Prescribed treatments for *Neisseria gonorrhoeae* infections and treatment failures in the Quebec sentinel network, 2015-2017

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Background

Neisseria gonorrhoeae is becoming increasingly resistant to the antibiotics used and many countries have reported therapeutic failures. Several measures were undertaken in Quebec, including, since 2015, instauration of a provincial sentinel network aiming to:

1) Maintain sufficient cultures for the surveillance of antimicrobial resistance;

2) Complement MADO and the reference laboratory antimicrobial surveillance by providing epidemiological and clinical information;

3) Complement the enhanced surveillance of treatment failures.

Table 1

Definition of treatment failure used in the Sentinel network

	Definitions
Retained cases : all criteria met	
1	Gonococcal infection confirmed by laboratory test, regardless of site of infection AND documented treatment
2	Positive test of cure using one of the following *N. gonorrhoeae* detection tests, even if the site is different from the initial site: Isolation of *N. gonorrhoeae* by culture from a specimen obtained ≥ 72h after the end of treatment OR a positive NAAT from a specimen obtained ≥ 2 weeks after the end of treatment The maximum period between the first and the second detection test is 42 days.
3	Subject reports no sexual contact between the start of treatment and the second positive result
4	When available, strain of bacteria is of the same type as the first culture, according to the NG-MAST genotypic analysis
Suspected cases : criteria not all met but case not considered as a new infection	
	Sexual contact reported but new infection seems unlikely: e.g. occurred after seven days of abstinence posttreatment, always condom protected with a treated partner and no other sexual partner since start of treatment.

Figure 1

Extracts from INESSS's guides for *Neisseria gonorrhoeae* treatment, last edition (2018).

***NEISSERIA GONORRHOEAE* INFECTION**

TREATMENT PRINCIPLES

- Dual therapy is recommended for treating *N. gonorrhoeae* infection. This therapy could:
  - Improve the treatment's effectiveness and may delay the increase in *N. gonorrhoeae* resistance;
  - Treat a possible co-infection with *C. trachomatis*, which is highly prevalent.
- In the presence of a **rectal *C. trachomatis* infection together with an *N. gonorrhoeae* infection**, use **triple therapy** by adding doxycycline[1] (100 mg PO BID x 7 days) to the treatment recommended for *N. gonorrhoeae* infection.

TREATMENT[2] (including pregnant or breastfeeding women)

	URETHRAL, ENDOCERVICAL OR RECTAL INFECTION[3]	PHARYNGEAL INFECTION[3]
INDEX CASE	Cefixime 800 mg PO as a single dose **OR** Ceftriaxone 250 mg IM as a single dose **AND** Azithromycin[4] 1 g PO as a single dose	Ceftriaxone 250 mg IM as a single dose **AND** Azithromycin[4] 1 g PO as a single dose

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PELVIC INFLAMMATORY DISEASE (PID)
PROCTITIS

CERVICITIS AND URETHRITIS

TREATMENT

1ST CHOICE:
Cefixime 800 mg PO in a single dose OR ceftriaxone 250 mg IM in a single dose
AND
Azithromycin[2] 1 g PO in a single dose

2ND CHOICE:
Cefixime 800 mg PO in a single dose OR ceftriaxone 250 mg IM in a single dose
AND
Doxycycline[3] 100 mg PO BID for 7 days

Abbreviations

MADO: Maladie à déclaration obligatoire, provincial registry for diseases that physicians and laboratories are required to report to public health
gbMSM : gay, bisexual and men who have sex with men.
TOC: Test of cure.

Methods

Three regions participated in the sentinel network:

- Montréal: two clinics recruiting mostly men having sex with men (MSM);
- Montérégie: 22 clinics recruiting mostly heterosexual men and women;
- Nunavik: two health centers recruiting mainly heterosexual Inuit people (their participation ended in 2017).

Epidemiological and clinical data of gonococcal infections are collected on a centralized secured web application, through a self-administered questionnaire or by file review. It includes:

- History and sex behaviors
- Reasons for visits
- Laboratory samples
- Treatments prescribed

Prescribed treatments were analyzed to specify if they were adequate to provincial guidelines at the time of data collection. Figure 1 illustrates some examples of current treatment guidelines. Before April 2018, azithromycin 2 g was considered acceptable in presence of 'history of severe or very severe delayed or immediate reaction to penicillins'.

Treatment was defined as **empiric** (prescribed at the first visit, generally based on the presence of symptoms - 68% - or following a contact with gonorrhea case - 25%) or **pathogen-guided** (after obtaining positive test results).

For treatment failures, cases were classified as retained (presence of all predefined criteria listed in table 1) or suspected. The same definitions are used for provincial and federal surveillance of treatment failures.

Results

From September 2015 to December 2017, 1240 episodes in 1115 individuals were recorded (111 women, 1000 men, 3 transgender, 1 unknown sex):

- One episode: 1 015
- Two episodes: 78
- Three episodes: 19
- Four episodes: 3

The adequacy of the first prescribed treatment with recommended first-line treatments is summarized in table 2. In 62/1227 (5%) episodes for which information was available, two treatments were sequentially prescribed. Those subsequent prescriptions added an adequate cephalosporin for 48% (30) of the episodes (for instance ceftriaxone when a pharyngeal infection was detected). For only 12 episodes the complete treatment was prescribed (including azithromycin 1g).

Among the 688 (59%) episodes with a test of cure performed, 32 (4.7%) were positive; specific questionnaires for the treatment failure assessment were available for 28 (Table 3):

- 5 episodes were classified as retained or suspected treatment failure, including 4 pharyngeal infections and 2 cases who received azithromycin monotherapy.

Table 3

Final decision about treatment failures for episodes with positive test of cure, 2015-2017, Quebec sentinel network

	2015-2016			2017			Total
	gbMSM n (%)	Hetero-sexual men n (%)	Women n (%)	gbMSM n (%)	Hetero-sexual men n (%)	Women n(%)	n (%)
TOC performed	281 (64.4)	20 (37.0)	25 (32.0)	316 (54.9)	8 (23.5)	24 (68.6)	**688 (55.5)**
Positive TOC	**15 (5.3)**	**2 (10.0)**	**3 (12.0)**	**12 (33.3)**	**0**	**0**	**32 (4.7)**
Unknown exposure	2	0	2	0	-	-	4
Sexual history (contacts vs. abstinence) between date of treatment and date of TOC available	13	2	1	12	-	-	28
Retained	3	0	0	2	-	-	5
Reinfection is strongly plausible	5	1	0	8	-	-	14
Rejected for other reasons*	5	1**	1**	2	-	-	9

*Including cases with spontaneous resolution without new treatment, but no history of reinfection.
** Did not remain treatment failure when examining the genotyped strain.

Table 2

First treatment prescribed per episode, according to the site of infection and timing of prescription, in 2015-2017

Site of infection	Treatment prescribed	Empiric treatment* n (%)	Empiric treatment* N	Pathogen-guided treatment*After reception of positive results n (%)	Pathogen-guided treatment* N
Anogenital only	Recommended treatment : cefixime 800mg or ceftriaxone 250mg + azithromycin 1 g	384 (86.1)	446	159 (75.7)	210
	Azithromycin 2 g	11 (2.5)		7 (3.3)	
	Cefixime 800mg or ceftriaxone 250mg + doxycycline (any dose)	30 (6.7)**		27 (12.9)	
	Others	21 (4.7)		17 (8.1)	
Pharyngeal (and possibly other sites)	Recommended treatment : ceftriaxone 250mg + azithromycin 1 g	201 (77.3)	260	265 (85.2)	311
	Azithromycin 2 g	11 (4.2)		15 (4.8)	
	Ceftriaxone 250mg + doxycycline (any dose)	19 (7.3)		18 (5.8)	
	Cefixime 800mg + azithromycin 1 g	25 (9.6)***		4 (1.3)	
	Cefixime 800mg + doxycycline (any dose)	0		0	
	Others	4 (1.5)		9 (2.9)	

***Empiric treatment:** prescribed at the first visit, generally based on the presence of symptoms - 68% of cases - or following a contact with gonorrhea case - 25%; **Pathogen-guided treatment:** prescribed after obtaining positive test results.
**The combination of a third-generation cephalosporin and doxycycline is considered adequate treatment for empiric treatment of cervicitis and urethritis; ceftriaxone and doxycycline is the first-line treatment of complicated infections.

***When pharyngeal infection was not diagnosed at the time of the first prescription, treatment could still be considered adequate, as long as a test of cure was performed.

Discussion

Some clinicians were used to substitute azithromycin by doxycycline when co-infections takes place (around 10% of the prescribed treatment when it occurs after the first visit). The 2018 recommendation from INESSS clarify this uncertainty and we anticipate to measure the adherence to guidelines change in the next two years.

The results of the sentinel network help to guide Quebec public health decision-making. When certain βlactam allergy forces clinicians to prescribe an alternative treatment, a dual therapy including gentamicin is now recommended. Overrepresentation of azithromycin monotherapies among treatment failures in the sentinel network and the enhanced provincial surveillance also contributed to this recommendation change.

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