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Antimicrobial susceptibility of clinical isolates of *Neisseria gonorrhoeae* to alternative antimicrobials with therapeutic potential

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Background: The prevalence of MDR *Neisseria gonorrhoeae* is increasing globally and represents a public health emergency. Development and approval of new anti-gonococcal agents may take years. As a concurrent approach to developing new antimicrobials, the laboratory and clinical evaluation of currently licensed antimicrobials not widely used for the treatment of gonorrhoea may provide new options for the treatment of gonococcal infections.

Objectives: To determine the *in vitro* activity of nine alternative, currently licensed and late-development antimicrobials with the potential to treat gonococcal infections against 112 clinical isolates of *N. gonorrhoeae* resistant to one or multiple antimicrobials.

Methods: The MICs of conventional anti-gonococcal antimicrobials (penicillin, ceftriaxone, cefixime, azithromycin, ciprofloxacin, tetracycline and spectinomycin) and alternative antimicrobials (ertapenem, gentamicin, netilmicin, tigecycline, eravacycline, fosfomycin, linezolid, ceftazidime/avibactam and ceftaroline) were determined by agar dilution.

Results: Ertapenem and the novel cephalosporins demonstrated similar MIC values to the third-generation cephalosporins, but increased MICs were observed for isolates with increased cefixime and ceftriaxone MICs. Tigecycline and eravacycline had MIC values below expected serum concentrations for all isolates tested. The aminoglycosides gentamicin and netilmicin were generally more potent than spectinomycin, with netilmicin demonstrating the greatest potency. Fosfomycin MICs were elevated compared with other agents, but remained within the MIC range for susceptible organisms, while linezolid MICs were generally higher than those for organisms considered resistant.

Conclusions: Among potentially therapeutically useful alternative agents, the aminoglycosides, eravacycline, tigecycline and fosfomycin had good *in vitro* activity. The novel cephalosporins and ertapenem had comparable activity to cefixime and ceftriaxone.

Introduction

Globally, gonorrhoea is the second most commonly acquired sexually transmitted infection after chlamydia, with ∼78 million new infections worldwide every year. Complicating increasing incidence is the rapid emergence of resistance to first-line antimicrobial treatments.[1,2]

One response to the emergence of antimicrobial-resistant gonococcal disease has been the development of novel agents with *in vitro* activity against gonococcal isolates, including solithromycin (a novel fluoroketolide),[3] eravacycline (a novel glycylcycline)[4] and novel fluoroquinolones and agents with novel mechanisms of action (e.g. VXc-486 and ETX0914).[1,5] However, among these agents, only solithromycin has been shown in a small Phase II clinical trial to be effective against gonococcal infection.[6] Given the long delay in developing and licensing novel antibiotics, the evaluation of older and recently released and licensed drugs for the treatment of gonococcal infection should also play a role in the global control of gonococcal infection. Indeed, the

injectable carbapenem ertapenem, fosfomycin and the injectable aminoglycoside gentamicin have all been suggested as possible agents with anti-gonococcal potential.[1,5]

We report the *in vitro* susceptibility of a collection of diverse *Neisseria gonorrhoeae* isolates with reduced susceptibility to antimicrobial agents from across Canada to currently available and late-development antimicrobial agents with the potential for use as empirical treatment for gonorrhoea.

Materials and methods

Isolates

Isolates were from the Canadian national surveillance system at the National Microbiology Laboratory (NML), Winnipeg, MB, Canada. From a total of 1200 isolates submitted to the NML in 2013, we selected a variety of phenotypes showing variable non-susceptibility to penicillin, ciprofloxacin, azithromycin, cefixime and ceftriaxone. Our goal was to assess the activity of a variety of agents versus a selection of non-susceptible isolates, rather than one representative of current resistance rates. In total, 112 isolates were selected for testing.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed using agar dilution with GC agar following CLSI recommendations for agar dilution.[7] The following antimicrobials were tested: penicillin (Sigma, Oakville, ON, Canada), ceftriaxone (Sigma), cefixime (Sigma), ertapenem (Sequoia Research Products, Pangbourne, UK), ciprofloxacin (Bayer, Mississauga, ON, Canada), azithromycin (Pfizer, Saint-Laurent, QC, Canada), spectinomycin (Sigma), gentamicin (MP Biomedicals, Santa Ana, CA, USA), netilmicin (Sigma), tetracycline (Sigma), tigecycline (Sigma), eravacycline (Tetraphase Pharmaceuticals, Watertown, MA, USA), fosfomycin (Sigma), linezolid (Sigma), ceftazidime/avibactam (Novexel S. A., Romainville, France) and ceftaroline (Forest Laboratories, New York, NY, USA). Where available, interpretation of susceptibility used CLSI interpretative criteria (M100-S26).[8] Reduced susceptibility to azithromycin was defined as an MIC of $\geq$2 mg/L.[9] Reduced susceptibility to the extended-spectrum cephalosporins was defined as a cefixime MIC of $\geq$0.25 mg/L or a ceftriaxone MIC of $\geq$0.12 mg/L.[9] Quality control strain ATCC 49226 and WHO F, G, K, L, M, N, O and P were used for the agar dilution susceptibility testing methods.

Statistical methods

Correlation between MICs of different antibiotics was determined by linear regression of $\log_2$-transformed MIC data. Significant positive correlations were those where a positive *R* value was reported corresponding with a *P* value <0.05 and negative correlations were reported where a negative *R* value corresponded with a *P* value <0.05.

Results

Of 112 isolates, 109 (97.3%) were resistant or had reduced susceptibility to at least one of penicillin, azithromycin, cefixime, ceftriaxone, ciprofloxacin and tetracycline, and 96.4% were resistant to two such agents. Multidrug resistance as defined by Tapsall *et al.*[10] occurred in 18.8% of isolates. Reduced susceptibility to cefixime and ceftriaxone was observed in 8.9% and 16.1% of isolates, respectively, and 13.4% had reduced susceptibility to azithromycin. With the exception of linezolid, the alternative antimicrobial agents tested generally demonstrated MIC values comparable to those for other organisms deemed susceptible to these agents (Table 1). Ertapenem demonstrated similar MIC_{50} and MIC_{90} values to cefixime and ceftriaxone, while ceftazidime/avibactam and ceftaroline demonstrated somewhat higher values. Increased ertapenem, ceftazidime/avibactam and ceftaroline MICs were observed for isolates with increased cefixime and ceftriaxone MICs. Tigecycline and eravacycline had low MIC_{50} and MIC_{90} values for all isolates tested, including those with reduced susceptibility to azithromycin, cefixime and ceftriaxone. The aminoglycosides gentamicin and netilmicin were generally more potent than spectinomycin. Fosfomycin MICs remained within the range of MICs that indicate susceptibility for other organisms, while linezolid MICs were generally higher than those that indicate resistance for other organisms.

Table 2 demonstrates the distributions of MICs of the alternative antimicrobials for *N. gonorrhoeae* isolates with reduced susceptibility to extended-spectrum cephalosporins. Table 3 demonstrates the distributions of MICs of the alternative antimicrobials for *N. gonorrhoeae* isolates with reduced susceptibility to azithromycin.

Discussion

Ertapenem, ceftaroline and ceftazidime/avibactam demonstrated low MIC_{50} and MIC_{90} values. Using *Haemophilus influenzae* breakpoints to interpret MIC data for ceftaroline ($\leq$0.5 mg/L), ceftazidime ($\leq$2 mg/L) and ertapenem ($\leq$0.5 mg/L), all isolates were susceptible to ceftaroline, ceftazidime/avibactam and ertapenem.[8] However, the MIC_{50}s were 2-fold (ceftaroline, ertapenem) and 4-fold (ceftazidime/avibactam) higher and the MIC_{90}s were 2-fold (ertapenem), 4-fold (ceftaroline) and 8-fold (ceftazidime/avibactam) higher than those of cefixime and ceftriaxone (Table 2). Therefore, it is unlikely, based on these data, that these agents would offer any significant advantage over conventional extended-spectrum cephalosporin treatments. We initially hypothesized that these agents may have greater activity against isolates with reduced susceptibility to cefixime and ceftriaxone, given their variable affinity for altered PBPs.[11] However, MIC values of these agents remained higher than those of ceftriaxone and cefixime even among the isolates with reduced susceptibility to the extended-spectrum cephalosporins, and a positive correlation existed between ceftriaxone MIC and ceftazidime/avibactam, ertapenem and ceftaroline MICs, suggesting that MICs of all of these agents increased in concert (data not shown).

The glycylcycline tigecycline and the fluorocycline eravacycline demonstrated activity against all isolates tested. Eravacycline was approximately twice as potent as tigecycline against the *N. gonorrhoeae* isolates tested (Table 1). Eravacycline is a novel orally bioavailable fluorocycline with pharmacokinetics suggesting that it could potentially be used as single-dose treatment for gonococcal infection.[4] Approximately 82% of isolates had a tigecycline MIC below the susceptible breakpoint provided by the FDA for *Streptococcus* spp. other than *S. pneumoniae* ($\leq$0.25 mg/L) and 99.1% had a tigecycline MIC below the susceptible breakpoint for *Staphylococcus* spp. ($\leq$0.5 mg/L) (Tygacil product insert, Wyeth Pharmaceuticals, Inc.). The MIC_{50} and MIC_{90} were essentially the same for isolates with reduced susceptibility to extended-spectrum cephalosporins and reduced susceptibility to azithromycin (Tables 2 and 3). However, we noted a positive correlation between both the azithromycin and cephalosporin MICs and those of eravacycline and tigecycline (data not shown). This suggests the

Table 1. Antimicrobial susceptibility testing results for 112 clinical isolates of *N. gonorrhoeae*; CLSI breakpoints (susceptible/resistant) are indicated in parentheses for each antimicrobial (in mg/L)

	MIC (mg/L)				MIC interpretation[a]			
Antimicrobial agent	range	mode	MIC_{50}	MIC_{90}	percentage susceptible	percentage intermediate	percentage resistant	Percentage of isolates with reduced susceptibility[b]
Penicillin (≤0.06/≥2)	0.06 to > 256	2	2	4	3.6	33.9	62.5	
Cefixime (≤0.25/NA)	0.002–0.5	0.12	0.06	0.12	98.2	NA	1.8	8.9
Ceftriaxone (≤0.25/NA)	0.002–0.12	0.06	0.06	0.12	100	NA	NA	16.1
Ceftaroline	≤0.008–0.5	0.25	0.12	0.5	NA	NA	NA	
Ceftazidime/avibactam	≤0.06–2	≤0.06	0.25	1	NA	NA	NA	
Ertapenem	0.008–0.5	0.06	0.12	0.25	NA	NA	NA	
Tetracycline (≤0.25/≥2)	0.25–64	4	4	32	2.7	12.5	84.8	
Tigecycline	≤0.03–1	0.25	0.25	0.5	NA	NA	NA	
Eravacycline	≤0.03–0.5	0.25	0.12	0.25	NA	NA	NA	
Ciprofloxacin (≤0.06/≥1)	0.002–32	16	8	16	38.4	0	61.6	
Azithromycin	0.03–16	0.5	0.5	2	NA	NA	NA	13.4
Gentamicin	2–16	8	8	16	NA	NA	NA	
Spectinomycin (≤32/≥128)	16–64	16	16	32	99.1	0.9	0	
Netilmicin	1–8	4	4	8	NA	NA	NA	
Fosfomycin	8–64	16	16	32	NA	NA	NA	
Linezolid	1–16	4	4	8	NA	NA	NA	

NA, CLSI MIC interpretative breakpoints not available.
[a]MICs were interpreted using CLSI criteria (10).
[b]Reduced susceptibility to the extended-spectrum cephalosporins was defined as a cefixime MIC of ≥ 0.25 mg/L or a ceftriaxone MIC of ≥ 0.125 mg/L.[9] For azithromycin, isolates were deemed to have reduced susceptibility if they had an MIC ≥2 mg/L.[9]

Table 2. MIC distributions of selected antimicrobial agents for 21 isolates of *N. gonorrhoeae* with reduced susceptibility to ceftriaxone (MIC ≥0.12 mg/L) or cefixime (MIC ≥0.25 mg/L)

	Number (cumulative %) of isolates for which the antimicrobial agent MIC (mg/L) was											
Antimicrobial agent	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
Cefixime		5 (23.8)	6 (52.4)	8 (90.5)	2 (100)							
Ceftriaxone		3 (14.3)	18 (100)									
Ceftaroline		2 (9.5)	8 (47.6)	6 (76.2)	5 (100)							
Ceftazidime/avibactam			1 (4.8)	2 (14.3)	8 (52.4)	8 (90.5)	2 (100)					
Ertapenem		4 (19.0)	4 (38.1)	12 (95.2)	1 (100)							
Tigecycline		1 (4.8)	5 (28.6)	9 (71.4)	5 (95.2)	1 (100)						
Eravacycline		7 (33.3)	3 (47.6)	10 (95.2)	1 (100)							
Gentamicin								2 (9.5)	17 (90.5)	2 (100)		
Netilmicin								14 (66.7)	7 (100)			
Fosfomycin										9 (42.9)	11 (95.2)	1 (100)
Linezolid							1 (4.8)	11 (57.1)	8 (95.2)	1 (100)		
Azithromycin			7 (33.3)	4 (52.4)	7 (85.7)	2 (95.2)	0 (95.2)	0 (95.2)	1 (100)			

possibility that multi-substrate resistance mechanisms such as mutations in the *mtrR* promoter of the *mtr* efflux system may be playing a role in reducing susceptibility to these agents concurrently.[12]

Among the aminoglycosides tested, gentamicin was twice as potent as and netilmicin was 4-fold more potent than the aminocylitol spectinomycin. A recent study of well-characterized reference isolates supports this finding.[13] MIC_{50} and MIC_{90} values were the same for the cephalosporin- and azithromycin-non-susceptible isolates as they were for the whole cohort of isolates. Spectinomycin is an approved treatment for urogenital and rectal gonococcal infection by the WHO[14] and in the USA,[15] Britain (https://www.bashh.org/guidelines) and Canada (http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/index-eng.php). However,

Table 3. MIC distributions of selected antimicrobial agents for 15 isolates of *N. gonorrhoeae* with reduced susceptibility to azithromycin (MIC ≥2 mg/L)

	Number (cumulative %) of isolates for which the antimicrobial agent MIC (mg/L) was												
Antimicrobial agent	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32
Cefixime	6 (40.0)	4 (66.7)	2 (80.0)	0 (80.0)	2 (93.3)	1 (100)							
Ceftriaxone	9 (60.0)	0 (60.0)	3 (80.0)	3 (100)									
Ceftaroline	1 (6.7)	0 (6.7)	3 (26.7)	6 (66.7)	1 (73.3)	2 (86.7)	2 (100)						
Ceftazidime/avibactam				9 (60.0)	0 (60.0)	3 (80.0)	2 (93.3)	1 (100)					
Ertapenem		3 (20.0)	4 (46.7)	4 (73.3)	3 (93.3)	1 (100)							
Tigecycline				1 (6.7)	1 (13.3)	5 (46.7)	8 (100)						
Eravacycline				4 (26.7)	4 (53.3)	5 (86.7)	2 (100)						
Gentamicin										1 (6.7)	12 (86.7)	2 (100)	
Netilmicin								1 (6.7)	2 (20.0)	8 (73.3)	4 (100)		
Fosfomycin												6 (40.0)	9 (100)
Linezolid								1 (6.7)	5 (40.0)	6 (80.0)	3 (100)		
Azithromycin									5 (33.3)	2 (46.7)	7 (93.3)	1 (100)	

since it has limited availability and both gentamicin and netilmicin appear more potent, clinical evaluation of these agents should be a priority. Limited trials with gentamicin in the 1970s and continued use of this agent as first-line therapy in Malawi suggest that it is effective for the treatment of urogenital infection with single-dose therapy (240–280 mg given intramuscularly), with the caveat that frequent co-administration of tetracyclines in the treatment of chlamydial infection may confound this observation.[1] At this time, the CDC 2015 Sexually Transmitted Diseases Treatment Guidelines recommend using gentamicin only under special circumstances, specifically those of treatment failure and allergy to first-line agents.[15]

Fosfomycin has been suggested as a treatment for gonococcal infection.[16] Although no clinical breakpoints exist, early pharmacokinetic studies suggested that isolates with an MIC ≤16 mg/L were susceptible, while those with MICs between 32 and 64 mg/L were moderately susceptible.[16] All the isolates studied had MICs <64 mg/L, suggesting that clinical cure may be feasible provided adequate doses are administered. Studies in the late 1970s demonstrated that intramuscular fosfomycin alone had the potential to cure acute gonococcal infections in a single dose, while oral fosfomycin had unacceptably high treatment failure rates.[16] Given that fosfomycin has no activity against *Chlamydia trachomatis*, concurrent administration with azithromycin would be required for empirical treatment and may enhance the gonorrhoea cure rates of intramuscular fosfomycin.

Linezolid is known to have activity against a number of Gram-negative pathogens, including *Moraxella* spp., *H. influenzae* and *N. gonorrhoeae*.[17] However, only 18/112 (16.1%) of the isolates tested had an MIC ≤2 mg/L, the clinical breakpoint for *Enterococcus* spp., and only 64/112 (57.1%) had an MIC value ≤4 mg/L, the clinical breakpoint for *Staphylococcus aureus*.[8] It is therefore unlikely that linezolid would achieve target concentrations and adequate clinical cure rates without extended-duration or very high-dose regimens that would be impractical in the treatment of gonococcal infection.

Our results show that a number of alternative antimicrobials have activity against recent clinical isolates of *N. gonorrhoeae* displaying resistance to one or more antimicrobials. Among these agents, the aminoglycosides, tigecycline, eravacycline and fosfomycin have qualities that make them potentially desirable for the treatment of acute gonococcal infections. However, although clinical breakpoints used for non-genital infections were considered in the interpretation of these data, they may not translate well for gonorrhoea due to different pharmacokinetic parameters involved in genital and other gonococcal infections. Given their *in vitro* activity, these agents may also play a role in combination therapy for gonococcal infection, especially in light of the recommendations by the WHO to treat gonococcal infections with dual therapy and that dual therapy be seen as a priority research area.[14] Therefore, clinical trials should be undertaken to define susceptibility breakpoints and determine clinical effectiveness, particularly in single-dose and combination therapy, in order to define their role in the treatment of susceptible and resistant gonococcal infections.

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