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Antimicrobial activity of temocillin on ceftriaxone-resistant and ceftriaxone-susceptible isolates of *Neisseria gonorrhoeae*

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In Europe, the notification rate of *Neisseria gonorrhoeae* (Ng) increased by 321% between 2014 and 2023; MSM accounted for more than half of the reported cases (58%) in 2023.[1] Consequently, Ng has become a major public health concern. European guidelines for uncomplicated gonococcal infections recommend first line treatment with a single dose of ceftriaxone 1 g administered intramuscularly.[2] However, XDR-Ng strains have emerged in Southeast Asia[3] and have been recently reported in Europe.[4] The increasing emergence of XDR strains supports the need for other treatments against Ng.[5]

Temocillin, a 6-α-methoxy derivative of ticarcillin β-lactam introduced in the 1980s, has a narrow spectrum of activity against Gram-negative bacteria, including *Neisseria* sp., and can be administrated either intramuscularly or intravenously. Temocillin had clinical breakpoints for treatment of Enterobacterales involved in urinary tract infections (16 mg/L), but not for Ng, and the literature on the susceptibility of Ng to temocillin is sparse.[6] The aim of this study was to determine the distribution of MICs for temocillin among Ng isolates, including those resistant against cefixime and ceftriaxone.

A total of 192 Ng isolates were included comprising 185 French Ng isolates from the French National Reference Centre for Sexually Transmitted Infections collected from 2017 to 2024 and 7 WHO strains. These isolates had been phenotypically and genotypically characterized in previous studies and were chosen to represent a diverse range of genotypes and phenotypes, including a wide diversity of *penA* alleles and phylogenetic backgrounds (Table S1, available as Supplementary data at *JAC* Online). For all Ng isolates, MICs for temocillin, cefixime and ceftriaxone were determined on PolyViteX® agar by Etests® (bioMérieux; Marcy-L'Etoile, France). Decreased susceptibilities to cefixime and ceftriaxone were defined as MICs ranging above the Ecoff from 0.032 to 0.125 mg/L and resistance was defined as MICs > 0.125 mg/L.

Of the 192 Ng isolates included, 49 had different sequence MLST types and 42 harboured different *penA* alleles (Table S1). The MIC_{50} and MIC_{90} values, respectively, were 0.016 and 0.064 mg/L for cefixime, 0.004 and 0.016 mg/L for ceftriaxone and 1 and 4 mg/L for temocillin. MIC ranges were ≤0.016–4 mg/L for cefixime, ≤0.002–2 mg/L for ceftriaxone and ≤0.064–16 mg/L for temocillin. Temocillin MICs were correlated to cefixime MICs (Spearman's ρ: 0.7121, $P < 0.0001$) and ceftriaxone MICs (Spearman's ρ: 0.6760, $P < 0.0001$). Sixty-nine isolates had decreased susceptibility or resistance to cefixime, of which 10 were also resistant to ceftriaxone. Of note, MICs for temocillin were ≤8 mg/L in 99% (191/192) and ≤2 mg/L in 90% (172/192) of isolates. Ng susceptible to ceftriaxone with decreased susceptibility or resistance to cefixime exhibited temocillin MICs consistently ≤4 mg/L. Ceftriaxone-resistant isolates exhibited temocillin MICs ranging from 4 to 16 mg/L (Figure 1).

In this large collection of Ng isolates, MIC for temocillin was ≤16 mg/L, which represents the breakpoint for treatment of Enterobacterales involved in urinary tract infections. Furthermore, for all ceftriaxone-susceptible isolates, the MIC for temocillin was ≤4 mg/L, and 98% of isolates with reduced susceptibility or resistance to cefixime and/or ceftriaxone, the MIC for temocillin was ≤8 mg/L. These results are consistent with a previous study in which 99% of the 76 tested Ng isolates showed an MIC for temocillin ≤ 8 mg/L.[6]

Given that ceftriaxone is a broad-spectrum antibiotic, it increases the risk of disturbances to the microbiota,[7] which can then lead to acquisition of multidrug-resistant bacteria, particularly ESBL-producing Enterobacterales (ESBL-E). Population studies among sexually active individuals at high risk for STIs, especially MSM, have already demonstrated higher prevalence of ESBL-E colonization compared to the general population, reaching up to 40%.[8] The high prevalence of ESBL-E increases not only the risk of transmission within the community but also the risk of infections caused by other multidrug-resistant bacterial, such as *Escherichia coli* and *Shigella* sp.[9]

The spread of multidrug-resistant strains of Ng, coupled with purportedly increased risk of developing ESBL-E, underscores

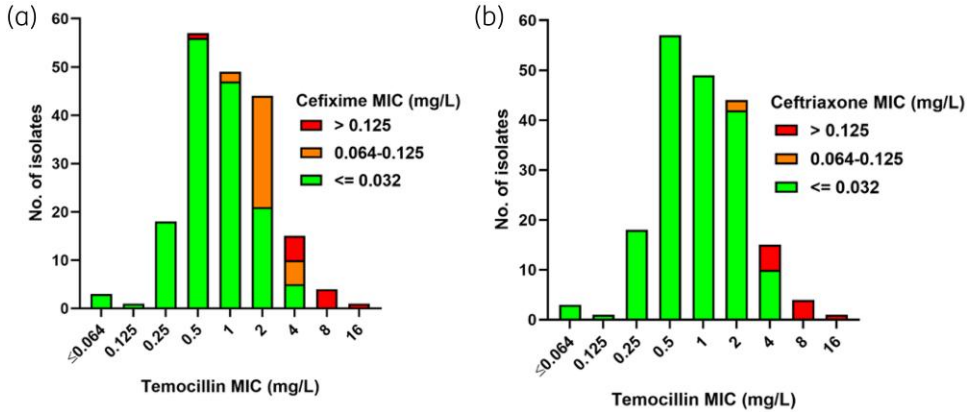

Figure 1. Distribution of MIC for temocillin in *N. gonorrhoeae* isolates, according to MIC for cefixime (a) and ceftriaxone (b). The distribution of MICs for temocillin is provided as histograms with the total number of isolates. Different coloured bars provide information on the degree of resistance to cefixime (a) and ceftriaxone (b). No., number.

the urgent need for new treatments that are effective at all infection sites (e.g. urogenital, rectal and pharyngeal) against strains of Ng resistant to currently recommended treatments, while minimizing the risk of selecting ESBL-E. Temocillin, with its narrow spectrum and long serum elimination half-life, shows promise as a single-dose treatment for gonorrhoea. Unlike ceftriaxone, temocillin does not promote the expansion of ESBL-producing *E. coli* in the faeces of colonized mice.[10] In addition, temocillin is inactive against *Pseudomonas aeruginosa*, Gram-positive bacteria and anaerobes, which helps to preserve colonization resistance.[6]

Temocillin was successfully used to treat Ng in Switzerland during the 1980s but was subsequently replaced by other β-lactams.[11] This study, possibly one of the first to examine the susceptibility to temocillin of recently isolated Ng, shows that these isolates are highly sensitive to this molecule. However, temocillin MICs were elevated in ceftriaxone-resistant isolates, and the clinical efficacy of temocillin in patients infected with such strains remains unknown. Randomized clinical trials should evaluate the efficacy of temocillin for treating Ng and its potential for preventing selection of other antibiotic resistant microorganisms, particularly against ESBL-E. Repositioning antimicrobials, such as temocillin, could provide effective alternatives.

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Author contributions

T.C. and L.S. conceptualized the design of the study; J.B. performed bacteriological analysis; F.C. performed the statistical analysis; J.B., F.C., B.B. and L.S. drafted the first version of the manuscript. All authors gave critical revisions and have approved the final version of the manuscript.

Supplementary data

Table S1 is available as Supplementary data at *JAC Online*.

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