

6. Public health response to suspected cephalosporin resistant *Neisseria gonorrhoeae*

There is a need for a national multi-disciplinary forum (microbiology, clinicians, and public health medicine) to monitor the development of antimicrobial resistance in *N. gonorrhoeae* in Ireland and to advise on treatment, prevention and control. The remit of the group should include reviewing these guidelines on an ongoing basis and updating them as required, in line with international evidence. This group could also advise on prevention and control of other STIs. The group should have a remit for training. It should include at least the following:

- MOH (Director of Public Health or Consultant in Public Health Medicine)
- Consultant in Public Health Medicine and Consultant Microbiologist, Health Protection Surveillance Centre
- Consultant in Infectious Diseases/Genitourinary Medicine
- Consultant Microbiologist
- Health Advisor
- Health Promotion Officer
- Surveillance Scientist
- Laboratory Scientist

Cases of possible antibiotic treatment failure are of considerable importance and verification of such an event requires collaboration between clinical, laboratory and public health medical staff.

Clinicians should treat cases of *N. gonorrhoeae* infection as outlined in Section 4.1 of this document. The required follow-up after recommended treatment is also outlined: follow-up is necessary to confirm resolution of symptoms, to exclude the possibility of reinfection and to pursue partner notification.

6.1 Single case of suspected Ceph-R *N. gonorrhoeae*

If a patient presents with a persistent gonococcal infection following appropriate treatment it is essential that the possibility of reinfection or infection with other pathogens (e.g. chlamydia) is ruled out and that appropriate (urethral, cervical or rectal) specimens are taken for microscopy, culture and susceptibility testing (Figure 7). NAATs and genotyping should also be performed. The laboratory should be informed that treatment failure is suspected and that cephalosporin resistance is a consideration. The case must be seen by an Infectious Disease Consultant/Consultant in Genitourinary Medicine. Where *N. gonorrhoeae* cephalosporin treatment failure is suspected by a clinician they should inform the local MOH promptly.

In the event of confirmed *N. gonorrhoeae* cephalosporin treatment failure the MOH should convene an incident control team. The role of this team will be to investigate the incident and to increase surveillance, prevention and control measures, as necessary.

Members of the team may include the following:

- MOH (Director of Public Health or Consultant in Public Health Medicine)
- Consultant in Public Health Medicine, Health Protection Surveillance Centre
- Consultant in Infectious Diseases/Genitourinary Medicine
- Director of STI clinic
- Consultant Microbiologist
- Surveillance Scientist
- Health Advisor

The ECDC Response Plan [2] has recommended a working definition of a confirmed treatment failure and a probable treatment failure (Table 9).

Where a probable or confirmed case of Ceph-R *N. gonorrhoeae* is identified, further laboratory evaluation (culture and susceptibility testing and molecular typing) should be performed at a gonococcal reference laboratory.

Clinical management of cephalosporin treatment failure is outlined in Section 4.2.

Figure 7 Flowchart for the Public Health management of a single case of suspected Ceph-R *Neisseria gonorrhoeae*

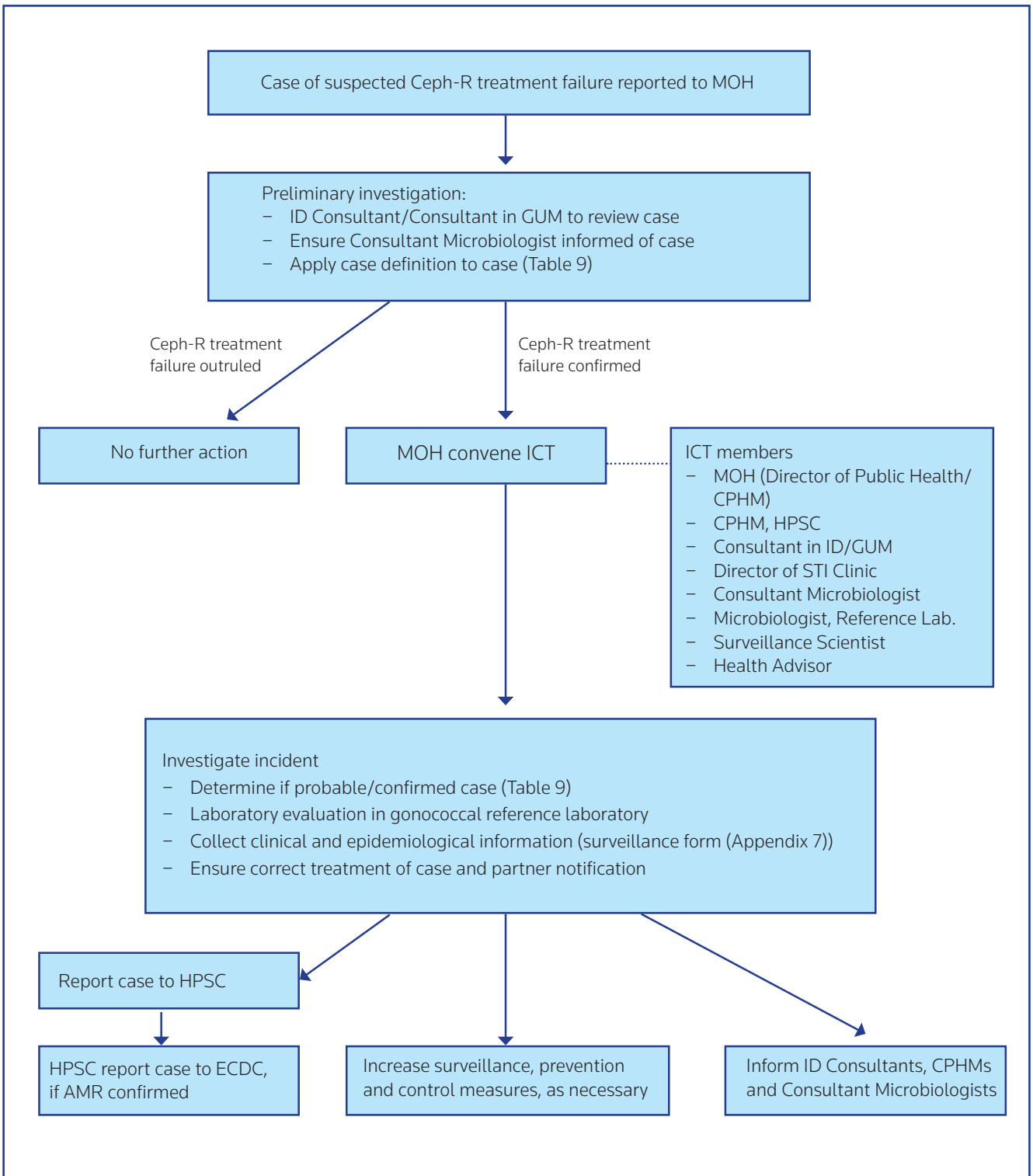


Table 9 Working case definition for probable and confirmed cephalosporin treatment failure: clinical and laboratory criteria [2]

Case definition for probable treatment failure	Case definition for confirmed treatment failure
<p>A gonorrhoea patient who returns for ToC or who has persistent genital* symptoms after having received treatment for laboratory-confirmed gonorrhoea with a recommended cephalosporin regimen (ceftriaxone or cefixime in appropriate dose)</p> <p>AND</p> <p>remains positive for one of the following tests for <i>N. gonorrhoeae</i>:</p> <ul style="list-style-type: none"> - Presence of intracellular Gram-negative diplococci on microscopy taken at least 72 hours after completion of treatment; <p>OR</p> <ul style="list-style-type: none"> - Isolation of <i>N. gonorrhoeae</i> by culture taken at least 72 hours after completion of treatment; <p>OR</p> <ul style="list-style-type: none"> - Positive nucleic acid amplification test (NAAT) taken two-to-three weeks after completion of treatment <p>AND</p> <p>Denies sexual contact during the post-treatment follow-up period</p>	<p>A gonorrhoea patient who returns for ToC or who has persistent genital* symptoms after having received treatment for laboratory-confirmed gonorrhoea with a recommended cephalosporin regimen (ceftriaxone or cefixime in appropriate dose)</p> <p>AND</p> <p>remains positive for one of the following tests for <i>N. gonorrhoeae</i>:</p> <ul style="list-style-type: none"> - Presence of intracellular Gram-negative diplococci on microscopy taken at least 72 hours after completion of treatment; <p>OR</p> <ul style="list-style-type: none"> - Isolation of <i>N. gonorrhoeae</i> by culture taken at least 72 hours after completion of treatment; <p>OR</p> <ul style="list-style-type: none"> - Positive nucleic acid amplification test (NAAT) taken two-to-three weeks after completion of treatment <p>AND</p> <p>Denies sexual contact during the post-treatment follow-up period</p> <p>AND</p> <p>Decreased susceptibility to cephalosporin used for treatment[†]:</p> <ul style="list-style-type: none"> - Cefixime: MIC > 0.12 mg/L[‡] - Ceftriaxone: MIC > 0.12 mg/L[‡]

*Gonorrhoea patient may have non-genital symptoms

[†]Ideally, the pre- and post-treatment isolates should be examined with an appropriate and highly discriminatory molecular epidemiological typing method to establish if isolates are indistinguishable

[‡]These thresholds are in accordance with EUCAST tentative breakpoints. Reporting of probable treatment failures where MICs are lower than the EUCAST breakpoints will be essential to evaluate if current breakpoints are clinically relevant.

The following clinical and epidemiological information should be collected from a case of Ceph-R *N. gonorrhoeae* and their sexual partners:

- Treatment taken and when,
- Anatomic site(s) of infection
- Demographic and behavioural risk factors:
 - Demographic characteristics
 - Sexual orientation and practices
 - Drug use
 - HIV status
- Source(s) of infection
 - Recent travel history of both the index patient and their sexual partner(s)
 - The place and type of sexual contact(s)
- Risk of secondary transmission
 - The place and number of recent sexual contacts

An enhanced surveillance form is available in Appendix 7 and on the HPSC website.

The case and enhanced surveillance information should be reported by the MOH to HPSC. If strains with unusually high MICs are confirmed by the reference laboratory an alert will be raised internationally (ECDC and WHO, as appropriate). In addition, an alert should be sent to STI and Infectious Disease clinicians, Consultants in Public Health Medicine and Clinical Microbiologists in Ireland to advise them of the finding and as an early warning of possible AMR in the community.

6.2 More than one case of Ceph-R *N. gonorrhoeae*

When cases of treatment failure occur with increasing frequency there is a need for further liaison between Public Health Medicine, clinicians and laboratories to determine the proportion of isolates that show resistance (Figure 8). WHO advises that, when the proportion of resistant strains obtained from tested samples is at a level of 5%¹ or more, or when an unexpected increase below 5% is observed in key populations with high rates of gonococcal infection (e.g. MSM or sex workers), steps should be taken to review and modify guidelines for STI treatment and management, while at the same time enhancing gonococcal surveillance [1]. This would be a role for the proposed national clinical forum on AMR in gonorrhoea.

If receiving repeated notifications of treatment failure then Departments of Public Health and/or HPSC need to initiate epidemiological assessments to measure the level of spread in affected locations. The following is proposed by WHO [1]:

- Epidemiological assessment to identify potential demographic and sexual-behavioural risk factors.
- Design and implementation of clinic-based activities to enhance case detection:
 - Targeted gonorrhoea screening and laboratory examination of samples,
 - Test-of-cure using culture for key populations at high risk of infection.
- Enhanced laboratory capacity to improve gonococcal culture and susceptibility testing.
- Enhanced local surveillance to monitor the occurrence and magnitude of Ceph-R *N. gonorrhoeae* and confirmed treatment failure cases in the affected areas. This includes conducting ad hoc rapid assessment studies (e.g. local GASP) using different sample-collection approaches, such as:
 - Prospective collection of gonococcal isolates,
 - Retrospective review of antimicrobial susceptibility test patterns of gonococcal isolates,
 - Laboratory evaluation of patients with repeat episodes of gonorrhoea within a short period
 - Communication strategies to increase awareness of local clinicians and laboratory staff about the presence of Ceph-R *N. gonorrhoeae* cases and/or confirmed cases of treatment failure.

It is important to rapidly identify, screen and treat the sexual partners of patients with Ceph-R *N. gonorrhoeae* or confirmed treatment failure, and, ideally, to test any identified isolates for antimicrobial susceptibility.

¹ It can be difficult to obtain a sample size large enough to confidently determine this rate. It may be necessary to determine the rate in approximately 100-200 samples initially and then, if 3-10% samples show resistance, to increase the sample size as necessary.

Recommendations

- A national multi-disciplinary forum (microbiology, clinicians, and public health) should be established to review national AMR data, to advise on changing patterns of resistance and to advise on treatment, prevention and control.
- Where *N. gonorrhoeae* cephalosporin treatment failure is suspected by a clinician they should inform the local MOH promptly.
- In the event of suspected or confirmed *N. gonorrhoeae* cephalosporin treatment failure the MOH should convene an incident control team.
- Where a probable or confirmed case of Ceph-R *N. gonorrhoeae* is identified, further laboratory evaluation (culture and susceptibility testing and molecular typing) should be performed at a gonococcal reference laboratory.
- Enhanced surveillance information needs to be collected from all probable or confirmed cases of Ceph-R *N. gonorrhoeae*.
- If the proportion of resistant strains obtained from tested samples is at a level of 5% or more, or, when an unexpected increase below 5% is observed in key populations, a multi-disciplinary group (ideally the forum referred to above) should take steps to review and modify guidelines for STI treatment and management, while at the same time enhancing gonococcal surveillance.

Figure 8 Flowchart for the Public Health management of more than one case of suspected Ceph-R *Neisseria gonorrhoeae*