The Shifting Sands of Gonococcal Antimicrobial Resistance

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(See the Major Article by Kirkcaldy et al on pages 1083–91.)

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In the current issue of Clinical Infectious Diseases, Kirkcaldy et al [1] report that extended-spectrum cephalosporins (cefixime and ceftriaxone) are likely to continue their inexorable march toward failure [2]. They propose that using combination therapy to treat gonococcal infection is the logical next step while awaiting the identification of a new antibiotic or class of antibiotics that can be used singly. Unfortunately, no antibiotic or unique class of antibiotics has emerged that is likely to overcome for long the gonococcus’s vast array of machinery that enables the organism to circumvent antimicrobial killing. Traditionally, effective therapy that meets Centers for Disease Control and Prevention (CDC) criteria for efficacy [3] requires treatment that shows mean efficacy of >95% across well-conducted trials using per protocol (PP) analysis (evaluable) and a lower 1-sided confidence interval (CI) bound by ≥95% CI [3]. This standard, translated to “real-world” efficacy, had in the past (1) used an acceptable mode of administration (single-dose oral or intramuscular); (2) was inexpensive; (3) demonstrated good patient tolerability; and (4) eliminated need to perform follow-up tests of cure. In the face of a potential epidemic with Neisseria gonorrhoeae, the “superbug,” these standards may now be impossible to meet and traditional expectations may have to be lowered while exploring new approaches to optimize therapy and control spread of infection.

This well-designed and conducted randomized clinical multicenter trial found that gentamicin plus azithromycin or cefixime plus azithromycin met CDC criteria for efficacy [3]; either regimen may serve as a potential alternative treatment option for uncomplicated gonorrhea when widespread resistance to ceftriaxone develops. Per protocol analysis was clearly defined based on a priori-determined inclusion and exclusion criteria. Modified intent-to-treat (mITT) analysis was used because 21% of subjects were deemed ineligible and excluded after randomization and treatment, most often due to negative cultures obtained at the time of enrollment. Appropriately conservative sensitivity analyses were used to set conservative lower bounds of real-world efficacy. The mITT analysis considered participants to have failed treatment if they vomited within 1 hour of drug administration; were lost to follow up; were not followed up in the appropriate time interval; took other antibiotics; or withdrew consent.

Nearly half of initially randomized and treated women were excluded, compared with 12% of similarly classified men, resulting in only 15% of evaluable (PP) participants being women. Not surprisingly, the diagnosis of gonorrhea in women relied heavily on a microbiologic diagnosis [4] performed after entry in the study. Gram stains are not as reliable (or as frequently used) for the diagnosis in women compared with men [4]. Therefore, this trial was conducted mostly in men; comparative efficacy in women vs men was not reported, but the small number of women included may have precluded sufficient power to determine if potential differences were significant. Notably, all women who remained in the study after randomization/treatment qualified for PP analysis (compared with only 79% of men), suggesting better tolerance of medications in women (no vomiting within 1 hour) and, perhaps not surprisingly, better (100%) compliance with the study protocol.

Gastrointestinal toxicities were the major adverse events encountered by subjects. Modest differences in gastrointestinal complaints seemed to occur between...
the 2 regimens overall in PP subjects, but vomiting within 1 hour contributed to exclusion from PP eligibility primarily in the gemifloxacin/azithromycin group; 37% of subjects excluded were in this group compared with 16% in the gentamicin plus azithromycin group (P = .04; 2-tailed Fisher exact test). Overall, mITT efficacy was similar in both groups (84%), also driven downward by other factors, particularly nonattendance at follow-up visits (men only). In the real world, tests of cure have not been necessary and, assuming subjects who did not return would have been cured, then approximate efficacy would have been 94% and 90%, respectively, in the 2 groups, the differences explained primarily by differences in vomiting after treatment.

Now we have 2 successfully tested alternatives to ceftriaxone plus azithromycin, the latter currently recommended by CDC to improve efficacy against strains with increased minimum inhibitory concentrations (MICs) to ceftriaxone. Ceftriaxone plus azithromycin has been preferred as dual therapy for gonorrhea (instead of ceftriaxone plus doxycycline) because of enhanced efficacy against pharyngeal infection [5]. In the current study, both trial regimens were 100% successful in eradicating the small number of pharyngeal infections that were encountered. But will any 1 of these 3 dual regimens stand up to advancing antimicrobial resistance? With the possible exception of gentamicin [6–8], each of the classes represented by the antibiotics described above can be circumvented by N. gonorrhoeae, and it is really only a matter of time before complete resistance develops. The use of dual therapies may retard resistance but is unlikely to prevent it, and dual therapies can be predicted to go the way of single therapy eventually. Whereas gonococci use specific mechanisms to render each of these antibiotic classes inactive individually (reviewed in [9]), they also possess generalized machinery that can dispose of antimicrobials by increasing efflux and decreasing influx of these agents. Most important, 3 of the 4 efflux pump systems (MtrCDE, MacAB, NorM, and FarAB) have been directly associated with increased resistance to antimicrobials. The MtrCDE, MacAB, and NorM efflux pump systems recognize antimicrobials that have been previously or are currently recommended for treatment of gonorrhea. The master regulator of mtrCDE is termed MtrR. Based on mutations in the mtrR promoter [10,11], overexpression of the MtrCDE efflux pump can occur. This results in increased efflux of structurally diverse hydrophobic antimicrobials, such as macrolides (eg, azithromycin); β-lactam antimicrobials such as penicillin and extended-spectrum cephalosporins; ciprofloxacin; and tetracycline [12], all resulting in increased MICs to these antimicrobials. Overexpression of the MacAB efflux pump increases MICs to macrolides [13], whereas increased expression of the NorM efflux pump increases MICs to fluoroquinolones [14].

The traditionally held notion that antibiotic-resistant strains are less fit is now changing. Recent work on the gonococcal MtrCDE efflux pump shows that control of its gene expression is determined by transcriptional regulators and cis-acting regulatory mutations [15]. The fourth efflux pump, FarAB, acts together with MtrCDE to recognize host-derived antimicrobials such as cationic antimicrobial peptides [15,16] and long-chain fatty acids. Upregulated efflux pumps are now being proposed to increase fitness and virulence based on results in whole animal experimental systems (female BALB/c mice) [17–19].

The MtrR repressor can regulate expression of nearly 70 genes scattered throughout the gonococcal chromosome, termed “multitasking” by Shafer et al [20]. This may be important, not only for repressing transcription of the mtrCDE-encoded efflux pump but also perhaps for processes involved in the basic metabolism, adaptation, biological fitness, and pathogenicity of N. gonorrhoeae [15,21]. De-repression of the mtrCDE efflux pump operon with resultant increased fitness threatens to create a “perfect” storm of increased antimicrobial resistance coupled with increased fitness. The former ensures survival of the gonococcus and the latter increases the time the organism has to encounter a new host.

Gonococci do have at least 1 potential “soft spot,” however, that might serve as a target for therapeutic intervention. Neisseria gonorrhoeae scavenges sialic acid from infected hosts to “cap” lipooligosaccharide (LOS) molecules. The result is uniform binding to all gonococci in situ (or in vivo) of factor H (FH), the downregulator of the alternative pathway of complement. This contributes to inhibition of complement-mediated killing [22]. Using recombinant systems, FH-like molecules that lack regulatory activity can be engineered to bind gonococci exclusively. These molecules can be engineered further to express covalently bound moieties that possess antigonococcal activity [23]. Global recognition of FH binding sites, for example, on human cell surfaces, must be avoided, of course, lest they interfere with the natural regulatory effects of FH on human cells. A separate strategy could employ sialic acid analogues that are taken up by gonococcal LOS, but lack the ability to inhibit complement and thereby outcompete native sialic acids that cap LOS molecules. Binding of certain analogues does not lead to FH binding and results in decreased fitness of the organism [24].

The simplest model of gonococcal dynamics, and indeed the dynamics of spread of sexually transmitted infections generally, in a homogenous population, states that $R_0 = \beta D_c$, where $R_0$ is the average number of secondary cases of infection generated by a primary case in a susceptible population, $\beta$ the probability of transmission within a sexual partnership, D the duration the person is infectious, and c the number of new sex partners the infected person has in a
unit of time \([25, 26]\). An \(R_0 \geq 1\) implies that an infection will persist, whereas an \(R_0 < 1\) predicts elimination of infection. Therapeutics and vaccines reduce \(D\) and may also reduce \(\beta\) by decreasing pathogen load or diminishing fitness. Understanding differences in strain transmissibility (\(\beta\)) has important implications for disease control using therapeutics, vaccination, and public health measures.

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**References**


