therapeutic complexities, often leading to severe complications. This study aims to evaluate the *in vitro* efficacy of cefditoren and amoxicillin/clavulanic acid against typical DFI pathogens. Clinical samples from 40 patients with mild SSTIs were analyzed, revealing a predominance of *Staphylococcus* spp. and *Streptococcus* spp. species. Cefditoren exhibited activity against 90% of isolates, with superior potency over amoxicillin/clavulanic acid. These findings underscore the utility of cefditoren in empirical treatment of DFI, although a larger sample size would be desirable for further validation.

KEYWORDS: Cefditoren; amoxicillin/clavulanic acid, diabetic foot infections, mild,

Alternativas terapéuticas en la infección leve del pie de diabético: estudio comparativo *in vitro* de cefditoreno frente a amoxicilina/ácido clavulánico

RESUMEN

Las infecciones de piel y partes blandas (IPPB), y en particular las infecciones del pie de diabético (IPD), presentan complicaciones diagnósticas y terapéuticas, que a menudo desembocan en complicaciones graves. El objetivo de este estudio fue evaluar la eficacia *in vitro* de cefditoreno y amoxicilina/ácido clavulánico frente a los microorganismos típicos de las IPD. Se analizaron muestras clínicas de 40 pacientes con IPPB leves mostrando un predominio de especies de *Staphylococcus* spp. y *Streptococcus* spp. Cefditoreno mostró frente al 90% de los aislados una potencia superior a la de la amoxicilina/ácido clavulánico. Estos resultados destacan la utilidad de cefditoreno en el tratamiento empírico de la IPD, aunque sería deseable disponer de un mayor tamaño muestral para una mejor validación.

PALABRAS CLAVE: Cefditoreno; amoxicilina/ácido clavulánico, infecciones del pie diabético, leve

INTRODUCTION

Skin and soft tissue infections (SSTIs) are common conditions involving a wide range of physiological structures with varying severity and prognosis [1,2]. Among them, diabetes-related foot infection (DFI) represents a diagnostic and therapeutic challenge [3]. DFIs are complex and debilitating consequences of diabetes mellitus. Diabetic neuropathy, peripheral artery disease and immune dysfunction predispose the foot to injury and exacerbation of bacterial infections [4]. Currently, DFI is the most common cause of lower extremity amputation and the most common reason for prolonged hospitalization for diabetic patients with high socioeconomic implications for patients and health systems [5-9]. Treatment of DFI requires a multidisciplinary approach and tailoring of antibiotic therapies to the causative pathogen to improve efficacy and reduce antimicrobial resistance [10]. Methicillin-susceptible *Staphylococcus aureus* (MSSA) and other Gram-positive cocci are predominant in DFIs without deep tissue involvement or systemic signs (mild infections) [10,11]. Therefore, DFI guidelines recommend oral amoxicillin-clavulanic acid as the first choice for empirical treatment of mild infections in patients with no history of MRSA infection or colonization and without recent hospitalization [10].

Cefditoren pivoxil, a third-generation cephalosporin exhibits promising activity against common DFI pathogens [12,13], making it a potential first-line treatment option.

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The aim of this study was to evaluate the antimicrobial activity of cefditoren against pathogens recovered from mild DFIs of patients requiring, at least initially, oral treatment.

METHODS

A prospective study was conducted to assess the antibiotic susceptibility of DFI bacterial isolates to amoxicillin-clavulanic acid and cefditoren. Clinical isolates from consecutive samples (tissue biopsies) collected between November 2023 and March 2024 from outpatients with mild DFIs treated in our teaching hospitals were analyzed. DFIs were classified as mild according to the depth and extent of the wound as defined by the Infectious Diseases Society of America guidelines [10]. Isolates were identified in the bacteriology laboratory using standard operating procedures after homogenization of the samples. Routine testing of penicillin and cefoxitin susceptibility was performed [14,15]. All isolates were stored at -80°C and subsequently used for broth microdilution susceptibility testing to amoxicillin-clavulanic acid and cefditoren according to CLSI recommendations [14]. MIC values were determined after 18-20 hours of incubation at 37°C in ambient or 5% CO_2. Interpretation of antimicrobial susceptibility for amoxicillin-clavulanic acid was performed using current EUCAST breakpoints and recommendations [15]. For staphylococcal species and *Streptococcus* group B isolates, susceptibility was inferred from cefoxitin and penicillin results respectively [15]. For *Streptococcus viridans* groups strains, a MIC≤0.12 mg/L was used as interpreting criteria. For cefditoren, susceptibility breakpoints based on pharmacodynamic data, ranging from ≤0.125 mg/L (FDA prescribing information) to ≤0.5 mg/L (approved by the reference Member State, Spain, during the Mutual Recognition Procedure in Europe) for community respiratory pathogens, or MIC ≤ 1 mg/L for non-respiratory pathogens were applied [13,16].

RESULTS

A total of 40 tissue specimens were received during the study period. All specimens were culture-positive and 34 showed the growth of a single microorganism. Six specimens were polymicrobial, yielding 2 to 3 microorganisms each. In total, 47 aerobic microorganisms were isolated (Table 1). In 27 out of 40 (67.5%) specimens, the isolated species was *S. aureus*; being 85.5% of them (23 out of 27) methicillin-susceptible with 78.3% (18 out 23) isolated in pure culture. In 4 out of 40 (10%) specimens, MRSA was the recovered isolate (8.5% of all microorganisms). Other species of staphylococci were recovered from 8 out of 40 (20.0%) specimens, including 4 *S. epidermidis* isolated in pure culture, 2 *S. lugdunensis* and 3 other coagulase-negative staphylococci, accounting for 19.1% (9 of 47) of all isolates. *Streptococcus* species were isolated from 11 of 40 (27.5%) specimens, representing 23.4% of total isolates (11 out of 47), with *S. agalactiae* as the most predominant streptococci.

Table 1 Distribution of isolated microorganisms

Microorganisms	No. isolates n=47	% total isolates	% within the genus	No. in pure culture n=34
Staphylococcus spp.	36	76.6		26
S. aureus	27	57.5	75.0	22
MSSA	23	48.9	63.89	18
MSRA	4	8.5	11.11	4
S. haemolyticus	1	2.1	2.78	-
S. epidermidis	4	8.5	11.11	4
S. lugdunensis	2	4.2	5.56	-
Other Staphylococci	2	4.2	5.56	-
Streptococcus spp.	11	23.4		8
S. agalactiae	7	14.9	63.64	6
salivarius group	2	4.2	18.18	1
anginosus group	2	4.2	18.18	1

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 2 MIC_{50}, MIC_{90} and MIC range for cefditoren and amoxicillin-clavulanic acid (mg/L)

	Cefditoren		Amoxicillin/clavulanic acid	
Microorganism	MIC_{50}/ MIC_{90}	Range	MIC_{50}/ MIC_{90}	Range
S. aureus	0.12/0.25	0.12-0.25	0.5/1	0.12-1
S. epidermidis	0.06/0.12	0.06-0.12	0.5/0.5	0.25-0.5
S. lugdunensis	0.06/0.12	0.06-0.12	0.5/0.5	0.5
S. haemolyticus	0.5/0.5	0.5	2/2	2
Other staphylococci	0.03/0.06	0.03-0.06	0.12/0.12	0.12
***Staphylococcus* spp.**	**0.12/0.25**	**0.12-0.5**	**0.5/1**	**0.12-2**
S. agalactiae	0.007/0.015	0.007-0.015	0.015/0.015	0.015
S. anginosus	0.007/0.015	0.007-0.015	0.015/0.12	0.015-0.12
S. salivarus	0.015/0.015	0.015	0.06/0.06	0.06
Streptococcus spp.*	**0.015/0.015**	**0.007-0.015**	**0.015/0.12**	**0.015-0.12**

*All isolates were penicillin-susceptible

The antimicrobial susceptibilities of the microorganisms isolated, excluding MRSA strains, are shown in Table 2. All staphylococci and streptococci strains tested were fully susceptible to amoxicillin-clavulanic acid and cefditoren with MICs ranging from 0.015-2 mg/L and 0.007-0.5 mg/L respectively. The MIC_{90} for cefditoren were 4-8 folds lower than those for amoxicillin-clavulanic acid.

DISCUSSION

Skin and soft tissue infections (SSTi) represent a significant burden on healthcare systems, particularly among persons with diabetes, who have predisposition to these complications due to their comorbidities [5,7,9]. The present study offers insights into the bacterial aetiology of diabetes-related superficial infections and highlights the activity of cefditoren against the isolated microorganisms, making it a potential therapeutic option for the management of this condition.

These findings underscore the predominance of S. *aureus* as the primary causative agent in early DFIs, consistent with previous reports emphasizing the significance of this microorganism in SSTIs [17,18]. Notably, most of the *S. aureus* isolated were susceptible to methicillin supporting beta-lactams with approved clinical indications for staphylococcal infections, as first-line agents for the treatment of mild DFIs.

Cefditoren has the indication for the treatment of uncomplicated SSTIs, but susceptibility breakpoints have not been defined to guide dosing in clinical practice. However, due to the unreliability of staphylococcal breakpoints, the International Committees on Antimicrobial Susceptibility Testing have decided to eliminate all breakpoints for anti-staphylococcal β-lactams, except penicillin, oxacillin, cefoxitin, and ceftaroline [14,15]. Current guidelines encourage laboratories to interpret susceptibility to beta-lactams using penicillin, oxacillin, or cefoxitin as surrogates [14,15].

This study demonstrates that cefditoren exhibits similar coverage to amoxicillin-clavulanic acid against common DFI pathogens (91.5%) but with 4 to 8 times greater antimicrobial potency. The acceptable case coverage threshold (90%), in line with the percentages of efficacy that cefditoren has previously demonstrated in SSTIs [12,13], makes it an optimal candidate for the empirical treatment of patients with mild DFIs. Studies involving a larger number of specimens are warranted.

In conclusion, our study sheds light on the microbial landscape and susceptibility patterns of SSTI in persons with diabetes and provides microbiological evidence supporting the clinical efficacy of cefditoren against SSTI common pathogens in published studies [12,13], emphasizing its microbiological adequacy for empirical treatment of DFI.

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CONFLICTS OF INTEREST

P. Coronel and E. Gómez-Rubio are employees of Meiji Pharma Spain. Rest of authors have no conflict of interest.

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