

Multidrug-resistant gonorrhoea: tackling a meaner bug in the UK

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Background

Reports of a gonorrhoea ‘superbug’ made the headlines last year following the description of a ceftriaxone-resistant isolate of *Neisseria gonorrhoeae*.¹ But is antimicrobial resistance a significant problem and what is the current reality of *N. gonorrhoeae* infection in the UK? Is gonorrhoea getting meaner?

Anogenital infection with *N. gonorrhoeae* has been highly responsive to single-dose antimicrobial treatment since the introduction of penicillin. However, the progressive development of resistance by *N. gonorrhoeae* to many classes of antimicrobial has necessitated periodic changes in treatment recommendations to maintain treatment efficacy and led to ever diminishing treatment options. Third-generation cephalosporins, notably ceftriaxone and cefixime, have been the mainstay of treatment recommendations since 2004. Surveillance data in the UK show a progressive drift in the minimum inhibitory concentrations (MICs) of ceftriaxone and cefixime to *N. gonorrhoeae*,² culminating in multiple case reports of treatment failure with cefixime,^{3–5} three case reports of ceftriaxone failure in the treatment of pharyngeal gonorrhoea^{6,7} and the identification of the ceftriaxone-resistant isolate in Japan in 2011.¹ There is growing concern that gonorrhoea may become untreatable unless new treatments can be found or new control strategies implemented. The prevention of sexually transmitted infections (STIs) assumes added importance and urgency with the prospect of another incurable infection.

Symptoms and treatment

The common symptoms of gonorrhoea are similar to those caused by infection with *Chlamydia trachomatis* and relate to inflammation of mucosal surfaces. Urethral discharge and/or dysuria are the most common presenting symptoms in men and altered vaginal discharge and

lower abdominal pain the most common symptoms in women.⁸ However, infection is often asymptomatic in women and is usually asymptomatic in the rectum and pharynx. Serious sequelae are uncommon but include pelvic inflammatory disease and its resultant impact on reproductive health. Importantly, gonorrhoea facilitates HIV transmission.⁹

Despite being the second most common bacterial STI, the incidence of gonorrhoea in the UK is around 10-fold less than that of chlamydial infection with 16 531 cases of gonorrhoea reported in genitourinary medicine (GUM) clinics in England and Wales in 2010. There was a 3% increase in cases between 2009 and 2010.¹⁰

Cases of gonorrhoea tend to be clustered in large urban centres, and men who have sex with men (MSM) accounted for 40% of all gonorrhoea diagnoses in England and Wales in 2010.¹⁰ In MSM, gonorrhoea is commonly extra-genital with the rectum or pharynx often being the sole infected site. Co-infection with other STIs commonly occurs and approximately one-third of gonorrhoea cases in the UK also have infection with chlamydia.¹¹

The potential development of multidrug-resistant *N. gonorrhoeae* is a major public health concern. The UK guidelines for the management of gonorrhoea were revised in 2011 to take account of the evolving resistance of *N. gonorrhoeae* to cephalosporins.⁸ The recommended treatment for uncomplicated gonorrhoea in adults is now ceftriaxone 500 mg intramuscularly as a single dose together with azithromycin 1 g orally as a single dose. This new recommendation is not based on evidence from clinical trials but from concerns following the recognition of multi-resistant gonorrhoea. The principle of single-dose treatment for gonorrhoea is maintained but the dose of ceftriaxone is increased to take account of pharmacokinetic simulation of the duration of the antibiotic

above the MIC.² In general, the clinical efficacy of β -lactam antibiotics against gonorrhoea relates to the time for which the free drug concentration exceeds the MIC of the bacteria. As the MIC of gonorrhoea rises above 0.125 mg/l for ceftriaxone, the free drug concentration of antibiotic no longer reliably exceeds this MIC for 10 or more hours using the 250 mg dose and treatment failures become increasingly predictable. The addition of azithromycin is no longer given to tackle possible co-infection with chlamydia but as a combination therapy to delay widespread cephalosporin resistance. Cefixime has less favourable pharmacokinetics than ceftriaxone² and the MIC drift for cefixime has been much more extensive with >6% isolates in the UK showing an MIC \geq 0.25 mg/l.¹¹ For those patients insisting on oral therapy to treat their gonorrhoea, cefixime 400 mg as a single dose remains an alternative but is not recommended as sole therapy for pharyngeal infection. Azithromycin 2 g as a single dose is another alternative but should be used with caution since high-level azithromycin resistance has been observed in the UK.¹² Test of cure at 2 weeks post-treatment is recommended to actively identify treatment failures and although this may not be practical for all settings, it is most important for those who remain symptomatic, who have extra-genital infection and for those treated with alternatives to ceftriaxone.⁸ Patients with persisting or recurrent symptoms after treatment should have testing by culture to enable determination of antimicrobial sensitivities.

Testing and diagnosis

Detection of *N. gonorrhoeae* has traditionally been by culture on selective media, which also allows antibiotic sensitivity testing. However, culture requires clinician-taken samples and careful attention to specimen transportation and handling. Nucleic acid amplification tests (NAATs) are less demanding in specimen quality, storage and transportation, and offer higher sensitivity compared with bacterial culture. They show high sensitivity with non-invasive and patient-taken samples, offer dual testing capability along with testing for *C. trachomatis* and have facilitated more widespread testing in the community.¹³ However, NAATs do not show 100% specificity and false-positive results are a concern in low prevalence populations and when used for testing non-genital sites.¹³ Importantly, NAATs do not allow for antimicrobial sensitivity testing. It is for this reason that UK national guidelines continue to promote use of cultures in selected circumstances, including in patients presenting with signs and symptoms suggestive of gonorrhoea, contacts of gonorrhoea, for pharyngeal infection and when symptoms persist after treatment.⁸ While testing for gonorrhoea has become more widespread in community and primary care settings, most cases in the UK are still managed within GUM clinics. This remains appropriate given the ongoing need for access

to specialised culture techniques, the need to administer parenteral antimicrobials for treatment and the renewed importance of partner notification and management. Unlike chlamydial infection, the low prevalence of gonorrhoea in most communities does not support widespread unselected screening in the community.¹³ Testing should be focused towards under 25-year-olds, MSM, urban communities and those with symptoms.^{10 11}

Conclusions

N. gonorrhoeae has demonstrated a relentless capability to develop resistance to antimicrobials and is on the cusp of becoming resistant to third-generation cephalosporins. Spectinomycin and gentamicin might fill the gap for a time but warnings that gonorrhoea could become untreatable look increasingly credible. At present gonorrhoea remains fully treatable in the UK. Careful monitoring of antimicrobial resistance, together with appropriate use of antimicrobials, are important to preserve treatment options for as long as possible. Maintaining culture for *N. gonorrhoeae*, vigilance for treatment failures and effective prevention are also necessary components of the strategy to control the gonococcus.

Competing interests None.

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