Multidrug-resistant urethritis caused by *Haemophilus parainfluenzae*: susceptibility pattern and fosfomycin as an alternative treatment

Urethritis is a common symptom of sexually transmitted infections (STIs), with *Chlamydia trachomatis* being the most identified cause in non-gonococcal urethritis (NGU).[1 2] However, a significant proportion of NGU cases have an unknown origin. The potential of *Haemophilus parainfluenzae* to act as an opportunistic pathogen causing respiratory tract infections or urogenital infections has been described, and the emergence of multidrug resistance in this species has been reported.[3–5] The main objective of the study was to describe the susceptibility profile and evaluate the effectiveness of fosfomycin as an alternative therapeutic option in the management of multidrug-resistant (MDR), including CTX-M producing *H. parainfluenzae* strains.

This observational, retrospective study analysed *H. parainfluenzae* strains isolated from urethral swabs of symptomatic men who have sex with men at Hospital Clinic, Barcelona, from January 2015 to June 2023. Clinical data were obtained from patient's hospital records (online supplemental table 1). Bacterial identification and antibiotic susceptibility were determined using MALDI-TOF MS and the gradient diffusion method. The detection of extended-spectrum beta-lactamase (ESBL) CTX-M type was carried out using the CTX-M NGbiotech lateral-flow test. Results were interpreted based on breakpoints provided by the EUCAST guidelines available at the time of diagnosis.

Owing to the absence of other oral treatment options for MDR *H. parainfluenzae*, sensitivity testing for fosfomycin started in 2020 based on previous data.[6–8] Results were interpreted according to the EUCAST *Escherichia coli* breakpoint for fosfomycin (MIC: 8).

A total of 360 strains of *H. parainfluenzae* from 322 patients were analysed. These correspond to 8% of 4510 urethral samples processed from 2015 to 2023. The percentage of *H. parainfluenzae* positive samples increased from 6% in 2015 to 12% in 2023 (online supplemental figure 1).

Figure 1 shows the antibiotic resistance trend from 2015 to 2023, illustrating an increase in resistance to all antibiotics used for *H. parainfluenzae* treatment. Notably, 76 isolates were considered MDR showing resistance to multiple antibiotics:ampicillin, amoxicillin/clavulanic acid, cefotaxime and levofloxacin, yet remaining susceptible to ertapenem. Two strains recovered between May 2022 and May 2023 were ESBL positive, belonging to the CTX-M group.[9] A total of 129 strains (47 of which were MDR, including the 2 CTX-M group) were tested for fosfomycin activity: 128 (99.2%) were susceptible and 1 (0.8%) was resistant (online supplemental table 2).

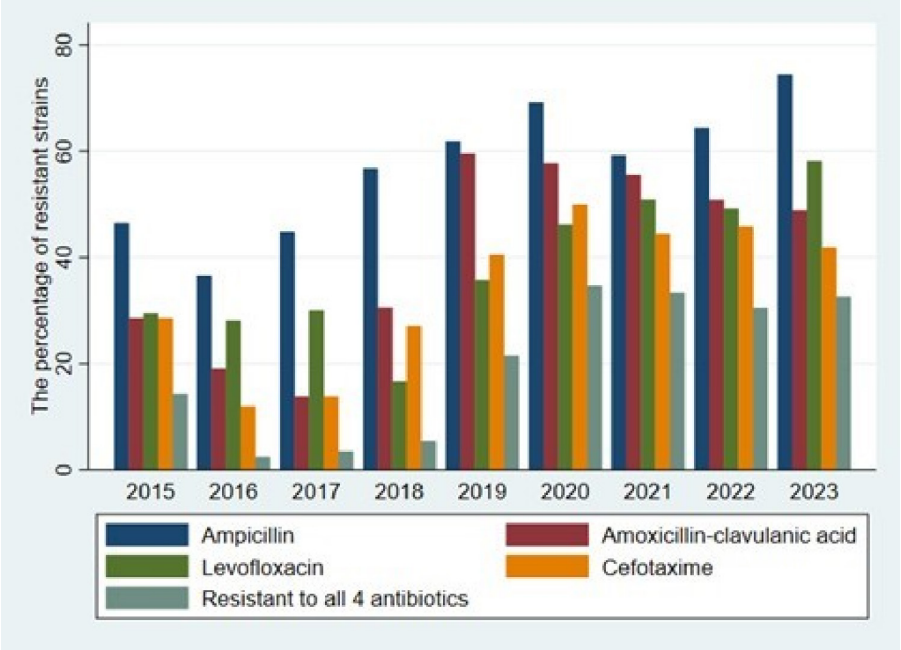

Figure 1 Evolution of *H. parainfluenzae* antibiotic resistance from 2015 to 2023.

Fosfomycin (3 g/48 hours in two doses) was prescribed in 36 cases of monobacterial urethritis when the spectrum of empirical treatment did not show activity against MDR *H. parainfluenzae* isolates. Of these, 30 received fosfomycin as first-line treatment, while 6 received it second-line due to persistent symptoms and positive culture results after previous antibiotic treatment failed. A test of cure was conducted on 21 patients, all being negative and considered cured. The remaining 15 were lost to follow-up, but no relapse was registered in the following 6 months.

This study shows the emergence of antibiotic resistance among *H. parainfluenzae* isolates collected from urethral swabs over the past decade in Barcelona. To our knowledge, this is the first study to evaluate fosfomycin as a treatment for *H. parainfluenzae* urogenital infection.

The emergence of *H. parainfluenzae* isolates in NGU and the observed increase in antibiotic resistance in our study concur with the findings reported by Sierra *et al*,[5] corresponding to the same geographic area.

Most strains exhibited a fosfomycin MIC ≤4 µg/mL, and there were no reported instances of therapeutic failure. This suggests that fosfomycin is a promising alternative for the treatment of MDR *H. parainfluenzae* infection. Effective treatment with fosfomycin in cases of persistent MDR *H. parainfluenzae* previously treated supports this theory. Unfortunately, data are only available regarding fosfomycin sensitivity in *Neisseria gonorrhoeae* but not in *H. parainfluenzae* or in urogenital or respiratory samples.[6 7]

Oral administration of fosfomycin, coupled with its short dosing duration, may enhance compliance. Its good safety profile and low interaction with other potential concomitant drugs make fosfomycin a better drug choice for the management of *H. parainfluenzae* infections in groups with sexual practices at risk of acquiring STIs.[10]

This study has limitations. Due to its retrospective design, crucial clinical data were unavailable. Additionally, the lack of fosfomycin breakpoints for the treatment of *H. parainfluenzae* poses a challenge. Consequently, *E. coli* breakpoints were used as a substitute to fulfil the aim of the study. Finally, resistance data for doxycycline and azithromycin were not available, hindering the calculation of the MDR strain rate.

This study suggests that fosfomycin could be an effective alternative for treating

MDR *H. parainfluenzae* urogenital infections, addressing the urgent need for new treatment strategies against resistant pathogens. However, randomised clinical trials are required to confirm these results and establish specific treatment guidelines.

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