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Use of Gentamicin as an Alternative Treatment for Gonorrhea

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A high gonorrhoea disease burden, increasing rates, and growing antimicrobial resistance portend a developing global public health crisis [1]. Gonorrhea can cause reproductive complications such as pelvic inflammatory disease and infertility, blindness in infants born to infected mothers, and can facilitate HIV acquisition and transmission. Effective treatment prevents sequelae and transmission. Yet *Neisseria gonorrhoeae* has developed resistance to each antimicrobial used for treatment [2]. Development of new antimicrobials has not kept pace.

Ceftriaxone is the only remaining recommended agent that reliably cures gonorrhea at all anatomic sites.[3] Declining cephalosporin susceptibility in the USA and elsewhere during 2009–12 raised concern about emerging ceftriaxone resistance [2]; in response, strategies to prolong ceftriaxone effectiveness included recommendations for use of ceftriaxone rather than oral cephalosporins (based on pharmacokinetic principles and site-specific differences in treatment efficacy) and combination therapy to potentially mitigate resistance [3]. Concerningly, azithromycin susceptibility has now declined in many countries [4]. A ceftriaxone- and azithromycin-resistant strain of *N. gonorrhoeae* was recently identified in the UK, and international transmission of a different ceftriaxone-resistant strain was recently described [5,6].

Although ceftriaxone remains effective in the USA, the threat of ceftriaxone resistance and challenge of treating cephalosporin-allergic patients necessitate the search for additional treatments. Results of phase 2 trials of new antimicrobials (gepotidacin and zoliflodacin) are encouraging [7,8], but commercial availability of these agents is not imminent. If ceftriaxone is not an option, identification of existing drugs that are effective and well-tolerated is needed. We previously investigated available drugs for gonorrhea treatment; one regimen was gentamicin 240 mg intramuscularly plus azithromycin 2 g orally [9]. Cure was based on negative cultures 10–17 days post-treatment. The gentamicin-based regimen demonstrated 100% efficacy for urogenital gonorrhoea in a group of 202 patients. Extragenital infections were cured, but the sample only included 10 participants with pharyngeal gonorrhea and one with rectal gonorrhea. Likely owing to the 2 g azithromycin dose, 56 (26%) participants in

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the gentamicin arm had mild to moderate nausea and 15 (7%) had mild to moderate vomiting. Among all participants who received gentamicin and azithromycin, ten (3%) vomited within 1 h. Subsequently, US Centers for Disease Control and Prevention's 2015 treatment guidelines listed gentamicin and azithromycin combination therapy as an alternative option in the presence of cephalosporin allergy but noted that gastrointestinal intolerability might limit use.[3]

In the Lancet, Jonathan Ross and colleagues advance our understanding of the potential utility of gentamicin.[10] 720 participants with uncomplicated gonorrhoea were randomly assigned to 500 mg of intramuscular ceftriaxone or 240 mg of intramuscular gentamicin; all participants received azithromycin 1 g orally. The primary outcome was clearance of *N. gonorrhoeae* by negative nucleic acid amplification testing (NAAT) 2 weeks post treatment. 409 participants had genital gonorrhoea (219 in the gentamicin group), 256 participants had pharyngeal gonorrhoea (128 in the gentamicin group), and 306 had rectal gonorrhoea (147 in the gentamicin group). At 2 weeks after treatment, infection had cleared for 299 (98%) of 306 participants in the ceftriaxone group compared with 267 (91%) of 292 participants in the gentamicin group (adjusted risk difference −6.4%, 95% CI −10.4% to −2.4%). Similarly, 151 (98%) of 154 participants with genital gonorrhoea were cleared of infection compared with 163 (94%) of 174 participants with genital gonorrhoea in the gentamicin group (adjusted risk difference −4.4%, −8.7 to 0). For participants with a pharyngeal infection, a greater proportion receiving ceftriaxone had clearance at follow-up (108 [96%] in the ceftriaxone group compared with 82 [80%] in the gentamicin group; adjusted risk difference −15.3%, −24.0 to −6.5). For participants with rectal infection, clearance at follow-up was also greater in the ceftriaxone group (134 [98%] in the ceftriaxone group compared with 107 [90%] in the gentamicin group; adjusted risk difference −7.8%, −13.6 to −2.0). Thus, efficacy of gentamicin for the treatment of gonorrhoea was inferior to efficacy of ceftriaxone. When recommending regimens, gonorrhea treatment guidelines have traditionally used efficacy estimates of individual agents [11]. Gentamicin efficacy in this trial might have been higher had culture rather than NAAT, been used for treatment outcome. Additionally, some apparent treatment failures might have been reinfections; 47 (16%) participants in the gentamicin arm reported interim condomless sex[10]. Adverse events following gentamicin and azithromycin were relatively uncommon; 41 (14%) participants had nausea and renal function was not compromised. These data seem to support the role of gentamicin 240 mg plus azithromycin 1 g as an alternative regimen for urogenital and possibly rectal gonorrhea for persons with cephalosporin allergy.

However, only 82 (80%) of 102 participants with pharyngeal infections were cleared of infection, so gentamicin plus azithromycin is not a reliable treatment. Treatment of pharyngeal gonorrhea is challenging: pharyngeal infections can be more difficult to eradicate than infections at other sites, and the pharynx might serve as a reservoir of asymptomatic infection and resistant gonococci [12].

The work by Ross [10] is a welcome step forward. However, because of ongoing management challenges and emerging resistance, new drugs with efficacy at all anatomic sites are still needed. Pharmacokinetic and pharmacodynamic studies of new drugs are needed to understand tissue penetration (especially at extragenital sites) and inform

treatment duration. Because few treatment options exist, we might have to re-think existing efficacy standards for treatment recommendations.[11] Strengthening prevention programs and developing new approaches (including vaccines) are necessary, and staying ahead of the threat of gonococcal resistance requires sustained action.

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