RECOMMENDATIONS FOR TREATMENT OF GONOCOCCAL INFECTIONS IN THE ERA OF MDR/XDR GONORRHOEA (Document for Sexual Health and Infectious Disease Specialists)

Summary Document of Discussions held by a Working Group established to report to the Communicable Diseases Network Australia on recommendations for gonorrhoea treatment in a new era of extensively drug resistant gonorrhoea.

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The primary purpose of this document is to offer recommendations for the effective management of gonorrhoea.

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1. Recommendations for Revision of the Current Treatment Guidelines for the Management of Uncomplicated Gonorrhoea

(i) Ceftriaxone/Azithromycin-based Dual Therapy for Gonorrhoea Treatment in Australia

Until recently, the Australian guideline for the management of uncomplicated gonorrhoea recommended treating infections with a dual therapy regimen, consisting of a single dose intramuscular of ceftriaxone (500 mg, suspended in 2ml of 1% lignocaine) plus single oral dose of azithromycin (1g). In considering this dual regimen, it is important to understand that ceftriaxone is the cornerstone of therapy. In 2014, azithromycin was added in the Australian Sexual Health Alliance's (ASHA) Australian STI Management Guidelines as a second drug to theoretically reduce the rate of emergence or onward transmission of ceftriaxone resistant *Neisseria gonorrhoeae* strains.

The decision to add azithromycin occurred in many countries as a strategic move, aimed at reducing the impact of escalating antimicrobial resistance after the reporting of the world's first microbiologically-defined ceftriaxone resistant *N. gonorrhoeae* strains in Japan, France and Spain (Ohnishi *et al.*; Unemo *et al*.; Camara *et al*.). One of the key reasons to choose azithromycin 1g as the co-administered drug (when studies have shown 2g is required for cure) was the suggestion that there may *in vitro* synergy between ceftriaxone and azithromycin. However, there is limited clinical evidence that such synergy exists (Barbee); one study did show that administering azithromycin and ceftriaxone together did result in a lower proportion of subjects (7.0%) presenting with repeat positive oro-pharyngeal *N. gonorrhoeae* tests compared to those who received ceftriaxone alone (9.1%) (Barbee *et al*.). In 2017, almost all (> 99.9%) gonococcal isolates cultured in Australia remain fully susceptible to ceftriaxone and most (> 90%) remain susceptible to azithromycin (Lahra *et al*., Figure 1).

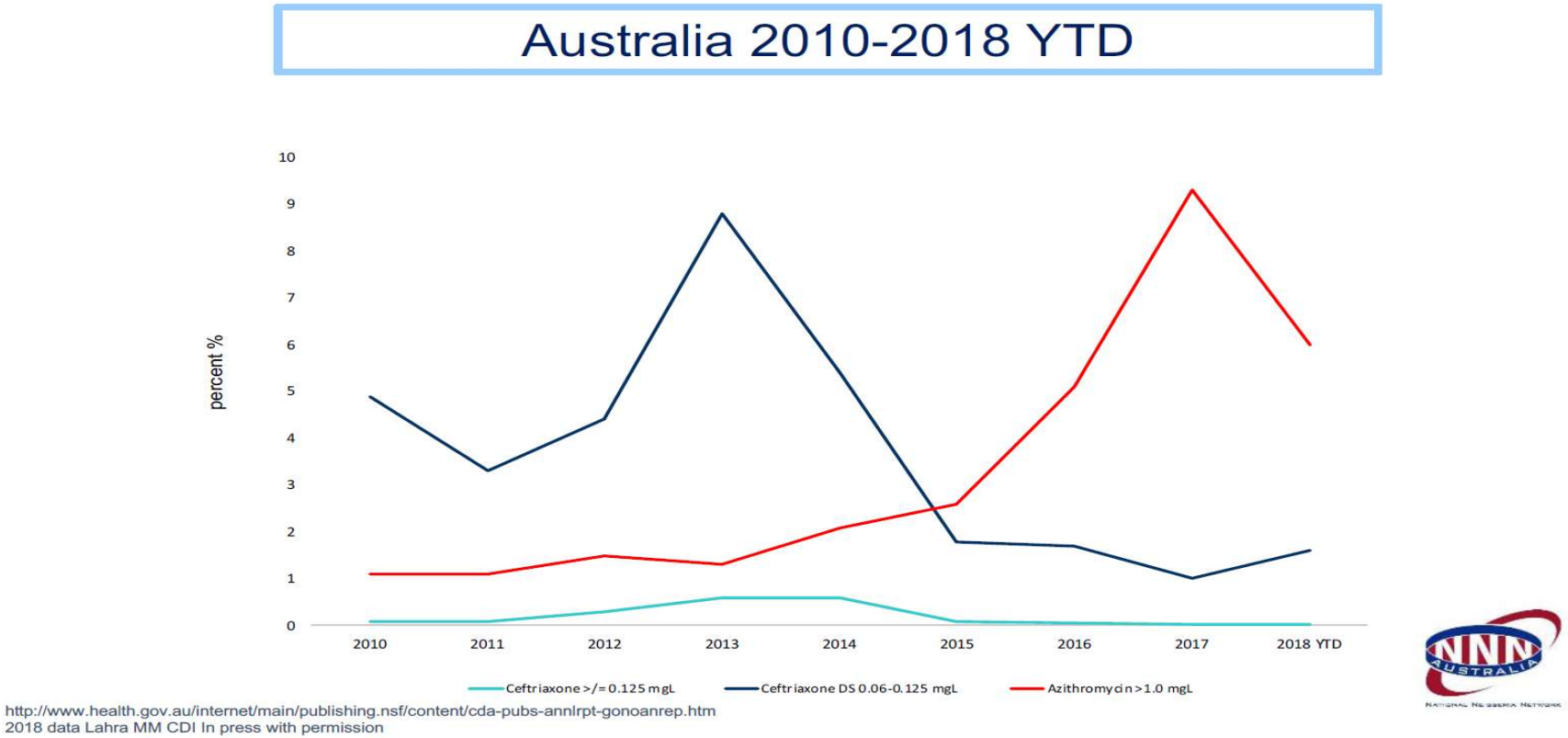

FIGURE 1. Prevalence of azithromycin resistant and ceftriaxone decreased susceptible/resistant *N. gonorrhoeae* strains detected in Australia from 2010-2018 (Lahra *et al*.).

(ii) Extensively Drug Resistant Gonorrhoea

In 2018, three extensively drug resistant (XDR) gonococcal infections were reported from the UK (one strain) and Australia (two cases) (European Centre for Disease Prevention and Control, 2018; Whiley D *et al*., 2018). These three isolates had very similar antibiograms and genetic analysis

found the two Australian isolates to be indistinguishable. All three isolates were resistant to ceftriaxone, azithromycin, penicillin and ciprofloxacin. Importantly, they all had similar minimum inhibitory concentration (MIC) values for ceftriaxone (MIC 0.5 mg/l) and azithromycin (MIC > 256 mg/l). The azithromycin MICs are consistent with high-level azithromycin resistance and no tolerable azithromycin regimen would be effective against such strains. The ceftriaxone MIC value of 0.5mg/l is two doubling dilutions above the WHO alert value of 0.125mg/l and had not been reported previously in conjunction with high-level azithromycin resistance. Given the absence of clinical correlate data to predict individual treatment failure, it should be appreciated that sometimes a clinical cure may be achieved even if the laboratory reports the gonococcal strain as resistant. As a case in point, one of the two Australian cases, a man with XDR gonococcal urethritis, did respond to conventional ceftriaxone and azithromycin dual therapy. It is recognized, however, that oro-pharyngeal infections pose a greater challenge, and treatment failures are more likely to occur at this anatomical site.

(iv) Ceftriaxone

It is known that the clinical efficacy of beta-lactam related antibiotics relates to the period for which free drug concentrations exceed the MIC ($fT_{>MIC}$). For cephalosporins, efficacy is predicted by a $fT_{>MIC}$ value approximately 20-24 hours (Chisholm *et al.*). Pharmacodynamic analyses undertaken by Chisholm *et al.,* indicate that, for a gonococcus with a MIC of 0.5 mg/l, a 500 mg ceftriaxone intramuscular injection would only result in a $fT_{>MIC}$ value of 15.6 hours (too low to safely rely on for clinical efficacy); in contrast, increasing the ceftriaxone dose to 1 g would be expected to increase the $fT_{>MIC}$ from 15.6 to 24.3 hours (clinically effective). To allow for diversity within patient populations, Monte Carlo simulations have shown that a 1g ceftriaxone intramuscular injection would give a median $fT_{>MIC}$ of 23.1 hours (95% CI, 11.1-49.8 hours)

Currently, the choice of a 500 mg intramuscular dose of ceftriaxone remains valid as the proportion of gonococcal strains with ceftriaxone MICs of ≥ 0.125 mg/l remains very low in Australia (< 0.05% in 2017). Any future decision to raise the ceftriaxone dose from 500 mg to 1g will depend on the proportion of circulating gonococci with MICs ≥ 0.125 mg/l. Regular review of these recommendations, in conjunction with the Australian Gonococcal Surveillance Program data, is recommended.

At the moment, there is no evidence to support the hypothetical concept that raising the ceftriaxone dose might slow down the rise in ceftriaxone MICs for circulating strains. We lack scientific evidence about when is the best time to change dosage in order to have a maximum impact on longevity for use of any given antibiotic. However, the Working Group did not feel that increasing the ceftriaxone dose to 1g would be associated with significant increases in cost, injection pain or generation of other side-effects. The Group also discussed the 5% level used by the WHO and expressed concerns that, given the absence of a suitable alternative therapy, this nominal 5% threshold was too high a threshold to entertain when considering a review of ceftriaxone dosing.

(v) Azithromycin

With respect to azithromycin resistance, there are two phenotypes. The first is low level resistance (also termed 'non-high level resistance' in this discussion paper) involving de-repression of the efflux pump and a variable number of mutations at position 2611, in one or more of the four 23S rRNA gene alleles present in *N. gonorrhoeae*; this may result in MIC values in the range of 1-64 mg/L. The second phenotype is high level resistance due to mutations in the 23S rRNA genes (position 2059), where MIC values are typically ≥ 256 mg/L (exhibited by the three recent XDR *N. gonorrhoeae* isolates). Depending on the method of *in vitro* susceptibility testing, the microbiological cut off for azithromycin resistance is a MIC of 1 or 2 mg/L. As with cephalosporins, treatment failure at the oro-pharynx is considered more likely given the potential for lower penetration of antibiotics to this site (Barbee). However, as mentioned above, it is expected that all strains with high level azithromycin resistance would fail azithromycin monotherapy, regardless of the dose and regimen used. Strains determined to have low level azithromycin resistance, where the azithromycin MICs are at or just above the breakpoint for clinical treatment failure, are more likely to respond to a single 2 g oral dose than a single 1 g oral dose.

The rationale for the addition of azithromycin to ceftriaxone monotherapy, led by the British in 2011, was that use of dual therapy may delay the development of ceftriaxone resistance. Whilst the use of dual therapy to treat gonococcal infections in Australia has been associated with a substantial decline in the number of *N. gonorrhoeae* strains with elevated MIC values to ceftriaxone, this has been at the cost of increasing resistance to azithromycin (Figure 1). Although most gonococci circulating in Australia remain susceptible to azithromycin, the Australian Gonococcal Surveillance Program has reported a rise in the proportion of gonococcal isolates with low-level resistance (LLR) to azithromycin since 2014 (Lahra *et al*., Figure 1).

Rationale for Increasing Azithromycin Dose to Treat Oro-Pharyngeal Gonococcal Infections

This rise in LLR to azithromycin is the basis for the Working Group's recommendation to increase the dose of oral azithromycin from 1 g stat to 2 g stat, as part of dual therapy, for the treatment of suspected/proven oro-pharyngeal gonorrhoea and ano-genital gonorrhoea caused by azithromycin susceptible gonococci exhibiting decreased susceptibility or resistance to ceftriaxone (Tables 1 and 3). This change has now been introduced in ASHA's updated Australian STI Management Guidelines (http://www.sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea#management). The Working Group also noted the growing number of reports of oro-pharyngeal treatment failures due to *N. gonorrhoeae* isolates with MICs for ceftriaxone at the upper end of the susceptible range, as well as the lower efficacy of alternative agents (e.g. spectinomycin, gentamicin) to eradicate gonorrhoea at this anatomical site. The Group also recommended that the dose of azithromycin used to treat ano-genital gonorrhoea, in combination with intramuscular ceftriaxone (500 mg), should presently remain as a single 1g oral dose, on the basis that susceptibility to ceftriaxone in Australia is currently in excess of 99.9% (Lahra *et al*.). The recent fall in the prevalence of *N. gonorrhoeae* isolates with decreased susceptibility or resistance to ceftriaxone also supports maintaining the single intramuscular dose of ceftriaxone at 500 mg in almost all clinical situations (Figure 1; Table 1; Figure 2).

Recommended Treatment for Uncomplicated Ano-genital Gonorrhoea

- Ceftriaxone 500 mg i.m. stat.* + Azithromycin 1 g PO stat

*dissolve ceftriaxone in 2ml of 1% lignocaine prior to intramuscular injection

Recommended Treatment for Uncomplicated Oro-Pharyngeal Gonorrhoea

- Ceftriaxone 500 mg i.m. stat.* + Azithromycin 2 g PO stat†

*dissolve ceftriaxone in 2ml of 1% lignocaine prior to intramuscular injection

†there is no need to re-treat patient with a 2g dose of azithromycin if the patient was already treated for uncomplicated ano-genital gonorrhoea on clinical grounds

TABLE 1. Recommended treatment for uncomplicated gonorrhoea.

For those patients with STI syndromes treated presumptively for gonorrhoea at initial presentation (e.g. men with urethral discharge, contacts of gonorrhoea, or women with pelvic inflammatory disease) and who are subsequently found to have oro-pharyngeal gonococcal infection by nucleic acid amplification testing, the Group recommend that a molecular test-of-cure should be undertaken at 21 days post-treatment completion and the patient managed according to the result. A culture-based test of cure may also be performed at seven days post-treatment completion in the subgroup of oro-pharyngeal gonorrhoea cases in whom oro-pharyngeal swab cultures were positive prior to treatment. For those patients who are subsequently diagnosed oro-pharyngeal gonorrhoea but treated at the initial visit with dual therapy including azithromycin 1g, it is not deemed necessary to re-treat them with an additional 2g single oral dose of azithromycin; this is because the lower 1g dose of azithromycin should still cure most oro-pharyngeal gonococcal infections in the oro-pharynx.

A primary concern with increasing the dose of azithromycin from 1g to 2g is the potential for increased gastrointestinal side effects such as nausea, vomiting and diarrhoea. One early trial (Handsfield *et al*.) reported that 35.5% participants' experienced GI side effects with azithromycin capsules; however, side effects were either low or not reported in another 12 treatment studies reviewed by Bignell & Garley. Tablets appear to have less side effects than capsules, and GI side-effects can be minimized by taking the azithromycin with some food. Trials assessing the efficacy of a single azithromycin 2g dose in treating early syphilis reported a lower prevalence of side-effects (11.4%); these were rated as mild-to-moderate and did not deter patients from repeating the treatment (Riedner *et al*.; Hook *et al*.). The higher azithromycin dose (2g) should

always be dispensed with advice to eat prior to taking the medication; an anti-emetic should be prescribed for those patients perceived to be at risk of vomiting.

2. Recommended Management of Multi-Drug Resistant (MDR) and Extensively Drug Resistant (XDR) Uncomplicated Gonorrhoea

Wherever possible, the management of MDR and XDR gonorrhoea infections, as defined by Tapsall *et al*. (Appendix 2), should be undertaken by clinicians with expertise in the management of antimicrobial resistant gonorrhoea, guided by local antimicrobial susceptibility data generated from testing either the index patient's or his/her sexual partners' gonococcal strains. Recommended treatment options for MDR and XDR uncomplicated gonorrhoea cases is provided in Table 2 and Figure 2. A further comparison of second-line drugs recommended to treat XDR gonorrhoea cases (i.e. spectinomycin, gentamicin, ertapenem and rifampicin) is available in Appendix 3. International guidance on the antibiotic treatment of these infections is not available (to April 2019).

General Practitioners (GPs) should urgently refer suspected XDR gonorrhoea cases to local Sexual Health or Infectious Disease physicians, where this is logistically possible, or seek specialist advice for managing the patient (e.g. in remote settings). In cases of XDR gonorrhoea, cultures should be performed on specimens from all other possible sites of infection (uro-genital, oro-pharyngeal and ano-rectal) prior to treatment, if possible. The local laboratory should be alerted to the presence of a possible XDR case and contact the jurisdictional Reference Laboratory to arrange MIC testing for any cultured *N. gonorrhoeae* isolate against an extended panel of antibiotics (including ertapenem, spectinomycin, tetracycline, and gentamicin). This should occur in addition to those antibiotics usually tested for clinical purposes (ceftriaxone, azithromycin, penicillin, ciprofloxacin). It should be noted that there are currently no MIC breakpoints for ertapenem and gentamicin. Test-of-cure should be performed from all positive sites using culture at 7 days post-treatment completion or NAAT at 21 days post-treatment completion.

	Azithromycin susceptible	**Azithromycin non-susceptible due to low-level resistance**	**Azithromycin non-susceptible due to high-level resistance (MIC ≥ 256 mg/l)**
Ceftriaxone Susceptible	**Ano-genital gonorrhoea** ceftriaxone 500 mg IM stat *plus* azithromycin 1 g PO stat	**Ano-genital gonorrhoea** ceftriaxone 500 mg IM stat *plus* azithromycin 2 g PO stat	**Ano-genital gonorrhoea** ceftriaxone 1 g IM stat
	Oro-pharyngeal gonorrhoea ceftriaxone 500 mg IM stat. *plus* azithromycin 2 g PO stat *(see footnote 3)*	**Oro-pharyngeal gonorrhoea** As above	**Oro-pharyngeal gonorrhoea** As above

Ceftriaxone less susceptible or resistant (MIC ≥ 0.125 mg/l)	**Ano-genital gonorrhoea** **Option 1:** spectinomycin 2g IM stat (*see footnote 4*) *Plus* azithromycin 2 g PO stat **Option 2:** gentamicin 240 mg IM stat *plus* azithromycin 2 g PO stat **Option 3:** ertapenem 1g IV/IM daily for 3 days *(see footnote 5)* *plus* azithromycin 2 g PO stat	**Ano-genital gonorrhoea** **Option 1:** spectinomycin 2g IM stat *(see footnote 4)* **Option 2:** gentamicin 240 mg IM stat **Option 3:** ertapenem 1g IV/IM daily for 3 days (*see footnote 5*)	**Ano-genital gonorrhoea** **Option 1:** spectinomycin 2g IM stat *(see footnote 4)* **Option 2:** gentamicin 240 mg IM stat **Option 3:** ertapenem 1g IV/IM daily for 3 days (*see footnote 5*)
	Oro-pharyngeal gonorrhoea As above	**Oro-pharyngeal gonorrhoea (proven or suspected)** To **Options 1, 2 and 3** above, *add* rifampicin 600 mg 12-hrly PO for 2 days (*see footnotes 6 and 7*)	**Oro-pharyngeal gonorrhoea (proven or suspected)** To **Options 1, 2 and 3** above, *add* rifampicin 600 mg 12-hrly PO for 2 days (*see footnotes 6 and 7*)

TABLE 2. Recommended treatment options for MDR/XDR *N. gonorrhoeae* according to susceptibility to ceftriaxone and azithromycin.

Table notes

1. Ceftriaxone should be dissolved in 2ml 1% lignocaine prior to intramuscular injection.
2. Always recommend taking Azithromycin 2g dose after eating.
3. No need to re-treat patient with a 2g dose of azithromycin if the patient was already treated with azithromycin 1g for uncomplicated ano-genital gonorrhoea.
4. Details on how to access spectinomycin are given in Appendix 1
5. Ertapenem may be given as a 1g infusion in 50 ml Sterile Normal Saline over 30 minutes or by intramuscular injection (1% lignocaine may be used as a diluent).
6. In situations where spectinomycin or gentamicin are used the treat suspected or proven oro-pharyngeal gonorrhoea due to azithromycin resistant *N. gonorrhoeae* strains, rifampicin should be provided as additional treatment as both spectinomycin and gentamicin have lower efficacy in treating oro-pharyngeal gonorrhoea. We are also recommending rifampicin as dual therapy with ertapenem in individuals with suspected or proven oro-pharyngeal gonorrhoea due to azithromycin resistant *N. gonorrhoeae* strains on the basis that we presently lack sufficient clinical experience with ertapenem mono-therapy as a treatment for infections at this anatomical site.
7. Patients taking rifampicin should be advised that their urine may appear orange, and their contact lenses may stain with prolonged use. Where appropriate, women should be informed of interactions between rifampicin and efficacy of the oral contraceptive pill. Concomitant medication should be reviewed for potential interactions.

3. Other Potential Treatment Options

(i) Ciprofloxacin 500 mg

If the laboratory susceptibility report indicates that a gonococcal isolate is susceptible to fluoroquinolones, oral ciprofloxacin 500 mg as a single dose could be used to treat uncomplicated gonorrhoea. Fluoroquinolones should never be prescribed in the absence of isolate-specific antimicrobial susceptibility data. In 2017, more than 70% of gonococcal strains in Australia's urban settings, and a much higher proportion in Aboriginal populations in remote settings, remain susceptible to fluoroquinolones (Lahra *et al*.) However, almost all the reported MDR/XDR strains reported to date have been fluoroquinolone resistant (Ohnishi *et al*.; Unemo *et al*.; European Centre for Disease Prevention and Control), so ciprofloxacin is unlikely to have any major role in managing cases of MDR/XDR gonorrhoea.

(ii) Options when spectinomycin, gentamicin or ertapenem cannot be used, or have been proven to fail

An expert opinion should be sought in the first instance from an experienced Microbiologist or Sexual Health Physician. A number of other drugs could be administered as part of an antibiotic combination to treat MDR/XDR cases in situations where spectinomycin, gentamicin or ertapenem cannot be used, or have been proven to fail (i.e. as salvage therapy). Such agents include rifampicin, fosfomycin, aztreonam and tigecycline. It should be noted that there are currently no MIC breakpoints for these four agents. Zoliflodacin and gepotidacin are new agents that are likely to go into Phase 3 clinical trials in late 2018 or 2019 and may provide further treatment options in the future.

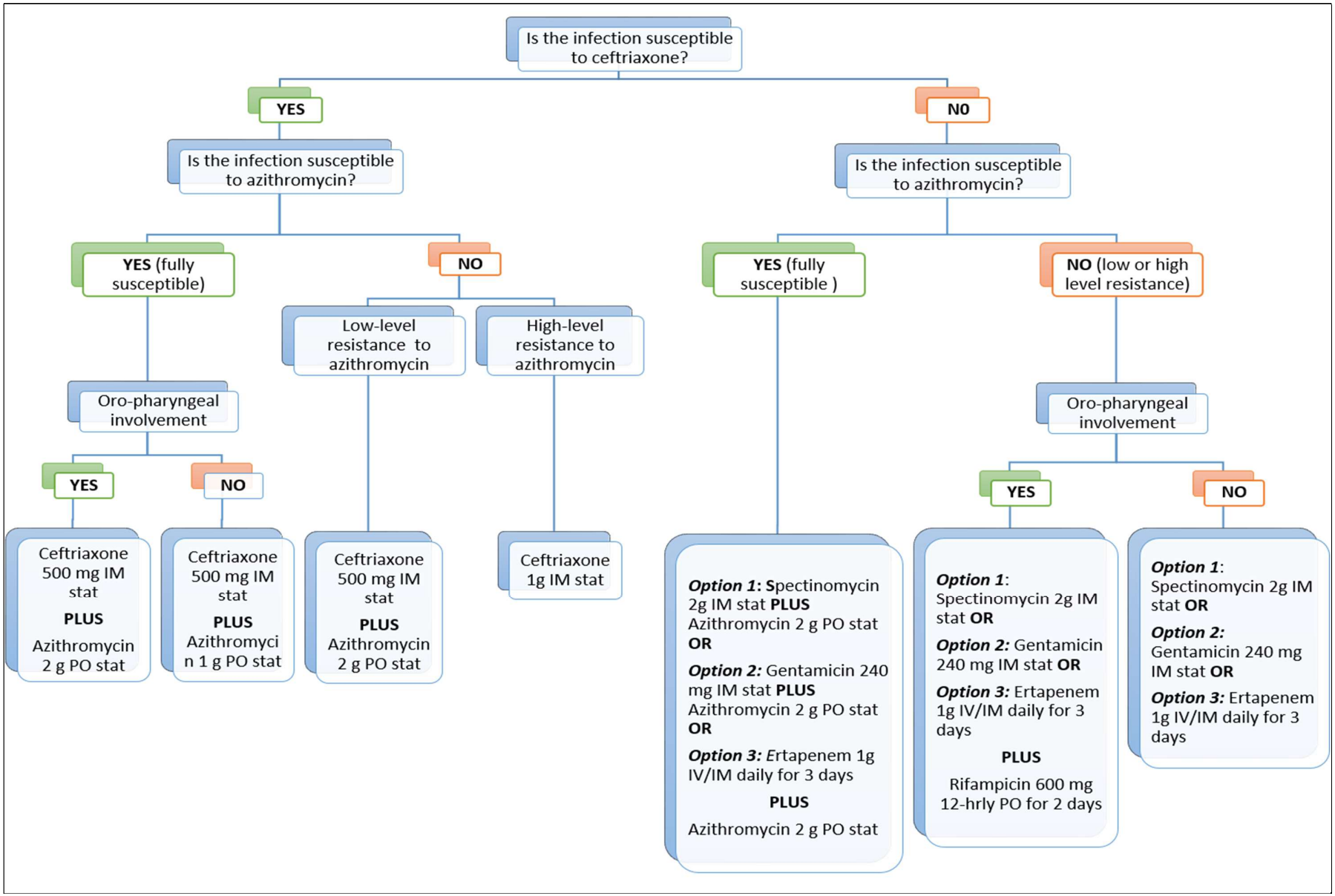

FIGURE 2. Recommended treatment for uncomplicated gonococcal infection

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APPENDIX 1: Spectinomycin Access in Australia

INFORMATION ON SPECTINOMYCIN ACCESS IN AUSTRALIA

Spectinomycin can be prescribed either using a Section 19(5) application to become an authorised prescriber or a TGA Category B form. The authorised prescriber route is preferred as there is no delay once approved; this is likely to be the only practical option for gonorrhoea.

Obtain spectinomycin from Medsurge at sales@medsurge.com.au

Medsurge offers the following:

- ***KIR200 Kirin (Spectinomycin) 2g Injection (Pack of 1) $109.00 (EX GST)***

Customer Service Team
Medsurge Healthcare Pty Ltd
Phone: 1300 788 261 | F: 1300 788 262
Address: Unit 2, 6-7 Gilda Court, Mulgrave, VIC - 3170
Website: www.medsurge.com.au

APPENDIX 2: Criteria used to define MDR and XDR *N. gonorrhoeae* strains (Tapsall *et al*., 2009).

Class I Antibiotics: Antibiotics currently recommended for gonorrhoea

- Injectable extended spectrum cephalosporins
- Oral extended spectrum cephalosporins
- Spectinomycin

Class II Antibiotics: Antibiotics used less frequently/proposed for more extensive use

- Penicillins
- Fluoroquinolones
- Azithromycin
- Aminoglycosides
- Carbapenems

MDR and XDR definitions:

MDR-NG: resistant to ≥ 1 class I antibiotic + ≥ 2 class II antibiotics

XDR-NG: resistant to ≥ 2 class I antibiotics + ≥ 3 class II antibiotics

APPENDIX 3: Comparison of agents that may be used in the treatment of XDR gonorrhoea

Agent	Ertapenem	Gentamicin	Spectinomycin	Rifampicin
Dosage	1g IV/IM daily for 3 days Reduce to 500mg daily if CrCl <30mL/min[1]	240mg IM stat	2g IM stat Dose adjustment not necessary in renal impairment[6,7]	600mg bd for 2 days
Contraindications	• Allergy to carbapenems[1] • Immediate/severe hypersensitivity to penicillin[1]	• Previous vestibular or auditory toxicity due to aminoglycoside[3] • Aminoglycoside hypersensitivity (rare)[3] • Myasthenia gravis[3] • Chronic renal impairment eGFR<40mL/min[3]	• Previous hypersensitivity to spectinomycin[8]	• Severe hepatic impairment[1, 10] • Alcohol abuse[10]
Side effects & Disadvantages	• Nausea, vomiting, diarrhoea, headache, injection site reactions (e.g. phlebitis)[1] • Increases risk of seizures. History of seizures/other CNS disorders increases risk[1]	• Possible inadequate pharyngeal exposure[4] • A/E: nephrotoxicity, ototoxicity[1] • Increases risk of muscle weakness and respiratory depression in neuromuscular disorders[1]	• Poor efficacy against pharyngeal infections[6] • A/E: soreness at injection site, urticarial, dizziness, nausea, chills, fever, insomnia[7] • Must be obtained via SAS pathway • Expensive ($109 from Medsurge)	• A/E: GI symptoms, rash, orange-red discolouration of bodily fluids, dizziness, drowsiness, headache[1] • 2-day course may reduce compliance
Drug interactions	• Other drugs that increase the seizure risk (e.g. quinolones, antidepressants, antipsychotics)[1] • May greatly reduce valproate concentration resulting in seizures.[1] Avoid combination	• Other nephrotoxic agents (e.g. diuretics, NSAIDs, ACEI)[5]	• Little information available. Case reports of decreased CrCl and reduced urine output but not considered to be nephrotoxic[6]	• Decreases concentration of many drugs via CYP enzyme and transporter protein induction • Includes anticoagulants, anticonvulsants, antiretroviral and hormonal contraceptives[1] • Enzyme induction lasts for about 2 weeks after stopping rifampicin[1] ***Advice for those taking oral contraceptives***: • As a precaution - Take an active pill during treatment and at least for a further 7 days • Use extra contraceptive precautions (eg abstinence or a barrier method) during treatment and for a further 28 days[1]

Agent	Ertapenem	Gentamicin	Spectinomycin	Rifampicin
Pregnancy	**NOTE: An expert opinion should be sought to discuss the benefit of using these medications in pregnancy versus risk of no treatment.**			
	No human data available, animal studies not shown to be teratogenic[2]	Use not associated with increased congenital malformations. Insufficient evidence to suggest an association between nephrotoxicity or ototoxicity in newborns[2]	Listed as second line alternative for gonorrhoea treatment in pregnancy in the BASHH guidelines.[9]	Considered safe in pregnancy but use in the last few weeks of pregnancy may be associated with increased risk of haemorrhagic disorders in the new born[2]
Breastfeeding	Considered safe to use[2] Small amounts excreted into breast milk[2]	Safe to use[2] Poorly absorbed - Small amounts excreted into breast milk, infant unlikely to experience side effects[2]	Not known whether excreted into breast milk[6]	Considered safe to use[2] Small amounts excreted into breast milk. Monitor infant for side effects such as fever, rash, vomiting & diarrhoea[2]

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