Medical Treatment of Osteomyelitis due to Carbapenemase-Producing *Klebsiella pneumoniae* in Diabetes-Related Foot Disease

Tratamento Médico da Osteomielite por *Klebsiella pneumoniae* Produtora de Carbapenemases no Pé Diabético

Keywords: Carbapenem-Resistant Enterobacteriaceae; Diabetic Foot; Klebsiella Infections; Klebsiella pneumoniae; Osteomyelitis
Palavras-chave: Enterobacteriaceae Resistentes a Carbapenemes; Infecções por Klebsiella; Klebsiella pneumoniae; Osteomielite; Pé Diabético

Chronic osteomyelitis in diabetes-related foot disease is commonly treated surgically, especially when involving midfoot or rearfoot infections or when caused by multidrug-resistant microorganisms.[1,2] Particularly for osteomyelitis caused by carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp), the optimal treatment remains poorly defined with available antibiotics including colistin, fosfomycin, and ceftazidime-avibactam.[3] Successful cases of medical treatment of osteomyelitis in diabetes-related foot disease caused by CP-Kp remain scarce.

A 46-year-old female patient with type 1 diabetes *mellitus* was evaluated at the Diabetic Foot Clinic "Dr.ª Beatriz Serra" in July 2021. She had been diagnosed at the age of 15, and showed poor chronic glycemic control and a history of recurrent antibiotic use and hospitalizations due to infected neuropathic foot ulcers, which inclusively led to the right hallux amputation. The patient presented with an infected plantar ulcer in the right midfoot, with exposed bone and a plantar phlegmon requiring urgent drainage. A bone sample was taken for microbiological study, and empirical antibiotic therapy using gentamicin (based on previous microbiological studies) was initiated in the ambulatory setting. The most recent study came to isolate *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae*, which was only susceptible to both gentamicin and ceftazidime/avibactam. Due to worsening inflammatory signs, she was subsequently hospitalized, and antibiotic therapy was switched to ceftazidime/avibactam (2000/500 mg q8h). A magnetic resonance scan of the foot revealed extensive osteomyelitis involving various tarsal bones and the epiphyses of the leg. Despite the recommendation for definitive surgical treatment, the patient refused to undergo the procedure. Antibiotic therapy was maintained for six weeks, showing good clinical progress. After 45 days of hospitalization, she was discharged, and the ulcer completely healed by October 2021, with no recurrence over a year later.

To the best of the authors' knowledge, this is the first reported case of successful medical treatment for CP-Kp osteomyelitis in diabetes-related foot disease. While surgical treatment is typically preferred for multidrug-resistant infections, carefully selected patients, especially those with forefoot diabetic foot ulcers, may benefit from antibiotic therapy alone.[1,2,4] Although avoiding surgical procedures has its benefits, such as preventing biomechanical changes that increase recurrent ulceration, there are risks associated with prolonged antibiotic therapy, concerns about the rise of multidrug-resistant bacteria, and increased hospitalization costs. Deciding the ideal treatment for diabetic foot osteomyelitis requires considering multiple factors, including soft-tissue and necrotizing infections, bone exposure, vascular disease, and ulcer location.[1,2,4,5] In this particular case, despite the preference for surgical treatment, the patient's refusal unexpectedly resulted in a successful clinical cure of chronic osteomyelitis caused by CP-Kp.

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AUTHOR CONTRIBUTIONS

RB: Study design, drafting of the manuscript.

SG, LC, RC: Study design, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Valproate in Psychiatric Practice: Risks to Fertility and Future Generations

Valproato na Prática Psiquiátrica: Riscos para a Fertilidade e para as Gerações Futuras

Keywords: Fertility/drug effects; Mental Disorders/drug therapy; Valproic Acid/adverse effects

Palavras-chave: Ácido Valpróico/efeitos adversos; Fertilidade/efeito dos fármacos; Perturbações Mentais/tratamento farmacológico

Dear Editor,

We are writing to express concerns about the use of valproate or valproic acid (VPA) in psychiatry, particularly its impact on fertility and future generations.

This medicine gained widespread use as a mood stabilizer following reports of teratogenic risks associated with lithium use.[1] However, VPA's significant teratogenic effects, identified since the 1990s – including a 20-fold increased risk of neural tube defects – have led to its contraindication during pregnancy and limited use in women of childbearing age unless other treatments fail.[2]

Besides structural abnormalities, *in utero* exposure to VPA is associated with neurodevelopmental disorders.[3] A French study demonstrated a dose-response relationship between VPA exposure during the second or third trimesters of pregnancy and neurodevelopmental risks.[3] In animal studies, VPA increased the risk of neurodevelopmental disorders up to the third-generation offspring. Additionally, VPA negatively affects fertility, with studies linking it to polycystic ovary syndrome and hyperandrogenism.[4] Given these risks, in 2018, the European Medicines Agency restricted VPA use, contraindicating its use during pregnancy and in women of childbearing potential, unless enrolled in a pregnancy prevention program with pregnancy tests, effective contraception, and specialist reviews.[2] Valproate has also been linked to reversible male infertility, impacting sperm parameters through the effect of gonadotropin , oxidative stress, and mitochondrial dysfunction.[4] Recent studies suggest paternal VPA use within three months before conception may increase the risk of neurodevelopmental disorders in children compared to the use of other antiseizure medications.[2]

Since 2018, the United Kingdoms' (UK) Medicines and Healthcare Products Regulatory Agency has reported a 38% reduction in valproate use among women of childbearing age. However, a concerning plateau in this decline has emerged, with two to three babies per month still exposed to the drug *in utero*. The evidence suggests healthcare professionals may not be consistently informing women of these risks.[2,5] As a result, in January 2024, the UK's medicines regulator mandated that VPA must not be started in new patients (male or female) under 55 years, unless two specialists document that there is no alternative treatment.[2] The decision by the UK regulator to maintain strict controls on valproate prescribing is controversial but reflects ongoing concerns about inconsistent adherence to safety regulations.[5]

In conclusion, while VPA remains important in psychiatric care, its impact on fertility and generational risks requires strict adherence to guidelines, informed patient choices, and the consideration of alternatives. It is essential to address these challenges responsibly.

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