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Review

# *Neisseria gonorrhoeae* and fosfomycin: Past, present and future

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ABSTRACT

Drug-resistant *Neisseria gonorrhoeae* has become a global health concern that requires immediate attention. Due to increasing resistance to cephalosporins, pursuing novel alternatives for treating *N. gonorrhoeae* infections is paramount. Whilst new drug development is often cumbersome, reviving antiquated antibiotic agents for treatment of modern infections has become prevalent in clinical practice. Fosfomycin exhibits bactericidal activity through a unique mechanism of action, and a variety of organisms including *N. gonorrhoeae* are susceptible. In vitro studies have demonstrated that fosfomycin can retain activity against ceftriaxone-resistant *N. gonorrhoeae*; however, it remains unclear whether there is synergy between fosfomycin and other antibiotics. Clinical investigations evaluating fosfomycin for the treatment of *N. gonorrhoeae* infections are confounded by methodological limitations, none the less they do provide some perspective on its potential role in therapy. Future studies are needed to establish a safe, convenient and effective fosfomycin regimen for treating *N. gonorrhoeae* infections.

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## 1. Introduction

Treatment of multidrug-resistant (MDR) organisms has become a major concern over the past decade. There have been a limited number of novel antimicrobial agents approved by the US Food and Drug Administration (FDA) or the European Medicines Agency for the treatment of Gram-negative bacterial infections [1,2]. Given the limited antibiotic armamentarium, clinicians are often forced to use combination therapy or existing, often more toxic, antimicrobial agents to treat these MDR infections [3,4]. In light of dwindling treatment options and increasing resistance, the US Centers for Disease Control and Prevention (CDC) has prioritised the threat level of organisms into three categories: urgent, serious and concerning [5]. *Neisseria gonorrhoeae* is one of three organisms identified by the CDC as an urgent threat and poses a great public health hazard [5]. Fig. 1 shows the increase in the percentage of *N. gonorrhoeae* isolates with elevated cefixime minimum inhibitory concentrations (MICs) (≥0.25 μg/mL), ceftriaxone MICs (≥0.125 μg/mL) and azithromycin MICs (≥2 μg/mL) in the USA during 2006–2012 according to the Gonococcal Isolate Surveillance Project [6].

Gonorrhoea is the second most commonly reportable infectious disease in the USA. In 2013, there were 333 004 gonorrhoea cases reported and the national rate was 106.1 cases per 100 000 population [7]. Due to the ease of transmission of *N. gonorrhoeae*, treatment of both the infected patient and sexual partner(s) is vital [8,9]. Unfortunately, *N. gonorrhoeae* resistance poses a significant global healthcare burden due to declining susceptibility rates to first-line agents (Fig. 1) [10,11]. Surveillance studies indicate that *N.*

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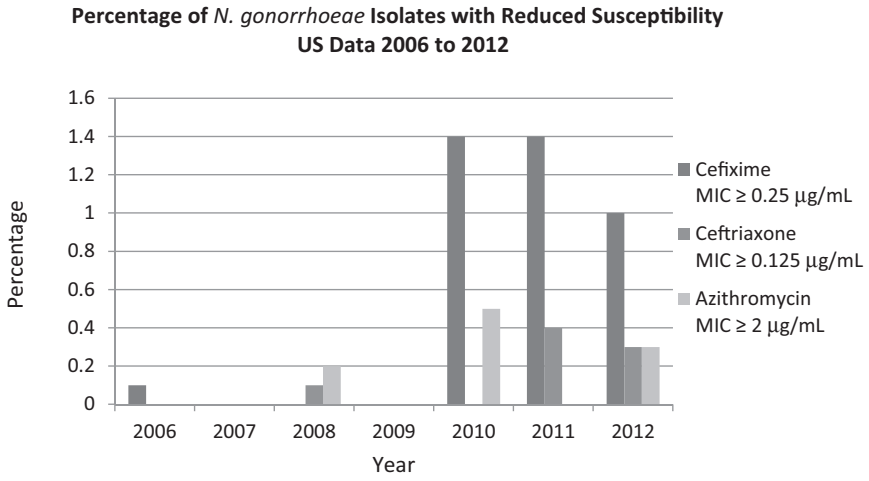


**Fig. 1.** Increase in percentage of *Neisseria gonorrhoeae* isolates with reduced susceptibility (i.e. elevated MICs) to cefixime (MIC ≥ 0.25 μg/mL), ceftriaxone (MIC ≥ 0.125 μg/mL) and azithromycin (MIC ≥ 2 μg/mL) in the USA during 2006–2012, according to the Gonococcal Isolate Surveillance Project. MIC, minimum inhibitory concentration.

*gonorrhoeae* has developed resistance to sulfonamides, penicillin, tetracyclines, macrolides and quinolones, leaving cephalosporins as the most effective class of antimicrobials [12]. Cefixime and ceftriaxone MICs have risen over the years, leading to additional concern about the effective treatment of *N. gonorrhoeae* [12]. Due to declining cefixime susceptibility, the 2012 CDC sexually transmitted diseases (STD) treatment guidelines recommend ceftriaxone plus azithromycin or doxycycline as first-line treatment [8]. These guidelines recommend ceftriaxone plus azithromycin [13]. The widespread emergence of ceftriaxone resistance would further limit treatment options and control of infection spread [14,15]. Combination therapy and revitalisation of existing agents, such as fosfomycin, becomes a valid consideration when treating infections caused by MDR *N. gonorrhoeae* [16,17]. The purpose of this review is to summarise the available data and the viability of fosfomycin as a treatment option for multidrug-resistant *N. gonorrhoeae*.

## 2. Methods

Online infectious diseases textbooks were used to identify relevant information about fosfomycin [18,19]. Studies were identified via search of PubMed, EMBASE and Web of Science databases using the following search terms: fosfomycin, phosphomycin, phosphonomycin combined with gonorrhoea, Gram-negative bacteria, multidrug-resistant, and *N. gonorrhoeae*, *Neisseria* spp. or gonococcus. The comprehensive search produced nine studies, including four studies pertaining to the in vivo activity of fosfomycin for the treatment of *N. gonorrhoeae* infections [20–23] and five studies evaluating the in vitro activity of fosfomycin against *Neisseria* spp. or *N. gonorrhoeae* isolates [17,24–27]. Articles written in English and those that were readily translatable into English using Google Translate were included.

## 3. Pharmacology

Fosfomycin, a phosphonic acid derivative, was isolated from *Streptomyces* species cultures in 1969 [4,28,29]. It exhibits bactericidal activity by inhibiting cell wall synthesis through inhibition of phosphoenolpyruvate transferase (PPT). PPT is an enzyme that is involved in the first phase of peptidoglycan synthesis in many Gram-positive and Gram-negative bacteria [28]. Due to the distinctive mechanism of action and structure of fosfomycin, there is minimal cross-resistance with other antibiotics and its activity against MDR pathogens has been preserved [29,30].

Fosfomycin exhibits a broad spectrum of activity against aerobic and anaerobic Gram-positive organisms such as meticillin-susceptible and meticillin-resistant *Staphylococcus aureus* (MRSA), cephalosporin- and penicillin-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococci (VRE), and Gram-negative organisms including those in the Enterobacteriaceae family and *Neisseria meningitidis* [4,29]. Whilst there have been promising studies examining the utility of intravenous (i.v.) fosfomycin for the treatment of MRSA, VRE and carbapenemase-resistant Enterobacteriaceae in critically ill patients, oral fosfomycin tromethamine is the only FDA-approved formulation in the USA [29,31]. Common adverse effects of fosfomycin are mild and often self-limiting, including diarrhoea, nausea, abdominal pain and headache. The serum concentration and urinary excretion of fosfomycin are decreased by co-administration of metoclopramide, but otherwise it has limited drug interactions [29]. Fosfomycin is in FDA Pregnancy Category B [31].

## 4. Results

### 4.1. In vitro data

In 1980, Bartmann and Tarbuc determined the fosfomycin MIC for 40 strains of *Neisseria* spp. isolated from patients with lower respiratory tract infections as well as 18 control strains [24]. Of note, at the time the strains were collected and analysed, *Moraxella catarrhalis* was formally classified as part of the *Neisseria* genus [24,32]. Of the 40 Gram-negative cocci strains, there were 16 strains of *Neisseria* spp. and 24 *M. catarrhalis*. *Neisseria* spp. susceptibility increased with higher doses of fosfomycin. Approximately 23% of strains were inhibited by fosfomycin at an MIC of 16 mg/L, 63% at an MIC of 32 mg/L, 85% at an MIC of 64 mg/L and 100% at an MIC of 128 mg/L. Using pharmacokinetic data from i.v. fosfomycin in humans, strains with an MIC of ≤16 mg/L and ≤64 mg/L were considered sensitive and moderately sensitive, respectively.

The first isolate of penicillinase-producing *N. gonorrhoeae* (PPNG) was isolated in Liverpool, UK, in 1976 [25]. Due to concerns of PPNG developing resistance to spectinomycin, Dickgiesser and Kuntz evaluated the in vitro activity of 51 PPNG isolates against alternative antimicrobials, including fosfomycin. The isolates were obtained from England ($n = 37$), Nigeria ($n = 3$), Hong Kong ($n = 1$), Saudi Arabia ($n = 2$), Cameroon ($n = 1$), South Korea ($n = 1$), The Philippines ($n = 2$) and Thailand ($n = 4$) [25]. Susceptibility testing was performed by agar dilution. Fosfomycin was interpreted as

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