

Lessons learnt from ceftriaxone resistant gonorrhoea in the United Kingdom and Australia

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Neisseria gonorrhoeae, the causative pathogen of gonorrhoea, has demonstrated impressive agility to develop resistance to successive classes of antimicrobials used for therapy, progressively reducing available treatment options. Ceftriaxone is the last-line treatment option, and many countries recommend 'dual therapy' with ceftriaxone (250mg-1g) in combination with azithromycin (1g-2g). However, following the introduction of dual therapy, the prevalence of azithromycin resistance globally has increased.¹ Additionally, international spread of the extensively drug resistant *N gonorrhoeae* FC428 clone, associated with ceftriaxone resistance and intermediate resistance to azithromycin has been reported, usually associated with epidemiological links to the Asia Pacific region.²

The first treatment failure to dual therapy was reported in the UK in 2016; a heterosexual man with urethral and pharyngeal gonococcal infection acquired in Japan (Table 1).³ In 2018 the first strain with ceftriaxone resistance (MIC 0.5mg/L) combined with high-level azithromycin resistance (MIC > 256mg/L) was reported, again in the UK, in a heterosexual man with urethral and pharyngeal gonococcal infection acquired in Thailand (Table 1).⁴ The urethral infection was successfully treated with ceftriaxone, but the pharyngeal infection persisted and was eventually cleared with three days of intravenous ertapenem 1g. Of particular concern was the identification of two genetically identical *N gonorrhoeae* cases in Australia several months later.⁵ As with the UK case, one of the Australian cases had

acquired the infection in South-East Asia, indicating intercontinental dissemination. Later in 2018, two women in the UK were diagnosed with infection caused by the *N gonorrhoeae* FC428 clone (Table 1).⁶ Both women reported sexual exposure with UK partners in Ibiza, Spain, again highlighting the potential for rapid international dissemination. One of the women remained symptomatic following ceftriaxone 1g, and subsequently gentamicin 240mg plus azithromycin 2g. She was eventually successfully treated with three days of intravenous ertapenem 1g. Although there is no clinical data for ertapenem, *in vitro* microbiological activity against *N gonorrhoeae* has been shown.⁷ The decision to give three-days of intravenous ertapenem was intended to maximise the duration that the plasma concentration would likely exceed the minimum inhibitory concentration.

Surveillance programmes cannot always detect emerging resistance in real-time, which is needed to contain the spread of highly resistant strains within the community. Often culture may not be attempted or is unsuccessful due to low infectious load or delays between sample collection to plating. The development of molecular tests which detect resistance determinants in real-time from culture-negative infections, are greatly needed. Assays are available to detect the penA60 allele which confers ceftriaxone resistance, however ongoing culture-based surveillance with additional whole genome sequencing is required to monitor for novel ceftriaxone resistance mechanisms.⁸

Alongside AMR surveillance, the detection of clinical treatment failure is critical to controlling spread. Public Health England has introduced a treatment failure reporting system, however the sensitivity and specificity of this system is suboptimal. Challenges include stringent case definition requirements that may be difficult to achieve, 'false positive' reports due to re-infection or persistent DNA at test of cure, and difficulty sustaining engagement with reporting rare events.

Two of the cases described above involved pharyngeal infection in heterosexually-identifying men, who are not routinely tested at the pharynx. Most heterosexual men with pharyngeal infection will likely have concurrent genital infection and so, in theory, treatment given for genital infection would clear any (undiagnosed) pharyngeal infection.⁹ However pharyngeal infection is harder to treat, and for infections with resistant strains

treatment may not clear pharyngeal infection. Given that routine pharyngeal testing for all men is unlikely to be cost effective, pharyngeal testing in heterosexual men should be recommended for those at higher risk of resistant infection i.e. those with exposure in the Asia-Pacific region, or who have genital infection with a confirmed ceftriaxone resistant strain.

Extensively drug resistant gonococcal infections require complex and expensive treatment that will not be possible in all settings. The reality is that untreatable gonorrhoea is foreseeable, and disease control will not be possible. Urgent global action is required. Improved STI testing and management pathways including extra-genital testing, test of cure and partner notification, supported by better primary prevention efforts, are essential to detect and limit the spread of AMR. Further research on vaccines, alternative treatment regimens, and the development of molecular tests for real-time detection of AMR mutations are priorities.

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