Gonorrhoea in Indonesia and the Netherlands

*Diagnostics and antimicrobial resistance*

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CHAPTER VIII: General Discussion

Part I: Gonorrhoea in Indonesia

Global gonorrhoea epidemic, diagnostics, treatment and the threat of antimicrobial resistance (AMR)

Gonorrhoea, caused by Neisseria gonorrhoeae, is among the main bacterial sexually transmitted diseases.[1-2] It is estimated that every year there are 78 millions new gonorrhoea cases world-wide, with 11.4 millions new cases estimated in World Health Organization (WHO) South-East Asian Region.[3] N. gonorrhoeae can infect the genital tract, rectum, and throat, and can cause discharge and pain at the infected anatomical sites.[1,4] Infection might also lead to complications, disproportionately affecting women, such as pelvic inflammatory diseases (PID), ectopic pregnancy, and infertility.[1] Gonococcal infections may also be asymptomatic (especially extragenital infections).[5-6]

Various tests are used to diagnose gonorrhoea.[4] The choice of test is often influenced by available resources and the health system in the setting: settings with limited health care resources tend to use less expensive diagnostic tests.

The simplest approach to diagnose gonorrhoea is syndromic management. Syndromic management was first proposed as a diagnostic algorithm to diagnose sexually transmitted infections (STI) in the 1990s.[7-8] Syndromic management is a clinical algorithm based on the symptomatology presented by a patient, without the identification of the exact causative pathogens; e.g. patients with genital discharge receive a treatment covering the various STI characterised by discharge. In 2003, WHO included syndromic management in the guidelines for the management of STI.[9] Syndromic management is easy, quick, of low cost, and with appropriate training even non-medical personnel can apply it. However, recently it is criticised for its low accuracy,
missing asymptomatic infections, leading to overtreatment and inappropriate use of antibiotics resulting in the induction of AMR.[10-11]

In the case of urethral or vaginal discharge, light microscopy of stained discharge samples is often added to syndromic management to improve the diagnostic quality.[12-14] The additional light microscopic examination can be performed while the patient waits and is relatively cheap. It requires some simple instruments and can be used in mobile services. Yet, light microscopy has low accuracy in diagnosing gonorrhoea for endocervical and extragenital samples.[14-15] Moreover, light microscopy cannot discriminate between several important pathogens (e.g. *Chlamydia trachomatis, Mycoplasma genitalium*). Therefore, presumptive treatment of chlamydia is recommended in a patient with light microscopical signs of inflammation, leading to overtreatment.[12,15]

As opposed to syndromic management, laboratory based diagnosis and treatment is an approach suitable for settings with an established health infrastructure and sufficient resources. Bacterial culture was considered the “gold standard” test for gonorrhoea for many years.[4] Using culture, we can identify the exact pathogen (by its morphology, its reaction to biochemistry tests, and/or a DNA-probing method). Moreover, a bacterial culture enables testing for antibiotic susceptibility subsequently. However, culture requires more time (thus delayed treatment) than syndromic management or light microscopy and requires more advanced instruments and specific laboratory conditions.[4, 16] Moreover, culture for extra-genital samples is frequently unsuccessful.[17]

NAAT is the current gold standard, and now widely used as a diagnostic tool for STI, including for gonorrhoea.[3,18] It is considered quick and, compared to culture, has a higher sensitivity, it can detect extra-genital infections, and can be utilized for molecular epidemiological studies.[18-21] However, the implementation of NAAT is limited by its high costs and the required advanced laboratory infrastructure.[18] Detection of non-viable organisms resulting in false positive results is also an issue in using NAAT.[22] Apart
from the sensitivity, to ensure the specificity of the result, it is also suggested that a second NAAT target is used if the test is performed in a low prevalence setting.[22-23]

A combination of targeted deferred *N. gonorrhoeae* culture and NAAT could also be a solution to diagnostic delay and AMR testing problems.[24] In the study by Wind et al., NAAT was used as standard diagnostic, and culture was performed if the NAAT result was positive. The study showed that of samples from patients that had a positive culture in the routine approach (same day culturing), 69% were culture positive if performed 1 day after collection, and 56% when culture was performed 2 days after collection. This means, compared to NAAT as diagnostic standard, deferred culture up to 2 days could still detect gonorrhoea in most samples.

In most countries, extended-spectrum cephalosporins (ESCs) are currently the drugs of choice to treat gonorrhoea.[2,25-26] In many countries ceftriaxone (250 mg, 500 mg, or 1 g, intramuscular injection, as single dose) or cefixime (200 or 400 mg, orally, as single dose) are used as monotherapy in the treatment. ESCs are the last remaining drugs considered effective to treat gonococcal infections. *N. gonorrhoeae* is among the priority pathogens listed by the WHO due to its ability to develop antimicrobial resistance.[27] *N. gonorrhoeae* has developed resistance against almost all antimicrobials that have been used as first line treatment option.[27-28] The emergence of *N. gonorrhoeae* strains with decreased susceptibility or even resistance against ESCs has been reported in many countries (e.g. Vietnam, Japan, India, and UK).[29-32] Several international guidelines now recommend combination therapy. The International Union against STI (IJSTI) Europe, Centers for Diseases Control and Prevention (CDC), and WHO recommend that ESC are combined with azithromycin (1 g, orally, single dose) for the treatment of uncomplicated gonorrhoea.[2,25-26]
In syndromic management, patients with genital discharge receive a presumptive diagnosis of chlamydia regardless of gonorrhoea status or diagnosis. Therefore, these patients are treated with drugs for chlamydial infection, e.g. azithromycin (1 g, orally, single dose) or doxycycline (100 mg, orally twice a day for 7 days).[12]

Current situation in Indonesia in relation to epidemiology, diagnostic, and treatment of gonorrhoea.

In 2013, the Indonesian Integrated Biological and Behavioural Survey (IBBS) conducted by the Ministry of Health of the Republic of Indonesia (MoH-RI) found a high prevalence of gonococcal infections, especially among MSM (21.2%), transwomen (19.6%), and female sex workers (17.7-32.2%).[33] The report also observed a low proportion of consistent condom use among the Indonesian population (20-40%) that might contribute to the spread of gonorrhoea and other STDs in Indonesia. However, the IBBS did not clearly report the proportion of asymptomatic cases in the survey, risk factors for gonorrhoea and antimicrobial susceptibility, that we elaborated further in chapter 3.[5]

To diagnose gonorrhoea and other STDs, syndromic management is generally implemented in Indonesian health care facilities.[12] The approach is not only used in outreach settings, but also in institutional settings (such as community health centres, known as “puskesmas”, private clinics, and hospitals). In addition to syndromic management, light microscopic examination of Gram-stained samples to support a urogenital gonorrhoea diagnosis is recommended by the Indonesian national guideline for the management of STI.[12] A routine bacterial culture is not recommended by the guideline, and is only performed in large facilities, such as some academic hospitals. NAAT is generally not available, and presumably is used for research purposes only.

According to the Indonesian guideline, gonorrhoea is to be treated with cefixime (400 mg, orally, as single dose), or ceftriaxone (250 mg,
intramuscular injection, single dose).[12] The guideline also recommends additional treatment with azithromycin (1 g, intramuscular injection, as single dose) or doxycycline (200 mg daily, orally, for 7 days) for the presumptive treatment of chlamydia.

As we reported in chapter 3, no resistance against ESCs was found among 78 Indonesian strains tested in our study.[5] However, we observed that resistance against ciprofloxacin and doxycycline was extremely common (>90%) in Indonesia, as also reported a decade ago.[34–35] Yet, it should be noted that our study included only a limited number of samples from 3 locations, and with high clonality.[5, 22] Thus the results may not represent the nation-wide situation. AMR in gonorrhoea has not been routinely monitored on a nation-wide scale in Indonesia, [29] and susceptibility testing is not part of routine procedures in the management of gonorrhoea.[12]

In Indonesia self-medication using "over-the-counter" drugs is a common practice.[36–37] As a result, antimicrobial drugs are used frequently without proper medical guidance, resulting in the emergence of AMR pathogens in the community. Ciprofloxacin and doxycycline are examples of antimicrobial drugs that are often used in self-medication in Indonesia, either for STI-related complaints or other diseases.[36–37] Those drugs are cheap, can be purchased without prescription, and are available as oral preparations. In addition, based on syndromic management, doxycycline is often prescribed presumptively in clinics to treat cases with discharge.[12] This undesired practice likely explains our AMR findings and might have implications for the spread of AMR gonorrhoea strains.

In Indonesia, several groups such as sex workers, men who have sex with men (MSM), and transwomen are strongly stigmatized by the society and are, in STI epidemiology, considered as "core groups" or "key populations".[33] Stigma hampers the access of these groups to institutionalized health care facilities (e.g. puskesmas or hospitals). Delivering the health care services via outreach services is often the only
possibility to reach core groups.[38-40] Outreach services are frequently performed in collaboration between clinics and community-based non-governmental organizations (NGOs).

**Improvements in the management of gonorrhoea in Indonesia**

In an ideal situation, a diagnostic test for STI should be highly accurate, of low cost, and produce results quickly.[3-4]. The accuracy of a diagnostic test influences the number of observable cases at the clinic, and hence the epidemiological picture of the disease in the society.[2, 24] Definition of the disease is influenced by the diagnostic test standard.[4]

An accurate diagnostic test is also needed to administer appropriate treatments.[2, 4] False positive results would lead to wasting clinical resources, including unnecessary treatments, and the induction of AMR. False negative results may lead to unnecessary morbidity and to ongoing transmission in the society.

Apart from culture and subsequent susceptibility testing, diagnostic tests for gonorrhoea do not provide AMR data.[4, 10, 16] and therefore presumptive treatment is prescribed. Ineffective treatments will be given when, due to lack of AMR data, pathogens are exposed to inappropriate drugs.[28] Despite its limitations, light microscopy can be rationally adopted by STI services that had been using syndromic management only, in order to improve quality of routine diagnostics.[12-14] However, a more advanced diagnostic test (NAAT) might be needed, in order to not miss endocervical and extragenital infections, as well as asymptomatic infections.[5, 10, 14, 16]

The choice of a diagnostic test may be different for daily service and for surveillance purposes.[3] Surveillance is done to provide data related to public health policy, e.g. to monitor and evaluate public health programs and to determine priority for allocating health care resources.[3] Surveillance can be periodic, cover a sufficiently large and representative population (in terms of gender, age, occupation, geographical locations, symptomatology, etc.), and includes extra-genital samples. NAAT, which is able to test a large
number of samples in a relatively short period, seems to be preferable for surveillance of gonococcal infection.[19-20] Yet, to provide AMR data in surveillance, culture needs to be performed as well.[16, 29]

MSM, transwomen, and female sex workers are considered core groups in Indonesia.[33] To reach those groups, health services can undertake outreach efforts.[39] This is done in settings that are relatively more convenient for the core groups, for example at a more convenient time (sometimes at evenings), and is preferably provided for free. However, outreach services are hampered by the lack of high quality diagnostics available in remote settings.[14, 39-40] Thus, investments are required to improve the available diagnostics and treatments offered in outreach settings. Outreach services may need also to take several other factors into account, such as: whether the setting allows sampling for laboratory tests, and whether patients can be followed up.

Another essential component in the management of gonorrhoea is the prevention of gonococcal transmission through correct and consistent condom use.[3, 41-42] As reported in chapter 3 and by others, consistency of condom use in Indonesia is low.[5,12] In MSM and transwomen we identified several partners factors that may influence the decision to use condoms in anal sex.[43] In targeted condom promotion it may be important to include partner profiling, e.g. age, ethnicity, and relationship status.[43-44]
Part II: Pharyngeal gonorrhoea

Epidemiology, diagnostic, treatment and antimicrobial resistant

Besides the genital tract and rectum, the pharynx can also be infected by *N. gonorrhoeae*. Pharyngeal gonococcal infection (pharyngeal Ng) accounts for up to 16.5% of all gonorrhea cases, and is especially common among MSM. Pharyngeal Ng may sustain gonococcal transmission in society through various types of sexual contact involving the oral and pharyngeal mucosa, including condomless oral sex, oro-anal contact (rimming) and the use of saliva as lubricant in condomless anal sex. Therefore, proper management of pharyngeal Ng is important.

To diagnose gonorrhoea, testing relevant anatomic sites of infection is essential. NAAT is able to test various specimen types, i.e. endocervical, vaginal, male urethral swab, rectal, pharyngeal, and also urine specimens from females and males. The simpler diagnostic tests (syndromic management, light microscopy) have low accuracy in detecting pharyngeal Ng. In addition, culture of pharyngeal samples is often not successful. Therefore, health care services using diagnostic tests other than NAAT, tend to miss pharyngeal Ng cases. Although the use of NAAT seems to be ideal, a highly sensitive NAAT could lead to detection of false positive cases, due to nucleic acid remnants of non-viable organisms promptly following an exposure, or during infection resolution.

Besides diagnostics, treatment of pharyngeal Ng is also a challenging aspect. To treat pharyngeal Ng, many international guidelines recommend similar regimens as for urogenital Ng, i.e. a combination of ESC with azithromycin. Pharyngeal Ng is often associated with emerging AMR in *N. gonorrhoeae*. This has been attributed (but not yet proven) to horizontal gene transfer of AMR characteristics (e.g. penA, porB, mtrR, gyrA) from several commensal Neisseriaceae (e.g. *N. meningitidis*, *N. sicca*, *N. perflava*, *N. subflava*) that colonize the pharynx.
Spontaneous clearance and persistence after treatment

Gonococcal infections may spontaneously clear, with variation by anatomical location of the infection.[52-53] In chapter 6, we reported 11% of 1,266 pharyngeal Ng cases spontaneously cleared after a median time of follow-up of 10 days.[17] NAAT is known to be highly sensitive, but there are challenges regarding specificity when used for pharyngeal samples due to the presence of the aforementioned commensal Neisseriaceae.[19, 23] To improve accuracy, confirmatory testing using a second nucleic acid target may be needed, especially in low-prevalence settings.[23] Furthermore, the bacterial load might influence gonococcal detection by NAAT, as well as duration of the infection.[52-53] The bacterial load in pharyngeal gonococcal infections was found to be lower than in rectal infections.[53] Although a proportion of pharyngeal Ng spontaneously cleared, the relevance of pharyngeal Ng in the transmission of gonococcal infections in the population seems substantial and therefore screening plus subsequent treatment are required.

In contrast to spontaneous clearance of pharyngeal Ng, several studies reported persisting pharyngeal Ng despite appropriate antibiotic treatment, and such persistence was often associated with AMR against ESCs.[54-55] In chapter 7, we reported that among 781 pharyngeal gonorrhoea cases that were treated using a standard treatment of 500 mg ceftriaxone (intramuscular injection) 4.6% of cases showed persistence. The median time between the treatment and the test-of-cure (TOC) was 8 days.[17] AMR is frequently associated with persisting pharyngeal Ng.[50-51] However, in our study, antimicrobial resistance is an unlikely explanation for the persistence after treatment: isolates of cleared and persisting cases showed a similar distribution of MIC against ceftriaxone, and none of those successfully cultured were resistant. Re-infection, caused by re-exposure, is another possible explanation for persisting pharyngeal Ng.[50]. Unfortunately, the data on re-exposure were not available in our study.[17]
We found that combining ceftiraxone with other antibiotics appears to lead to a faster clearance of pharyngeal Ng, yet a TOC 7 days after treatment may be too soon. A time-dependent effect of ceftiraxone might be explained by its pharmacodynamic properties.[56]. An ideal TOC requires adequate timing to allow complete clearance of the infection but also to minimize possibility for re-exposure (and further re-infection). In addition, the clearance rate may be influenced by the infection site, the used diagnostic test, and the treatment regimen.[50,55] The recommended timing for pharyngeal Ng TOC using NAAT varies from 7 to 30 days after treatment.[50, 55]

Concluding remarks

In Indonesia, there are several aspects in the management of gonorrhoea that need improvement. Since the accuracy of a diagnostic test is essential, health care facilities in Indonesia need to improve their capacity in diagnostic testing. More concern needs to be taken for asymptomatic cases, and endocervical and extra-genital infections, by considering the use of more advance diagnostic tests (NAAT).

A more rational treatment for gonorrhoea in Indonesia is expected. Treatment should be based on the most recent national guideline or, if possible, AMR testing. Furthermore, the national treatment guideline needs to be updated based on the most recent evidence. The practice of "self-medication" using antimicrobial drugs in society needs to be tackled (e.g. via health promotion, more strict regulation, monitoring by authority).

AMR surveillance is urgently needed in Indonesia, as part of regional and global gonococcal AMR surveillance. The surveillance can be integrated with the periodical IBBS that has been established, yet to provide national data, the surveillance should be more representative and include individuals of various locations and demographic background. Indonesian gonococcal AMR data can be further integrated to regional data to provide a more comprehensive picture of gonorrhoea epidemiology in the region.
Pharyngeal Ng significantly contributes to the overall spread of gonorrhoea. Thus, improved diagnostic and treatment of pharyngeal gonorrhoea is needed. Simple diagnostic tests (syndromic management, light microscopy) have a low accuracy in detecting pharyngeal Ng. NAAT might be highly sensitive to detect pharyngeal Ng, yet it may also be false-positive (by detecting non-viable nucleic acid remnants). Duration of infection might be also influenced by bacterial loads. Furthermore, to properly evaluate treatment outcomes of pharyngeal Ng, if a TOC is to be applied at the clinic, an appropriate timing is essential. TOC 7 days after the first consultation seems to be too soon to evaluate the treatment outcome. Persisting pharyngeal Ng is influenced not only by treatment failure and AMR but also reinfection. A careful investigation is required to elaborate those issues.