Review

New treatment options for *Neisseria gonorrhoeae* in the era of emerging antimicrobial resistance

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Abstract. *Neisseria gonorrhoeae*, the causative agent of gonorrhoea, has rapidly evolved from an exquisitely susceptible pathogen into a 'superbug' with the capacity to exhibit an extensively drug resistant (XDR) phenotype. The threat of untreatable gonorrhoea now looms on the horizon while the arsenal of effective antimicrobial agents diminishes with time. Ceftriaxone remains the mainstay of first-line therapy as a single agent or as the backbone of a dual therapy regimen. The implementation of new assays to facilitate 'precision' treatment, based on the prediction of *N. gonorrhoeae* susceptibility to old anti-gonococcal drugs, may enable sparing use of ceftriaxone in those countries that can afford this technology. A few existing drugs, such as ertapenem, can be repositioned to help manage multi-drug resistant and XDR gonorrhoea. Recent clinical trials involving solithromycin and delafloxacin have generated disappointing results in that both agents failed to show non-inferiority to conventional ceftriaxone-based regimens. At present, zoliflodacin and gepotidacin appear to be the most promising antimicrobial agents in clinical development. Both drugs performed well in eradicating urogenital gonorrhoea in recent Phase 2 trials; however, treatment failures were reported at the oropharyngeal site, which is an important site of infection in men who have sex with men and sex workers. Given this observation, it is unlikely that either of these new agents could be promoted for monotherapy of gonorrhoea. The pre-clinical pipeline remains relatively empty of agents likely to progress to clinical development for gonorrhoea treatment and increased investment into gonorrhoea-specific drug discovery is recommended.

Additional keywords: gonorrhoea, multi-drug resistance, new therapies.

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Introduction

Neisseria gonorrhoeae, the causative agent of gonorrhoea, was easily eradicated when antimicrobial agents were first introduced to treat gonococcal infections in the 1930s.[1] Indeed, when penicillin was introduced as first-line therapy for gonorrhoea in 1944, a total dose of just 72 mg (120 000 units) of intramuscular (IM) penicillin could reliably treat gonococcal urethritis in men.[2] Over time, *N. gonorrhoeae* acquired a variety of antimicrobial resistance determinants through several mechanisms, including chromosomal mutations, plasmid acquisition and, most recently, mosaic *penA* genes.[3] Given the continued emergence of multi-drug resistant (MDR) and extensively drug resistant (XDR) *N. gonorrhoeae* strains, clinicians can no longer presume that antimicrobial agent(s) will cure gonorrhoea at every occasion that they are prescribed.[4]

The increasing number of MDR or XDR cases have also highlighted the high cost and, in some cases, absence of readily available therapeutic agents required to manage them.[5] There are only very limited second-line options available and very few new anti-gonococcal agents in clinical development. The shortage of available therapies was highlighted by the World Health Organization (WHO) in 2017 when it listed *N. gonorrhoeae* as a priority pathogen for research and development of new antimicrobial agents.[6] Pending the introduction of novel and potent drugs to treat this highly infectious sexually transmissible infection (STI), treatment strategies have to rely on approaches that utilise multi-drug therapy, recycling of old drugs or repositioning of existing drugs. This review will discuss briefly new approaches to treat gonorrhoea and then describe new antimicrobial agents that are in the late stage of clinical development.

Effect of antimicrobial resistance on therapeutic options for gonorrhoea

The length of time in years between the introduction of a particular class, or type, of antimicrobial agent and the first report of clinical treatment failure varies according to the drug concerned. The antibiotics with the shortest time interval between clinical introduction and emergence of resistance include orally administered sulfonamides and fluoroquinolones (5 years for each), whereas the longest period of full efficacy has been seen with injectable ceftriaxone (30 years).[7] The reasons underlying these different time intervals are complex, but clearly vary by class of antimicrobial agent. The available data suggest that injectable antimicrobial agents last longer than single-dose oral antimicrobials, as evidenced by the longevity of use of both IM ceftriaxone and gentamicin.[7,8] The reasons underlying this observation likely include higher inhibitory quotient ratios associated with IM injections and the limited access to injectable antimicrobial agents outside of clinical settings.

It is important to appreciate that antimicrobial agents vary in their clinical efficacy at the oropharynx, an anatomical site that is increasingly being recognised as a critical niche for the evolution of antimicrobial resistant *N. gonorrhoeae*.[9,10] The propensity to develop antimicrobial resistance is enhanced when only single step mutations in one gene are required to change a susceptible phenotype into a resistant phenotype, as has been seen with the emergence of resistance to spectinomycin, kanamycin, azithromycin (23S rRNA-associated) and ciprofloxacin.[3,11,12] In contrast, it has taken much longer for chromosomal resistance to develop against penicillins, tetracyclines and cephalosporins after their initial introduction; in each case, several discrete mutations are required in several different genes in order to generate gonococci with sufficiently high minimum inhibitory concentrations (MIC) to result in treatment failure.[3]

The emergence of plasmid-mediated resistance to antimicrobial agents is always a cause for concern because this type of resistance is associated with high-level resistance and rapid spread of resistant gonorrhoea within communities. Plasmids are mobile genetic elements that may express resistance determinants and are typically present in multiple copies in each bacterial cell. These strains have the potential, under drug pressure, to re-shape gonococcal populations and render previously effective antimicrobial agents useless. This was classically seen with the emergence of penicillinase-producing *N. gonorrhoeae* in the 1970s and the emergence of the TetM-expressing high-level tetracycline resistant *N. gonorrhoeae* strains in the 1980s.[1]

Current treatment options for gonorrhoea

Following the demise of fluoroquinolones as a single-dose oral treatment for gonorrhoea, extended spectrum third-generation cephalosporins were introduced as first-line therapy in many countries.[5] The preference of clinicians to prescribe oral drugs within this class, such as cefixime and ceftibuten, proved to be less than ideal and provided the evolutionary environment required to support the rapid emergence of *N. gonorrhoeae* strains possessing mosaic *penA* genes.[5,13,14] Many of these mosaic *penA*-containing gonococci were resistant to oral

cephalosporins and accounted for most of the early treatment failures observed in Japan.[15] With time, however, it became clear that resistance to oral cephalosporins could also occur in *N. gonorrhoeae* strains lacking these mosaic genes; such strains possessed distinct point mutations in *penA* and other gonococcal genes responsible for drug entry into, and efflux from, the gonococcal periplasmic space.[1,16] Some clones with the mosaic *penA* genotype have proved to be highly successful in terms of international spread.[16] The emergence of the H041 and F89 *N. gonorrhoeae* strains, possessing extremely high MICs to both ceftriaxone and cefixime, generated substantial international concern regarding the potential emergence of untreatable gonorrhoea.[17–19] International, regional and national response plans emerged shortly thereafter to provide strategic direction to manage this threat.[20–22]

Despite lack of clinical trial data or a strong evidence base to support the decision to implement multi-drug therapy for the treatment of *N. gonorrhoeae* infections, several countries opted to change their national guidelines to treat gonorrhoea cases with dual therapy consisting of IM ceftriaxone, at varying doses, in combination with either single-dose oral azithromycin or a 1 week's course of doxycycline. Some countries were doing this already, but in the guise of syndromic therapy for genital discharges where either azithromycin or doxycycline was co-administered with ceftriaxone to treated potential chlamydial co-infection. The rationale for dual therapy was that it would prevent or reduce the further emergence of ceftriaxone-resistant strains. However, gonococci with dual resistance to both ceftriaxone and azithromycin have now emerged and the threat of untreatable gonorrhoea looms once more on the horizon.[4,23] This changing landscape has prompted a recent change in the UK's gonorrhoea treatment guidelines where, in the context of concerns over outbreaks of high-level azithromycin-resistant gonorrhoea, dual therapy has been discontinued and IM ceftriaxone recommended as single-dose monotherapy at a higher 1-g dose.[24]

Recycling of antimicrobial agents previously used to treat gonorrhoea

Given the lack of alternative oral drugs to ceftriaxone to treat gonorrhoea cheaply and reliably, efforts are being made to recycle 'old' antimicrobial agents that were used as first-line agents to treat gonorrhoea in the past. The use of phenotypic or genotypic antimicrobial susceptibility testing to guide appropriate antimicrobial therapy remains a critical enabler of effective management of MDR or XDR gonorrhoea when considering non-ceftriaxone-based treatments.[25] Within the microbiology laboratory, studies have also examined the synergistic effect of various multi-drug combinations; for example, one such study recently evaluated 21 antimicrobial combinations and suggested five potential new dual candidate combinations, containing either gentamicin or ertapenem, for treatment of MDR and XDR *N. gonorrhoeae* infections.[26]

Attention has once again focussed on ciprofloxacin as a potential agent for the treatment of gonorrhoea in settings where the prevalence of fluoroquinolone resistance is lower than 50%. Ciprofloxacin has the advantage that it can be prescribed as a single-dose oral regimen and it is highly efficacious in treating

fluoroquinolone-susceptible gonococci in the oropharynx. New diagnostic assays that can both detect *N. gonorrhoeae* and predict its susceptibility to ciprofloxacin are being established, which support effective treatment of fluoroquinolone-susceptible gonorrhoea and, at the same time, reduce ceftriaxone use as an antimicrobial stewardship measure.[27–29]

Single-dose IM gentamicin has been used in Malawi to treat gonorrhoea for over 20 years in the context of syndromic management.[8] Clinical researchers are now re-evaluating gentamicin as part of a dual second-line therapy approach to manage ceftriaxone-resistant gonorrhoea, or gonorrhoea in patients with a cephalosporin allergy.[30] In combination with single-dose azithromycin (1 g), gentamicin (240 mg) achieved 100% (95% CI: 98.5–100%) microbiological cure of 202 evaluable patients; it should be appreciated, however, that the gonococcal strains isolated were not MDR or XDR in nature and mostly susceptible to azithromycin.[30] Although the numbers of extragenital gonorrhoea cases were low (10 oropharyngeal and one anorectal case), all were cured with the gentamicin–azithromycin dual combination.

The efficacy of gentamicin has recently been compared with ceftriaxone in the context of dual therapy in the UK-based G-TOG trial.[31,32] This blinded two-arm multi-centre non-inferiority randomised trial enrolled 720 participants with a diagnosis of urogenital, oropharyngeal and/or anorectal gonorrhoea. Participants received a single IM injection of either gentamicin 240 mg (358 participants) or ceftriaxone 500 mg (362 participants); all participants additionally received single-dose oral azithromycin as part of a dual therapy regimen. The primary outcome was clearance of *N. gonorrhoeae* at all infected sites by a negative nucleic acid amplification test at 2 weeks post treatment. Primary outcome data were available for 598 (82%) of participants. The bacteriological clearance at 2 weeks was 91% (267/292) in the gentamicin arm and 299/306 (98%) in the ceftriaxone arm. Gentamicin failed to show non-inferiority to ceftriaxone in the treatment of gonorrhoea. Relevant for the sexual health care of men who have sex with men (MSM) and sex workers, bacteriological clearance at the oropharyngeal site was substantially lower in the gentamicin arm (80%) compared with the ceftriaxone arm (98%).[32]

New uses for existing antimicrobial agents

Ertapenem is a member of the carbapenem family of antibiotics, which share the basic β-lactam ring of penicillins with a few modifications, including the substitution of a carbon for the sulfur at position one in the five-membered thiazolidine ring.[33] Ertapenem is stable in the presence of renal tubular dehydropeptidase-1 (DHP-1) and does not require co-administration with cilastatin (a DHP-1 inhibitor). Ertapenem possesses broad activity against a variety of Gram-positive and Gram-negative bacteria, including *N. gonorrhoeae*. Ertapenem has activity against gonococci with ceftriaxone MICs up to 4 mg L^{-1} and can therefore be used in the management of ceftriaxone-resistant gonorrhoea.[34] Ertapenem was recently successfully used to treat XDR gonorrhoea cases in the United Kingdom and Australia.[4] The drug has an elimination half-life of 3.8 h in healthy volunteers and is available for both IM and intravenous

(IV) injection in many countries.[35] Ertapenem MICs are higher in those *N. gonorrhoeae* strains with high MICs for ceftriaxone, but still fall within the MIC range expected to achieve clinical cure.[34]

Some of the more modern fluoroquinolones, such as gemifloxacin, sitafloxacin and delafloxacin, have been evaluated as components of dual therapy regimens on account of their improved activity against *N. gonorrhoeae* over second-generation fluoroquinolones, such as ciprofloxacin.[30,36–38] While *in vitro* studies suggest good activity, clinical evaluations of these drugs as sole therapeutic agents for gonorrhoea are lacking. It is inherently problematic to assign an effective clinical outcome to any one antimicrobial agent that is administered to patients or research participants in the context of dual therapy for gonorrhoea, as typically both drugs are highly effective in their own rights.

Gemifloxacin, a fourth-generation oral fluoroquinolone introduced to treat acute bacterial exacerbations of chronic bronchitis and community pneumonia, has shown to achieve 99.5% (95% CI: 97.6–100%) microbiological cure of predominantly macrolide-susceptible *N. gonorrhoeae* infections in 199 evaluable patients when given as dual therapy with single dose azithromycin (1 g).[30] In this study, the gemifloxacin–azithromycin combination cured all oropharyngeal (*n* = 15) and anorectal (*n* = 5) gonococcal infections.[30]

Sitafloxacin, another fourth-generation fluoroquinolone, possesses activity against many Gram-positive and Gram-negative bacteria, including strains resistant to other fluoroquinolones. A recent *in vitro* study reported that sitafloxacin maintains good activity against ciprofloxacin-resistant *N. gonorrhoeae* isolates, although the sitafloxacin MICs reported for these isolates were at the high end of the susceptible range.[37] The implication of this observation is that sitafloxacin would not be a suitable monotherapeutic agent for gonorrhoea in those areas of the world where ciprofloxacin-resistant gonorrhoea is highly prevalent; however, it could potentially be a valuable component of a dual therapy regimen designed to manage cephalosporin-resistant gonorrhoea or gonorrhoea occurring in a patient with cephalosporin allergy.[36,37]

Delafloxacin is a somewhat unusual fluoroquinolone in that it demonstrates a more balanced activity against both DNA gyrase and topoisomerase IV in the context of both Gram-negative and Gram-positive infections.[39] Delafloxacin possesses activity against *N. gonorrhoeae in vitro* and, importantly, a low tendency to select spontaneous mutants in the laboratory setting.[38] An open-label, non-inferiority, multi-centre, randomised Phase 3 study recently assessed the efficacy and safety of single-dose oral delafloxacin (900 mg) compared with single-dose IM ceftriaxone (250 mg).[40] The primary endpoint was culture-based microbiological cure of urogenital gonorrhoea at the follow-up visit (day 4–10). Azithromycin was dispensed at the test-of-cure visit for those participants co-infected with *Chlamydia trachomatis*. In the microbiological intention-to-treat (micro-ITT) analysis, the cure rate for delafloxacin was 85% (194/228) compared with 91% (91/100) for ceftriaxone. The authors concluded that delafloxacin did not demonstrate non-inferiority to ceftriaxone.[40]

New antimicrobial agents in clinical trials

It has been estimated that it takes 15 years and over US $2,500 million to take a drug from target to product.[41] Many pharmaceutical companies regard the 'anti-infective' market as 'risky' when compared with likely returns associated with development of new drugs for chronic non-infectious conditions. The genomic revolution failed to identify many new antimicrobial targets, particularly for Gram-negative bacteria, and pharmaceutical research capacity has been reduced due to organisational mergers and reduction in available grant funding. In response, the WHO recently released a global priority list of antibiotic-resistant bacteria to guide research, discovery and development of new antibiotics.[6] There are now three promising antimicrobial agents in late-stage clinical development, namely solithromycin, zoliflodacin and gepotidacin.[42]

Solithromycin

Solithromycin (CEM-101) is a novel fluoroketolide that has been undergoing clinical development for the treatment of community-acquired pneumonia and gonorrhoea. Ketolides differ chemically from macrolides in a few distinct ways, including attachment of a heteroaryl-alkyl side chain to the macrocyclic ring through a suitable linker. This side chain is oriented down the ribosomal exit tunnel and binds to a second binding site on the 23S rRNA, resulting in a lower propensity for the emergence of antimicrobial resistance.[43,44] The presence of this extra binding site confers very low MICs towards macrolide-susceptible strains and low MICs towards macrolide-resistant strains.[43] As a result, solithromycin is highly active *in vitro* against most *N. gonorrhoeae* strains, including the XDR strains, H041and F89.[45]

A Phase 2, open-label, non-comparative safety trial of solithromycin to treat uncomplicated urogenital gonorrhoea was undertaken in the USA during 2012–13.[46] Two single-dose oral treatment regimens (1 g and 1.2 g) were assessed in 59 enrolled participants. Solithromycin efficacy was assessed in the 46 (78%) participants who had culture-proven gonorrhoea at urogenital sites; there were an additional eight oropharyngeal and four anorectal concomitant gonococcal infections. All cases of culture-proven gonorrhoea were cured. In terms of safety, the authors reported that mild dose-related gastrointestinal side-effects were common, but that these did not affect the ability of the participants to take their therapy.

Cempra Inc. progressed clinical development into an open-label randomised multi-centre Phase 3 trial (SOLITAIRE-U) of single-dose oral solithromycin (1 g) for the treatment of uncomplicated urogenital gonorrhoea, with or without concomitant *C. trachomatis* infection, in comparison with IM ceftriaxone (500 mg) plus single-dose oral azithromycin (1 g). An interim micro-ITT analysis, based on a negative urogenital *N. gonorrhoeae* culture at day 7–8 post-treatment for the 252 enrolled participants, showed a lower cure rate for the solithromycin arm (99/123, 80.5%) compared with the ceftriaxone-based dual therapy arm (109/129, 84.5%).[47] None of the baseline or follow-up *N. gonorrhoeae* isolates demonstrated *in vitro* resistance to solithromycin. The conclusion of the interim micro-ITT analysis was that solithromycin failed to demonstrate a non-inferiority margin when compared with the ceftriaxone-based standard of care regimen.

Attempts to progress solithromycin for gonorrhoea treatment have now stalled, in part as a consequence of these disappointing interim results, but also because of a request by the US Food and Drug Administration (FDA) for additional safety data regarding risk of solithromycin-related hepatotoxicity in the context of treatment of community-acquired bacterial pneumonia.[48]

Zoliflodacin

Zoliflodacin, also known as ETX0914 and AZD0914, is a first-in-class oral spiropyrimidinetrione with dual DNA topoisomerase II inhibitory activity targeting the *gyrB* and *parE* genes. In a manner similar to fluoroquinolones, zoliflodacin inhibits bacterial DNA biosynthesis through accumulation of double-strand cleavages, which arise following arrest of the cleaved covalent DNA gyrase complex with double-strand broken DNA.[49] Zoliflodacin displays antibacterial activity against several Gram-positive and Gram-negative pathogens, including *N. gonorrhoeae*.[50] In line with concerns over the threat of untreatable gonorrhoea and the need to prioritise research and development of new drugs to treat gonococcal infections, this new antimicrobial agent has received 'qualified infectious disease product' and 'fast track' designations from the US FDA for development as an oral treatment for uncomplicated *N. gonorrhoeae* infection.[6,19,51]

The results of Phase 1 studies, which investigated the safety, tolerability and pharmacokinetics (PK) of zoliflodacin, were recently published.[49] These studies also generated data on the absorption, distribution, metabolism and excretion of this new antimicrobial agent. The PK studies facilitated selection of dosage regimens for further clinical trials.

The multi-centre Phase 2 trial, undertaken in 2014–15, subsequently assessed the efficacy and safety of zoliflodacin in uncomplicated urogenital gonorrhoea.[51] This trial, which enrolled 179 participants, incorporated three treatment arms and compared single-dose zoliflodacin (2 g or 3 g) in an oral formulation, with single-dose IM ceftriaxone (500 mg). The micro-ITT analysis analysed the results of 141 (84%) participants on the basis of a positive urogenital *N. gonorrhoeae* culture at baseline. This analysis demonstrated that all 28 (100%) participants who received ceftriaxone were cured at follow up compared with 96% of participants in both zoliflodacin arms (55/57, 2 g arm; 54/56, 3 g arm). In a further per-protocol analysis of those 117 participants with a positive *N. gonorrhoeae* culture at baseline who returned for follow up, all but one participant receiving 2 g of zoliflodacin was cured (48/49, 98%); in contrast, all participants receiving 3 g of zoliflodacin (47/47, 100%) or IM ceftriaxone (21/21, 100%) were cured. There was no microbiological evidence of reduced susceptibility to zoliflodacin in the post-treatment *N. gonorrhoeae* isolates.[51] All 15 concomitant anorectal gonococcal infections were cured (12 with zoliflodacin, three with ceftriaxone); however, oropharyngeal cure rates were lower in the two zoliflodacin

arms (50% of eight participants treated with 2 g, 82% of 11 participants treated with 3 g) compared with a 100% cure rate for the four participants receiving ceftriaxone. Analysis of the safety data showed that zoliflodacin was generally well tolerated and most adverse events were mild and gastrointestinal in nature.[51]

Entasis Therapeutics (Waltham, MA, USA), whose anti-infective discovery platform produced zoliflodacin, has developed a new partnership with the not-for-profit Global Antibiotic Research and Development Partnership (GARDP).[52] Together they will progress zoliflodacin into a global Phase 3 clinical trial to be undertaken in several countries, including The Netherlands, South Africa, Thailand and USA.

Gepotidacin

Gepotidacin (GSK2140944) is a first-in-class triazaacenaphthylene antimicrobial agent. It is bactericidal in nature due to its novel DNA topoisomerase II inhibitory activity targeting the *gyrA* and *parC* genes.[53] Crystal structural analyses of novel type IIA topoisomerase inhibitors in a complex with bacterial DNA gyrase and DNA have indicated that the binding site of this new class of antimicrobial agents is close to, but distinct from, that of fluoroquinolones. As a result of this observation, it was initially predicted that gepotidacin would be active against fluoroquinolone-resistant *N. gonorrhoeae*; however, data from the recent Phase 2 study (described below) has highlighted higher MIC_{90} values for gepotidacin among fluoroquinolone-resistant *N. gonorrhoeae* strains and, in a few cases, failure of gepotidacin to cure fluoroquinolone-resistant gonorrhoea.[54,55] Gepotidacin appears to have potent *in vitro* activity against a range of *N. gonorrhoeae* isolates, including those exhibiting an XDR phenotype, and significant cross-resistance between gepotidacin and other relevant classes of antimicrobial agents does not appear to be an issue.[56] Checkerboard analyses of gepotidacin with other drugs potentially useful for gonorrhoea treatment failed to show any evidence of antagonism, indicating that gepotidacin could be administered as part of a dual therapy regimen.[53]

Phase 2 studies of gepotidacin have assessed its efficacy, safety and tolerability in participants with suspected or confirmed Gram-positive skin infections (IV formulation) and in participants with gonorrhoea (oral formulation).[57,58] With respect to gonorrhoea, the Phase 2 study undertaken in 2015–16 assessed the efficacy and safety of gepotidacin in a randomised, multi-centre, open-label, dose-ranging approach.[58] Participants with a laboratory-confirmed diagnosis of *N. gonorrhoeae* infection were randomised to receive either 1.5 g or 3 g of gepotidacin. In terms of safety, no treatment-limiting adverse events were recorded for either dose of gepotidacin. The study's primary efficacy endpoint was culture-confirmed eradication of urogenital gonorrhoea at 4–8 days post-treatment. In the per-protocol analysis of the microbiologically evaluable population, consisting of 69 (65%) of 106 enrolled participants with positive *N. gonorrhoeae* cultures at baseline, gepotidacin cured 29 (97%) of 30 participants receiving a 1.5 g dose and 37 (95%) of 39 receiving a 3 g dose; overall, this equated to a 96% cure rate. A low number of participants had concomitant

infections at the anorectal and pharyngeal sites; the three anorectal infections were all cured with gepotidacin, whereas one of two oropharyngeal infections failed therapy.

The three treatment failures were caused by fluoroquinolone-resistant gonococci, with the highest observed gepotidacin MIC value at baseline (1 mg L^{-1}); all three isolates also had a D86N substitution in the *parC* gene, which is known to affect gepotidacin binding.[55] The gepotidacin MIC for the test-of-cure isolate obtained from two of these three participants was markedly raised (32 mg L^{-1}) compared with the baseline MIC (1 mg L^{-1}), demonstrating the emergence of resistance whilst on therapy. It should be noted, however, that a further five baseline *N. gonorrhoeae* isolates from cured patients also had the same D86N mutation in their *parC* genes. The gepotidacin MIC of the *N. gonorrhoeae* isolate responsible for the oropharyngeal failure was 0.12 mg L^{-1} at both baseline and test-of-cure time points, and this strain lacked fluoroquinolone resistance-associated *gyrA* and *parC* mutations. Further analysis of the Phase 2 study data demonstrated that the ratio of the area under the free-drug concentration time curve to the MIC (fAUC/MIC) appears to be the most critical factor in determining a treatment outcome with gepotidacin.

Further drugs in the development pipeline

Although not the focus of this review, several other drugs at varying stages of development are being investigated for potential use in the treatment of gonorrhoea and have been eloquently reviewed by Unemo and Shafer.[59] These include further eravacycline (TP-434), dalbavancin, new broad-spectrum carbapenems (e.g. SM-295291 and SM-369926), novel broad-spectrum fluoroquinolones (avarofloxacin), single or dual target topoisomerase inhibitors (e.g. VT12–009811 and AZD0914), pleuromutilins (lefamulin, BC-3781), a boron-containing inhibitor (AN3365), FabI inhibitors (e.g. MUT056399), efflux pump inhibitors, carbon monoxide-releasing molecules (Trypto-CORM), inhibitors of UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC), defensin mimickers and immune modulators (e.g. LL-37 and IL-12 NanoCap).

Concluding remarks

The most important public health initiative for today is to stem the global rise in new gonorrhoea cases while we still have drugs that can reliably cure gonococcal infections. Rational drug prescribing is a requirement for an effective public health response and efforts to strengthen antimicrobial stewardship, both among prescribers and users, must be prioritised. When prescribing drugs for gonorrhoea, it is always important to consider the relationships between the antimicrobial agent, the host and the pathogen. Many countries still recommend the use of dual treatment regimens, albeit on the basis of weak evidence and expert opinion. If single agents are to be used, it is important to optimise dosing strategies and avoid those drugs that are characteristically associated with a rapid emergence of resistance. Implementation of molecular susceptibility-guided therapy will support antimicrobial stewardship efforts to spare ceftriaxone and enable recycling of older drugs. Global rationing and controlled use of the antimicrobial agents in late-stage clinical development will be essential to maintain

longevity of their use. Furthermore, substantial investment will be essential to support the research and development required to generate more candidates for the drug pipeline.

Conflicts of interest

The author is a former member of the GARDP Advisory Panel for the Phase 3 trial of Zoliflodacin and his organisation has signed an Expert Agreement for him to provide expert advice to GlaxoSmithKline with respect to the clinical development of Gepotidacin.

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