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▶ **To cite this version:**

A. Loncle, C. Piau, N. Ndeikoundam Ngangro, M. Gousseff, V. Cattoir, et al.. Current profile and management of gonococcal infections: A population-based study in Western France. Infectious Diseases Now, 2021, 51 (2), pp.201-204. 10.1016/j.idnow.2020.11.010 . hal-03285409

HAL Id: hal-03285409
https://hal.science/hal-03285409

Submitted on 10 Mar 2023

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Manuscript_e0da8295d4ccfc99b4f3c932280c2619

Current profile and management of gonococcal infections: a population-based study in Western France

Profil et prise en charge des gonococcies: une étude à base populationnelle dans l'Ouest de la France

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ABSTRACT

Objective. To characterize the current profile of gonococcal infections in France, and to describe their management.

Patients and method. A population-based retrospective study of all gonococcal infections documented by PCR in two French departments (Ille-et-Vilaine, Morbihan), in 2014-2016. Cases were identified through hospital databases and the Rénago sentinel network.

Results. We enrolled 245 patients (96 females, 149 males), with a median age of 25 years [interquartile range, 21-33]. The incidence rate was estimated at 4.54 per 100,000 inhabitants-year. Cases were diagnosed mostly by a general practitioner (n=122, 49.8%) or a gynecologist (n=45, 18.4%). The main clinical presentations included urethritis (n=59), pelvic inflammatory disease (n=40), cervicitis (n=12), and anorectitis (n=11). The main coinfections were *Chlamydia trachomatis* (n=40) and HIV (n=8). Ceftriaxone MIC was $\leq$0.12 mg/L in 146/147 patients with positive culture. Treatment was appropriate in 52/74 (70.2%) patients with available data.

Conclusions. In France, general practitioners are at the front line in management of gonococcal infections.

Keywords *Neisseria gonorrhea*; general practitioner; population-based study

1. Introduction

Since the late 1990s, the incidence of sexually transmitted infections (STI) has been gradually increasing [1]. A recent study in France estimated that between 2014 and 2016, the number of gonorrhea cases had increased by 127% in men who have sex with men, by 21% in heterosexual women, and by 40% in heterosexual men [2]. In parallel, the advent of nucleic acid amplification tests (NAATs), including PCR, has dramatically improved the diagnosis of various STIs. While the diagnosis of gonococcal infections in men used to require painful urethral sampling and immediate processing in a microbiology lab, it is currently easily obtained through NAATs on urinary samples [3][4][5][6]. Hence, a growing proportion of cases are currently diagnosed outside of referral centers and STI clinics [7][8].

In the absence of mandatory notification in France, the surveillance of gonococcal infections is currently based on two sentinel networks: RésIST (clinician network for STI surveillance), and Rénago (laboratory network for surveillance of gonococcal infections) [2][9][10]. However, contemporary data on the characteristics and management of gonococcal infections are scarce [10][4]. We performed a three-year retrospective population-based study of all gonococcal infections having been documented in two departments in Western France.

2. Materials and Methods

2.1 Setting and design

Morbihan and Ille-et-Vilaine are two predominantly rural departments in Western France, with 747,548 and 1,052,779 inhabitants respectively during the study period (source:

Institut National de la Statistique et des Etudes Economiques, INSEE, https://www.insee.fr/fr/information/4172214).

2.2 Inclusion criteria

We enrolled all cases of gonococcal infections documented by PCR from January 2014 to December 2016. Cases were identified through i) laboratory databases of the 4 major hospitals in the two departments (Rennes, Vannes, Lorient, St Malo/Dinan); ii) the Rénago database for cases diagnosed outside of hospitals. To avoid duplicates, only one gonococcal infection per patient per year was included.

2.3 Data collection

For patients managed in hospitals (inpatients and outpatients), clinical and microbiological data as well as those on management were collected from medical files by one investigator (AL), using a standardized questionnaire. For patients enrolled through the Rénago network, baseline data were extracted from the Rénago database. Antibiotic susceptibility testing was performed in accordance with CA-SFM guidelines (www.sfm-microbiologie.org) and MICs were determined using ETEST strips (bioMérieux) according to manufacturer's recommendations. As regards patients enrolled through the Rénago database, no information on treatment and outcome was available.

2.4 Ethics

RésIST and Rénago networks were approved by the French Personal Data Protection Authority (Comité National Informatique et Libertés, CNIL, authorization numbers 10362 and 999298). Patients' informed consent was required before any data collection. The number of people having opted out of this surveillance system by not providing their consent remains

unknown. For patients enrolled through a hospital database, the study was approved by the Rennes University Hospital review board. Informed consent was waived.

2.5 Statistics

Continuous variables were reported as median with interquartile range [IQR]. Qualitative variables were expressed as number and proportion and compared using chi-square, or Fisher exact test, as appropriate. The mean yearly incidence rate of gonococcal infections during the study period was estimated by dividing the number of documented cases by the number of inhabitants living in the two departments (2016 census), and then by the study duration in years.

3. Results

During the study period (2014-2016), 245 cases of gonococcal infections were documented by PCR in the two departments, identified from the Rénago (n=132) or the hospital (n=113) databases. The incidence of documented gonococcal infections was estimated at 4.54 per 100,000 inhabitants-year. There were 149 males (60.8%), and 96 females (39.2%). Median age was 25 years [21-33], with extremes of 10 days and 64 years. Median age was 23 years in women [19-29], and 27 years [22-33] in males.

Most cases were diagnosed by a general practitioner (n=122, 49.8%) or a gynecologist (n=45, 18.4%). Other places of diagnosis were hospital emergency department (n=17, 6.9%), family planning (n=15, 6.1%), and proctology consultation (n=11, 4.5%). Clinical manifestations, available for only 134 cases, included urethritis (n=59, 44.0%), pelvic inflammatory disease (n=40, 29.9%), cervicitis (n=12, 9.0%) and anorectitis (n=11, 8.2%). The

main coinfections were *Chlamydia trachomatis* (n=40, ?? %), and HIV (n=8, ??%). *C. trachomatis* coinfection was more common in females (30/96, 31.2%), than in males (10/149, 6.7%), *P*<0.001. Ceftriaxone MIC was <0.12 mg/L in 146/147 patients with positive culture.

The medical files of the 113 patients diagnosed in the participating hospitals were consulted. Partner(s) screening was reported in 56 cases (49.6%), and details on antibacterial treatment were available for 74 cases (65.5%). Most patients (63/74, 85.1%) received a combination of antibacterial treatments, which included ceftriaxone (54/74, 73.0%), metronidazole (29/74, 39.2%), doxycycline (24/74, 32.4%), ofloxacin (22/74, 29.7%) and azithromycin (8/74, 10.8%). While the treatment regimen was in agreement with national guidelines for gonococcal infections in 52 patients overall (70.2%), the rate of agreement varied according to site of gonococcal infection, ranging from 47.4% (18/38) in patients with pelvic inflammatory diseases, to 100% (14/14) in those with urethritis, *P*<0.001.

4. Discussion

The main findings of this population-based study on 245 gonococcal infections from 2014 to 2016 in Western France during years 2014-2016 are the following: i) almost half of the cases were managed by general practitioners; ii) the main clinical manifestations were urethritis and pelvic inflammatory disease; iii) >99% of isolates were susceptible to ceftriaxone; iv) partner screening was mentioned in only 50% of medical files; v) antibacterial treatment was in line with current recommendations for 70% of patients, to a much greater extent in urethritis (100%) than in pelvic inflammatory diseases (50%); vi) the

incidence of documented gonococcal infections was estimated at 4.54 per 100,000 inhabitants-year in two rural departments of Western France.

To the best of our knowledge, no previous study has documented the predominant role of general practitioners in the management of gonococcal infections in France. Although this observation is a reflection of health system organization in France, where general practitioners are at the front line for primary care, STIs have long been considered as diseases for specialists. This may have been related to the need for comprehensive STI testing (not readily available in primary care settings until recently), along with the reluctance, among some patients and some general practitioners, to disclose sexual practices; moreover, general practitioners are traditionally considered as 'family doctors'. Of note, these hypotheses have not been substantiated by rigorous studies. Our documentation of the fact that in France, general practitioners are of paramount importance in the management of gonococcal infections, is consequential: GPs henceforth need to be integrally involved in numerous areas having to do with STIs, including medical education, guidelines, and operational research.

The second major finding of our study is the rate of agreement between guidelines and practices, which ranges from very good for urethritis (100% concordance), to sub-optimal for antibiotic treatment of pelvic inflammatory diseases and for partner notification (around 50% of concordance for both). A 2008 study in France was much less encouraging, as only 20% of general practitioners prescribed the recommended treatment for urethritis [7], but it was conducted only two years after guidelines had first recommended ceftriaxone as first-line treatment for gonococcal urethritis [11], and was based on clinical vignettes sent by electronic questionnaire, with a response rate of only 35% [7]. Being population-based,

with systematic collection of data from all documented cases, our study is more likely to reflect real-life contemporary practices. Another study, by the French network of general practitioners, showed that the proportion of males with urethritis having received a combination of third-generation cephalosporin with macrolide or tetracycline had increased from 17.5% in 2009 (27/154), to 32.4% in 2017 (47/145, *P*=0.0327) [8].

The low rate of partner notification in medical files is probably an underestimate, as it is not the main information to be collected. As regards management of pelvic inflammatory diseases, our study was carried out at a time when significant discrepancies were observed between the guidelines of different medical societies. Fortunately, a consensus document recently published by the main societies of gynecology, obstetrics, and infectious diseases in France [12] should improve the rate of agreement between guidelines and practices regarding a puzzling disease.

Our study has limitations. First, it was retrospective, relied on passive surveillance, and only included documented cases. In addition, it was performed in two rural departments, whereas most STI hot spots have been reported in large cities. Hence, our estimates of yearly incidence most likely represent a sizable underestimation. It bears mentioning that the incidence of gonococcal infections in France has been estimated at 39 per 100,000 people aged 15-59 years [9]. Second, data available from the Rénago sentinel included no information on treatment and outcome, and they were retrospectively collected, with missing data, and limited sample size.

However, our study has strengths, including its population-based design, which enabled enrollment of the whole spectrum of gonococcal infections diagnosed during the study period, from asymptomatic to complicated cases; referral bias was thereby prevented.

In addition, the fact that we enrolled only cases with microbiological documentation contributes to the robustness of our findings.

In France, gonococcal infections are managed primarily by general practitioners. While the antibiotics they prescribe are in line with national recommendations for the most common manifestation (urethritis), they have remained sub-optimal for pelvic inflammatory diseases.

Funding: None

Potential conflict of interests: None for any of the authors

Acknowledgements: We are indebted to all the health care workers who cared for of the patients, and to the participants from the Rénago network.

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Fig. 1. Flow chart

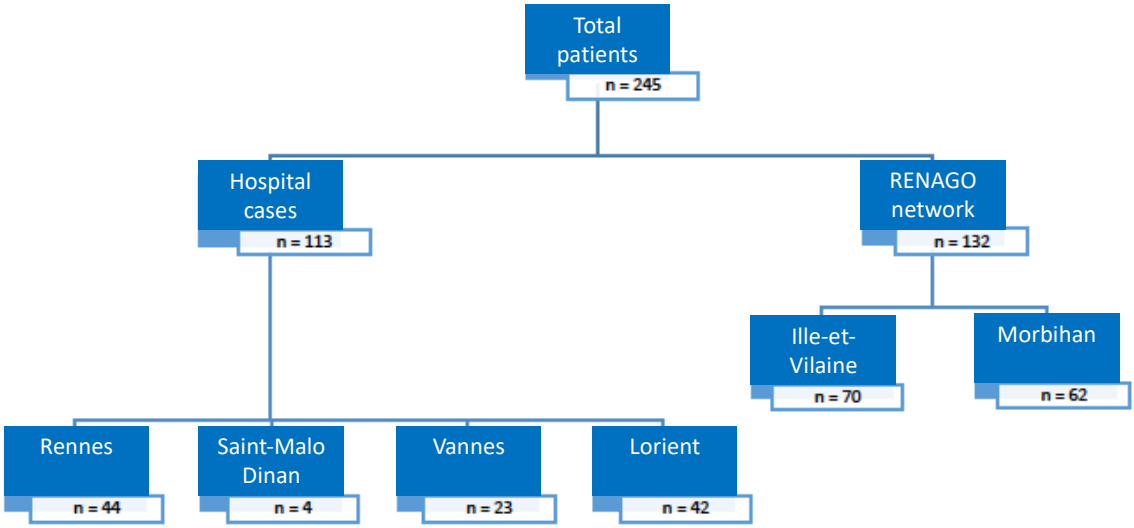


Table 1. Patient characteristics

Characteristics	**Number (%) or median [interquartile range]**
Age (years)	25 [21-33]
Sex	96 females (39.2%), 149 males (60.8%)
Clinical manifestations [#]	
Urethritis	59/134 (44.0%)
Pelvic inflammatory diseases	40/134 (29.9%)
Cervicitis	12/134 (9.0%)
Anorectitis	11/134 (8.2%)
Miscellaneous *	15/134 (11.2%)
Coinfections	
Chlamydia trachomatis	40/245 (16.3%)
- Females	30/96 (31.2%)
- Males	10/149 (6.7%)
HIV	8/245 (3.3%)
Partner notification [$]	56/113 (49.6%)
Antibacterial treatment [£]	
Ceftriaxone	54/74 (73.0%)
Combination [&]	63/74 (85.1%)
Treatment in line with recommendation	52/74 (70.2%)
- Pelvic inflammatory disease	18/38 (47.4%)
- Urethritis	14/14 (100%)

[#] data available for only 124 cases

* arthritis (n=4), asymptomatic (n=3), orchitis (n=2), endocarditis, conjunctivitis, pyelonephritis (one patient each)

[$] data available for only 113 cases, i.e. patients managed in participating hospitals

[£] data available for only 74 cases

[&] metronidazole (n=29), doxycycline (n=24), ofloxacin (n=22), azithromycin (n=8)