

Update on French recommendations for the treatment of uncomplicated *Neisseria gonorrhoeae* infections

In October of 2020, the Int J STD AIDS published the updated European guideline on *Neisseria gonorrhoeae* (NG) infections.¹ Its main therapeutic recommendation for anogenital infections is now dual therapy with a 1000 mg stat dose of intramuscular ceftriaxone (CRO) and a 2000 mg stat dose of oral azithromycin (AZM). This extends in the current decade the 2012 European guideline's strong advocacy for combination therapy with AZM, in line with the World Health Organization's 2016 guideline, and doubles the recommended CRO single dose.^{2,3}

Indeed, NG's propensity to antimicrobial resistance has led to the successive demises of sulfonamides, penicillin, tetracyclines and fluoro quinolones.⁴ With minimal inhibitory concentrations (MICs) of CRO to NG rising steadily and actual CRO-resistant clones being reported, there is a true risk of gonorrhea becoming untreatable.⁵

Two main strategies have been implemented in response: dual therapy with AZM, and CRO single-dose increments - from 125 mg in the 1980s to the current 1000 mg (500 mg in the US).⁶ Though pharmacokinetic and pharmacodynamic models predict that raising doses does not lead to a proportional increase of time spent by antibiotic plasma concentrations above MIC - the relevant criterion for betalactam success—their observed non-linear increase has allowed the uninterrupted use of CRO since the mid 1980s.^{4,7} On the other hand, AZM has a poor track record against sexually transmitted infections (STIs): its efficacy against *Chlamydia trachomatis* infections seems sub-optimal compared to that of doxycycline⁸; early 2000s attempts to use it as a single-dose treatment of syphilis soon resulted in widespread resistance⁹; finally, its unrestricted use in the empiric treatment of urethritis has probably led to the current therapeutic impasse in *Mycoplasma genitalium* (MG) infections.¹⁰

In France, monitoring by the National Reference Centre for Bacterial STI (NRC) shows that between 2012 and 2020 the percentage of AZM-resistant NG isolates went up from 0 to 7% while that of CRO-resistant ones remained

at 0%¹¹ and unpublished data (excluding two strains retrieved in 2017 and 2019).^{12,13} In view of these figures, of the risk of losing any AZM activity against NG while increasing selective pressure on MG and of the bad digestive tolerance of high AZM doses, many French STI specialists (FSS), uncomfortable with the new guideline, turned to the NRC, the French Society of Dermatology and Venerology (SFD) and the French Society of Infectious Diseases (SPILF) for advice. A survey of 26 FSS representing 18 of the largest French STI clinics showed that 96.2% had not implemented the 2012 European recommendation and only 7.7% were intent on complying with the 2020 update.¹⁴

In order to address the urgency of providing FSS with guidance, pending a formal update on French recommendations (in process)¹⁵ and considering national resistance figures, the NRC, the SPILF and the SFD jointly recommend that uncomplicated anogenital NG infections be treated with CRO, 1000 mg as a single dose, effective even on isolates with an MIC to CRO between 0.125 and 0.5 mg/L.¹⁶ Regarding oropharyngeal infection, which is asymptomatic in at least 90% of cases and for which efficacy of most antibiotics is hampered by suboptimal pharyngeal diffusion, one should, whenever possible, tailor therapy to the resistance profile of NG isolates involved and refer to the algorithm in Figure 1. If impossible, CRO 1000 mg monotherapy remains the appropriate probabilistic choice with emphasis on a mandatory test of cure 2 weeks after treatment completion. In patients returning from Asia Pacific where the prevalence of CRO resistance is high¹⁷ a dual CRO 1000 mg + AZM 2000 mg regimen will be preferred.

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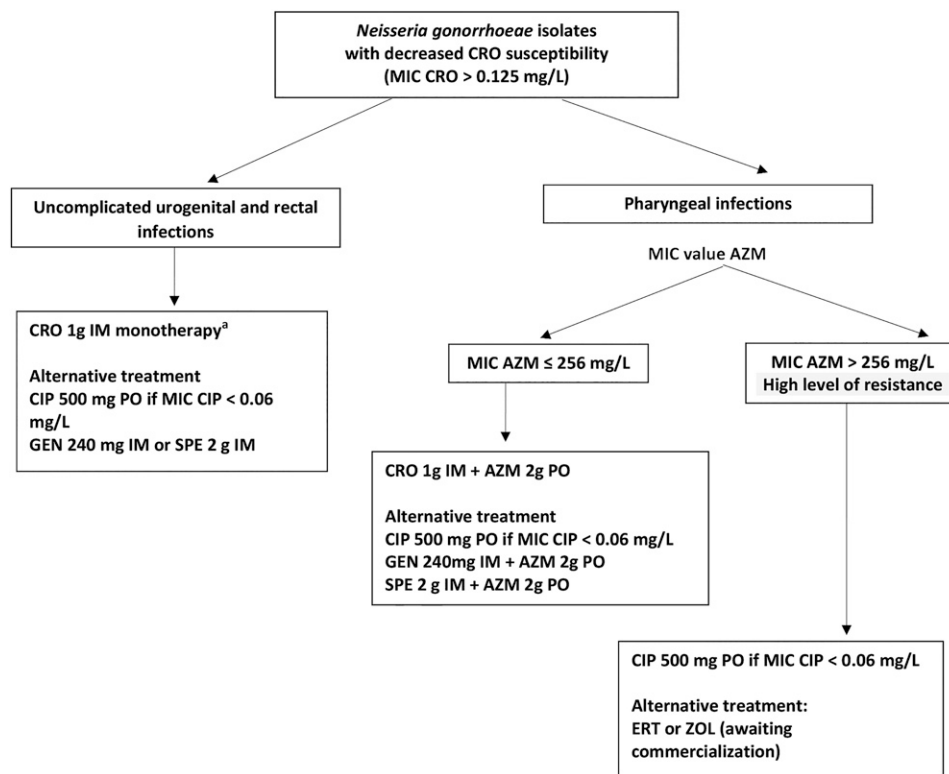


Figure 1. Treatment algorithm for NG isolates with decreased ceftriaxone susceptibility

Note: CRO: ceftriaxone, AZM: azithromycin, CIP: ciprofloxacin, GEN: gentamycin, SPE: spectinomycin, ERT: ertapenem, ZOL: zoliflodacin, IM: intramuscularly, PO: per os.

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