The Clinico-Epidemiological Profile of Patients with Gonorrhoea and Challenges in the Management of Neisseria gonorrhoeae Infection in an STI clinic, Ternopil, Ukraine (2013-2018)

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Abstract
Gonorrhea is the second most common sexually transmitted infection spreading worldwide and a serious public health problem. However, further data are required to improve the management of gonorrhea.

Our aim was to review the features of gonococcal infection and characterize the challenges of its management.

A retrospective descriptive study of the medical records of 136 adult patients with gonorrhea that visited Ternopil Regional Sexually Transmitted Infections Clinic (Ukraine) in 2013-2018 was performed.

The male-to-female ratio was 6.6:1. Homosexually-acquired gonorrhoea was 3.7%. Also, most patients acquired gonorrhea in Ukraine (98.4%). The mean infectious period lasted 2-16 days, including the incubation period of 1-9 days and the period from the onset of symptoms to the first visit of the clinic of 1-7 days. The probability of N. gonorrhoeae transmission within the frame of the epidemiologic sexual chain was 1:2.4. Concurrent T. vaginalis (39.7%) and C. trachomatis (2.2%) were detected. HIV and syphilis screening rates were 1.6% and 0.7%, respectively. The examining rate of sexual partners was 11%, testing extragenital specimens - 0.7%, screening coverage for HIV - 46.3%, compliance with follow-up visits - 41.9%. Part of patients (16.2%) received monotherapy with clarithromycin, doxycycline, benzylpenicillin, azithromycin, or ofloxacin.

The management of N. gonorrhoeae infections was compromised by a low rate of examining sexual partners, females and testing extragenital specimens, screening for HIV, compliance to follow-up visits, access to nucleic acid amplification tests, and receiving questionable or even obsolete antimicrobial treatment. Therefore, more accurate and comprehensive management of gonorrhea is urgently needed in Ukraine.

Keywords: Neisseria gonorrhoeae, gonorrhea, sexually transmitted infections, epidemiology, management

Introduction
Gonorrhea is the second most common sexually transmitted infection (STI) spreading worldwide [1-2]. It is a serious public health problem causing severe secondary sequelae, including pelvic inflammatory disease, first-trimester miscarriages, ectopic pregnancy, and infertility. N. gonorrhoeae infection may facilitate HIV acquisition and transmission [3-5]. Having been treated successfully before, nowadays, gonorrhea is considered to be one of the challenging STI due to the extraordinary ability of N. gonorrhoea to develop resistance to almost all antimicrobials [6].

In 2018, the annual data of the Centre of Medical Statistics of the Ministry of Health reported that the incidence of gonorrhea has decreased to 9.7/100.000 and 9.2/100.000 population of Ukraine and Ternopil, respectively, which was 2.8 and 2.5 times lower than reported in 2008. Many cases of gonorrhea are not registered officially, and the real prevalence remains unknown in Ukraine [7]. Conventional, microscopy, and culture, which are less
sensitive compared with molecular tests, are used prefera-
bly to detect gonorrhea in Ukraine [8].

Studying the socio-demographic, epidemiological, clinical and laboratory diagnostics data of patients with gonorrhea could highlight the main issues in the manage-
ment of N. gonorrhoea infection at the Ternopil regional STI clinic in Ukraine in 2013-2018.

Material and Methods

A retrospective single-center descriptive study was per-
formed at a tertiary dermatology and venerology care center, Ternopil Regional STI Clinic, Ukraine, from July 2013 to August 2018. One-hundred-thirty-six adult patients with gonorrhea were enrolled after giving their written in-
formed consent. All personal information used in the study was confidential, and patient’s identification information was not disclosed. Patients and their sexual partners were managed according to the national guidelines. Diagnosis of gonorrhea, urogenital chlamydiosis, and trichomonia-
sis was made as it was previously described in the col-
laborative project [8, 9]. Urogenital smears were stained by methylene blue and Gram for microscopic detection of Gardnerella vaginalis and Candida spp. Herpes simplex type 2 was recognized by enzyme-linked immunosorben-
t assay for detection of specific IgG (Vitrotest HSV2-IgG re-
agent kit, Ramintek Ltd., Ukraine) and by microscopy using Romanovsky-Giemsa-stained smears. The syphilis status was determined by the reaction of microprecipitation using cardiolipin antigen (Public Joint-Stock Company “Pharm-
standard-Biolik", Ukraine) and Wasserman reaction using cardiolipin antigen for the complement fixation reaction, dried complement and diagnostic hemolytic serum for the complement fixation reaction (Public Joint-Stock Company “Pharmstandard-Biolik", Ukraine).

The HIV-status was determined according to the Eu-
ropean guidelines by using point-of-care tests - SD Bioline HIV ½ -3.0 (Standard Diagnostics, Inc., Korea) and Alere DetermineTM HIV-1/2 SET (Alere Medical Co., Ltd, Japan) [10]. Anogenital warts were diagnosed according to the 2012 European guidelines [11]. Molluscomum contagiosum was diagnosed according to the guideline of the British Association for Sexual Health and HIV [12].

The mean incubation period of gonorrhea was 4.6
days (ranging from 1 to 9). The patients visited the STI clinic in 4.4 days (range: 1-7) after the first symptoms of gonorrhea. A total mean of the infectious period from the infectious sexual intercourse to the first clinic visit (start of treatment) was 9 days (range: 2-16). Males were symptomatic in 94.1% and females in 61.1% of cases. The most prevalent symptoms were urethral discharge (78.8%) in males and vaginal discharge (38.9%) in females. Non-spe-
cific symptoms were reported by 14.4% male and 22.2%
females. Detailed clinical characteristics are shown in Table 2.

The Bioethics Commission of I. Horbachevsky Temopil National Medical University approved the study (Excerpts from Minutes No. 29, dated 20.05.2015).

Results

All 136 patients with gonorrhea included 86.8 % males and 13.2 % females. The male-to-female ratio was 6.6:1. The mean age of patients was 29.4 years (range 16 - 80). The majority of patients were residents of Ukraine (94.9%), ur-
ban citizens (71%), and single (75.6%). Detailed socio-de-
mographic characteristics are presented in Table 1.

Most of the patients were heterosexuals (96.3%), and only 3.7% of patients reported themselves as men-who-
have-sex-with-men (MSM). The majority of patients had occasional partners (62.1%). Most patients (75%) had 2 - 4 sexual partners during the last three months.

The total sexual-chain comprised 400 persons. Those included 136 studied patients with gonorrhea and 264 sexual partners in the previous three months period. Less than half of persons from the sexual-chain group were examined (41.3%), including 136 patients with gonorrhea (34%) and 29 sexual partners (7.3%). The majority of sexual partners (89%) were not examined. Gonorrhea was detected in 41.4% (12/29) of the examined sexual partners. The probability of N. gonorrhoea transmission within the frame of the epidemiologic sexual chain was high (1:2.4).

Most of the patients (98.4%) reported Ukraine as be-
ing the country of gonorrhea acquisition, mostly specifying the Ternopil region in 92.9% of cases. Females reported the Ternopil region as an area of acquiring gonorrhea sig-
nificantly more frequently than males (p=0.031).

Sixteen patients (13.9%) reported a history of previ-
ous STI, including gonorrhea (5.1%), chlamydiosis (3.7%), trichomoniasis (6.6%), and syphilis (1.5%). The detailed epidemiologic characteristics of patients with gonorrhea are presented in Table 2.

The mean incubation period of gonorrhea was 4.6
days (ranging from 1 to 9). The patients visited the STI clinic in 4.4 days (range: 1-7) after the first symptoms of gonorrhea. A total mean of the infectious period from the infectious sexual intercourse to the first clinic visit (start of treatment) was 9 days (range: 2-16). Males were symptomatic in 94.1% and females in 61.1% of cases. The most prevalent symptoms were urethral discharge (78.8%) in males and vaginal discharge (38.9%) in females. Non-spe-
cific symptoms were reported by 14.4% male and 22.2%
female patients. Detailed clinical characteristics are shown in Table 3.
Table 1: Population characteristics of adult patients with gonorrhoea in Ternopil region of Ukraine, 2013-2018.

| Population characteristics | All | Male | Female | p-value |
|----------------------------|-----|------|--------|---------|
| Age, years                 |     |      |        |         |
| < 25 years                 | 44  | 37   | 7      | 0.4326  |
| 25-34 years                | 60  | 51   | 9      | 0.4729  |
| > 34 years                 | 30  | 29   | 1      | 0.0819  |
| Country of origin          |     |      |        |         |
| Ukraine                    | 129 | 111  | 18     | 0.2918  |
| Foreigner                  | 7   | 5    | 0      | 0.2918  |
| Place of residence         |     |      |        |         |
| Urban                      | 93  | 81   | 14     | 0.2847  |
| Rural                      | 38  | 35   | 3      | 0.2881  |
| Occupation                 |     |      |        |         |
| Students                   | 18  | 13   | 5      | 0.0998  |
| Employed                   | 12  | 10   | 2      | 0.8870  |
| Unemployed                 | 55  | 49   | 6      | 0.1288  |
| Marital status             |     |      |        |         |
| Married                    | 32  | 27   | 5      | 0.7216  |
| Single                     | 99  | 86   | 13     | 0.4846  |
| p-value                    | <0.0001 | <0.0001 | 0.0002 |

Note: CI, confidence interval; NA, not applicable.

Table 2: Epidemiological data of adult patients with gonorrhoea in the Ternopil region, Ukraine, 2013-2018.

| Patient's characteristics | All | Male | Female | p-value |
|---------------------------|-----|------|--------|---------|
| Relationship to the source of last sexual contact |     |      |        |         |
| Occasional partner        | 82  | 101  | 8      | <0.0001 |
| Constant partner          | 50  | 14   | 9      | <0.0001 |
| Number of sexual partners during the last 3 months |     |      |        |         |
| 1                         | 34  | 25   | 9      | 0.0088  |
| 2                         | 80  | 76   | 4      | 0.0007  |
| 3                         | 18  | 15   | 3      | 0.6420  |
| 4                         | 4   | 2    | 2      | 0.0286  |
| Sexual contact examination |     |      |        |         |
| Examined                  | 29  | 16   | 13     | <0.0001 |
| Not examined              | 235 | 214  | 21     | 0.0534  |
| Reported country of infection |     |      |        |         |
| Ukraine                   | 127 | 109  | 18     | 0.5677  |
| Abroad                    | 2   | 2    | 0      | 0.5677  |
| p-value                   | <0.0001 | <0.0001 | NA     |
Reported region of infection

\[
\begin{array}{lrrrrrr}
\text{Region} & n=127 & n=109 & n=18 \\
\text{Ternopil} & 118 & 92.9 & 100 & 78.7 & 18 & 100 & 81.5-100 & 0.0310 \\
\text{Other regions of Ukraine (Kyiv, Rivne, Lviv, Sumy, Lutsk)} & 9 & 7.1 & 9 & 21.3 & 0 & 0 & 0-8.5 & 0.0310 \\
\end{array}
\]

**Ternopil**

| N | % | CI [95%] |
|---|---|---------|
| 118 | 92.9 | [87.96-7] |
| 100 | 78.7 | [69.8-86] |
| 18 | 100 | [81.5-100] |

**Other regions of Ukraine (Kyiv, Rivne, Lviv, Sumy, Lutsk)**

| N | % | CI [95%] |
|---|---|---------|
| 9 | 7.1 | [3,3-13] |
| 9 | 21.3 | [14-30.2] |
| 0 | 0 | [0-8.5] |

**p-value**

| N | All | p-value |
|---|-----|---------|
| 127 | < 0.0001 | |
| 109 | < 0.0001 | |
| 18 | NA | |

**History of STI**

\[
\begin{array}{lrrrrrr}
\text{Any STI previously} & n=115 & n=97 & n=18 \\
\text{Reported STI history} & 99 & 86.1 & 83 & 78.7 & 16 & 88.9 & 78.8 & 14.4 & 65.3-98.6 & 0.7112 \\
\end{array}
\]

**p-value**

| N | All | p-value |
|---|-----|---------|
| 115 | < 0.0001 | |
| 97 | < 0.0001 | |
| 18 | < 0.0001 | |

**Note:** CI, confidence interval; MSM, men who have sex with men; STI, sexually transmitted infections; NG, *Neisseria gonorrhoeae*; CT, *Chlamydia trachomatis*; TV, *Trichomonas vaginalis*; NA, not applicable.

### Table 3: Clinical characteristics of adult patients with gonorrhoea in the Ternopil region, Ukraine, 2013-2018

| Patient’s characteristics | N | % | CI [95%] |
|--------------------------|---|---|---------|
| **Male symptoms** | n=118 |
| Urethral discharge | 93 | 78.8 | [70.3-85.8] |
| Urethral burning sensation with urination | 83 | 70.3 | [61.2-78.4] |
| Other | n=18 |
| Rash on genitalia | n=13 |
| Unpleasant smell | n=1 |
| Swelling and redness of the glans penis | n=2 |
| Lower abdominal pain | n=1 |
| Frequent urination | n=1 |
| Itching of the penis | n=1 |
| **Male clinical diagnosis** | n=118 |
| Urethritis | 112 | 95 | [89.4-98.2] |
| Balanitis | 7 | 5.9 | [2.4-11.8] |
| Balanoposthitis | 4 | 3.4 | [0.9-8.5] |
| Proctitis | 1 | 0.8 | [0.02-4.6] |
| **Female symptoms** | n=18 |
| Vaginal discharges | 7 | 38.9 | [17.3-64.3] |
| Other | n=4 |
| Vaginal itching | n=1 |
| Rash on genitalia | n=1 |
| Discomfort during urination | n=1 |
| Unpleasant smell | n=1 |
| **Female clinical diagnosis** | n=18 |
| Endocervicitis | 13 | 72.2 | [46.5-90.3] |
| Colpitis | 6 | 33.3 | [13.3-59] |
| Cervical erosion | 3 | 16.7 | [3.6-41.5] |

**Note:** CI, confidence interval

Concurrent STIs were detected in 45.6% of patients, being represented by *T. vaginalis* in 39.7%, *C. trachomatis* in 2.2%, anogenital warts in 2.2%, *Gardnerella vaginalis* in 2.2%, *Herpes simplex type 2* in 1.5%, molluscum contagiosum in 0.7%, and *Candida spp.* in 1.6% of cases. HIV testing was performed in 46.3% of patients, and a positive rate was found in 1.6% of cases. The rest of the patients (53.7%) refused to be tested for HIV. All patients were screened for syphilis, and 0.7% positive results were received.

*N. gonorrhoeae* isolates were obtained from the male urethra in 86% specimens, from the cervix in 13.2%, from the rectum of MSM in 0.7% of cases. No specimen was collected from the pharynx.

Ceftriaxone-based therapy was used for 83.8% of patients. Dual therapy was administered the most frequently, based on ceftriaxone combined with other antimicrobials (67%). Monotherapy by ceftriaxone 1 g was used in 16.8% of cases. Nevertheless, 16.2% of patients were not treated with ceftriaxone, receiving monotherapy instead with clarithromycin, doxycycline, benzylpenicillin, azithromycin, or ofloxacin. Recovery was detected in all patients who had follow-up visits (58.1%), but 41.9% of patients ignored their follow-up testing.

### Discussion

Gonorrhea is spreading worldwide, and its prevalence is rising, especially in well-developed countries, as proved by highly sensitive and specific modern laboratory methods.
for screening and diagnosis [1-2]. However, the incidence of gonorrhea has dropped down in Ukraine during the last decade [7]. Nowadays, the management of gonorrhea remains quite challenging [13]. Population, epidemiological, clinical, and diagnostic data were analyzed to reveal the main existing challenges of management of \textit{N. gonorrhoea} infection in Ukraine.

In our study, males were examined disproportionately more often than females, and the male to female ratio was 6.6:1. Dave and Tshokey et al. presented almost the same rate of gonorrhea in females [14-15], while Giomi B. et al. reported a higher level in males [16]. Our data suggest that a majority of potentially infected females probably have been missed.

Homosexually-acquired gonorrhea was only 3.7% of the total. Other authors reported a higher level of MSM (25.9 - 52%) and bisexuals (1%) in STI clinics [14,16]. Our study supposes that patients in Ukraine have a stigma to inform about their sexual behavior.

According to our study, gonorrhea had been a local infection during 2013-2018, because most patients were residents and reported Ukraine and the Ternopil region as the geographical area where they acquired the infection. Giomi B. et al. reported that the same data was received in STI clinics in Italy in 2001 [16]. A significant level of antimicrobial resistance of \textit{N. gonorrhoeae} has been reported in Europe as well as over the world [17-20]. Therefore, exporting of gonococcal infections in the future can not be excluded, including antimicrobial-resistant isolates of \textit{N. gonorrhoea}.

According to the European gonorrhea guidelines, all sexual contacts of patients with gonorrhea should be traced within at least the preceding two months of symptoms onset, and three months after the diagnosis [21]. Our study showed that only 11% of the sexual partners passed the medical examination, and gonorrhea was detected in 41.4% of partners, which indicates a high probability of \textit{N. gonorrhoea} transmission (1.2:4) within the frames of epidemiologic sexual chains. Worryingly, 89% of sexual contacts were not examined, guessing that almost a half could be infected with \textit{N. gonorrhoeae}.

A mean infectious period from the infectious sexual intercourse to the first visit at the clinic before the patients were diagnosed and started treatment was comparatively long (2-16 days). This fact may facilitate a transferring of 


gonococcal infection. Worryingly, 53.7% of observed patients were not tested for HIV, as it was the same reported in other studies [26]. Li et al. suggest that a high level of HIV infection is present in patients with STI and particularly with gonorrhea [27]. Our study highlighted that improving HIV counseling is needed among patients with gonorrhea in Ukraine. Nevertheless, the concurrent syphilis was detected in 0.7% of patients with gonorrhea; the real level of \textit{T. pallidum} infection is supposed to be underestimated because of using non-treponemal tests during screening [28, 29]. Accordingly, a highly sensitive and quality assured molecular tests are imperative in Ukraine.

A significant part of patients (41.9%) who missed their follow-up visits could form a reservoir of persistent infection and be a source of further transmission of \textit{N. gonorrhoea}.

Some patients (16.2%) received questionable treatment using monotherapy with clarithromycin, doxycycline, benzylpenicillin, azithromycin, or ofloxacin [21]. Ukrainian gonorrhoea treatment guidelines were not updated since 2009. It is essential to make further improvement of treatment based on the European gonorrhoea guidelines or adapted national evidence-based guidelines [9, 21, 23, 24].

An issue of social stigma associated with gonorrhea was raised previously [1, 15]. Our study supposed that gonococcal infection is stigmatized in Ukraine as well because of low levels of (a) reporting homosexual behavior, (b) willing to be screened for HIV, (c) compliance to have follow-up visits, and sporadically collection of extragenital samples by clinicians.

Conclusions

The key challenges of the management of \textit{N. gonorrhoeae} infection in Ukraine are the low level of examined females, asymptomatic infection in patients and sexual partners;
disregarded testing of extragenital specimens, using of conventional laboratory tests (microscopy and culture) for screening and diagnostics of gonorrhea; deficient access to nucleic acid amplification tests in the public leading specialised STI clinics in Ukraine, low level of screening for HIV; low compliance of the follow-up visits; receiving questionable or even obsolete antimicrobial treatment. It is also supposed by our data that gonococcal infection is stigmatised. Therefore, more accurate and comprehensive management of gonorrhea is urgently needed in Ukraine.

**Conflict of Interest**

The authors confirm that there are no conflicts of interest.

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