GONORRHOEA

Antibiotic susceptibility of *Neisseria gonorrhoeae* in Arkhangelsk, Russia

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Sex Transm Infect 2007;83:133–135. doi: 10.1136/sti.2006.021857

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Accepted 30 August 2006
Online first
13 September 2006

Objectives: To characterise comprehensively the antibiotic susceptibility of *Neisseria gonorrhoeae* in Arkhangelsk, Russia, and to investigate whether the recommended treatment guidelines are updated and effective.

Methods: The susceptibility of *N gonorrhoeae* isolates, cultured during June–November 2004 mainly from consecutive patients with gonorrhoea (n=76) in Arkhangelsk, to penicillin G, ampicillin, cefixime, ceftriaxone, ciprofloxacin, erythromycin, azithromycin, kanamycin, spectinomycin and tetracycline was analysed using Etest. Nitrocefin discs were used for β -lactamase detection.

Results: The levels of intermediate susceptibility and resistance to the different antibiotics were as follows: penicillin G 76%, ampicillin 71%, cefixime 0%, ceftriaxone 3%, ciprofloxacin 17%, erythromycin 54%, azithromycin 14%, kanamycin 49%, spectinomycin 0% and tetracycline 92%. Of the isolates 55 (72%) were determined as multiresistant—that is, they showed intermediate susceptibility or resistance to three or more classes of antibiotics. However, none of the isolates were β -lactamase producing.

Conclusions: In Arkhangelsk, and presumably in many other areas of Russia, penicillins, ciprofloxacin, erythromycin, azithromycin, kanamycin and tetracycline should not be used in the treatment of gonorrhoea if the results of antibiotic susceptibility testing are not available. In Russia, optimised, standardised and quality-assured antibiotic susceptibility testing needs to be established in many laboratories. Subsequently, continuous local, regional and national surveillance of antibiotic susceptibility is crucial to detect the emergence of new resistance, monitor changing patterns of susceptibility and be able to update treatment recommendations on a regular basis.

As a result of the break-up of the Soviet Union, during the past decade, Russia and the other newly independent states have gone through major changes, which have considerably influenced the healthcare system too. Regarding the incidence of gonorrhoea, reliable figures are still lacking mainly because of suboptimal diagnostics, incomplete epidemiological surveillance and reporting of new cases, as well as self-medication.¹ Furthermore, the prevalence of antibiotic resistance of *Neisseria gonorrhoeae* is unknown in most Russian areas, and this knowledge is crucial for empirical treatment. Owing to the worldwide rapid increase of antibiotic resistance, empirical treatment strategies need constant re-evaluation,² and antibiotic susceptibility testing is the main tool for updating them.³ Consequently, it is also essential to monitor the level of antibiotic resistance of *N gonorrhoeae* in Russia.^{1–4} As in most of the east European countries, it is crucial to establish local, regional and national antibiotic resistance networks and, in addition, monitor antibiotic consumption in Russia.⁵ During the 1990s, controlled, centralised provision of antibiotics and/or antibiotic resistant surveillance ended and the consumption of antibiotics increased markedly in Russia.⁶

The Arkhangelsk region, with a population of approximately 1.3 million inhabitants,⁷ is located in the north-western part of Russia. In 2004, the estimated incidence of gonorrhoea in the Arkhangelsk region was 136 cases per 100 000 inhabitants.⁸ This study is the first-ever measurement of the level of antibiotic resistance of *N gonorrhoeae* in the Arkhangelsk region.

The aims of this study were to analyse comprehensively the antibiotic susceptibility of *N gonorrhoeae* isolates in the Arkhangelsk region, Russia, and to investigate whether the recommended treatment guidelines are updated and effective.

PATIENTS AND METHODS

Patients and bacterial strains

A total of 76 clinical isolates of *N gonorrhoeae*, mainly from consecutive patients (one per patient), were collected at the Dermatologic and Venereologic Dispensary of Arkhangelsk region, Arkhangelsk, Russia, during June–November 2004. This comprised 68 (89%) urethral isolates from male patients and 8 (11%) urethral/cervical isolates from female patients. Two of the isolates were from girls of age 2 and 4 years (3%). The rest of the isolates were from adults (16–65 years; n = 74, 97%); 57 (75%) of the patients were between 16 and 30 years old and the median age of the men and women was 26 and 19 years, respectively.

Laboratory diagnostics, culture conditions and species confirmation

In Arkhangelsk, the clinical samples were “bedside” cultured on non-selective Russian media (NPO Microgen, Stavropol, Russia) at 37°C in 10% CO₂ for 24–72 h. According to routine procedure, the isolates were presumptively identified as *N gonorrhoeae* on the basis of characteristic colony morphology, presence of Gram-negative diplococci and rapid positive oxidase reaction. The isolates were preserved at –70°C.

Subsequently, the isolates were cultured on selective medium and species were confirmed as *N gonorrhoeae* by standard methods^{9–10} at the Department of Microbiology, University Hospital of North Norway, Tromsø, Norway, and at the National Reference Laboratory for Pathogenic *Neisseria*, Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden.

Antibiotic susceptibility testing

The susceptibility of penicillin G, ampicillin, cefixime, ceftriaxone, ciprofloxacin, azithromycin, erythromycin, kanamycin,

spectinomycin and tetracycline was determined using the Etest method according to the instructions of the manufacturer (AB, Biodisk, Solna, Sweden). Suspended bacteria were incubated with Etest strips on GC II agar (BBL, Becton Dickinson, Cockeysville, Maryland, USA) supplemented with 1% haemoglobin and 1% IsoVitalEx enrichment medium (BBL, Becton Dickinson) for 16–18 h at 35–37°C in 5% CO₂ atmosphere, and minimum inhibitory concentrations (mg/l) were determined. Interpretative criteria of the Swedish Reference Group for Antibiotics (SRGA; <http://www.srga.org/MICTAB/MICTAB.HTM>) were used for all antibiotics except kanamycin, for which the World Health Organization criteria were utilised¹⁰ (table 1). β -Lactamase production was analysed by the chromogenic cephalosporin test using nitrocefin discs according to the instructions of the manufacturer (AB, Biodisk). Multiresistance was defined as intermediate susceptibility or resistance to three or more classes of antibiotics.

RESULTS

Table 1 summarises the antibiotic susceptibility of the *N gonorrhoeae* isolates (n = 76) from Arkhangelsk, Russia, analysed in this study.

A high level of intermediate susceptibility and resistance to tetracycline (92%), penicillin G (76%), ampicillin (71%), erythromycin (54%) and kanamycin (49%) was identified. The level of resistance was highest for penicillin G (18%),

ciprofloxacin (17%) and tetracycline (12%). In all, 11 (14%) and 2 (2.6%) isolates had intermediate susceptibility, but not resistance, to azithromycin and ceftriaxone, respectively. All 76 isolates were susceptible to cefixime and spectinomycin (table 1). No β -lactamase-producing isolate was found. The rate of multiresistance was very high (ie, 72%). The most frequently encountered multiresistance profile was intermediate susceptibility or resistance to penicillin G, tetracycline, ampicillin and erythromycin (14 isolates).

DISCUSSION

This study shows that the level of resistance to traditional antibiotics used in the treatment of gonorrhoea is high in Arkhangelsk, Russia. In addition, recent local surveillance data (unpublished data) indicate that the prevalence of gonorrhoea is higher than predicted,⁸ and also increasing in the Arkhangelsk region. Consequently, it is crucial to optimise the diagnostics of *N gonorrhoeae* in accordance with international recommendations¹⁰—that is, to introduce a quality-assured selective culture medium, thorough species confirmation, as well as optimised and quality-assured antibiotic susceptibility testing, in Arkhangelsk as well as in many other Russian areas.¹ In addition, establishment of local, regional and national surveillance of the antibiotic susceptibility of *N gonorrhoeae* is urgently needed in Russia.

In Russia, ceftriaxone, cefotaxime, spectinomycin, ciprofloxacin and ofloxacin are the recommended first-line antibiotics

Table 1 Percentages of *N gonorrhoeae* isolates (n = 76) from Arkhangelsk, Russia, comprising susceptibility, intermediate susceptibility and resistance to 10 different antibiotics

Antibiotic/MIC (mg/l)	Strains, n (%)		
	Susceptible	Intermediate	Resistant
Penicillin G S, susceptible ≤ 0.064 R, resistant > 1	18 (24)	44 (58)	14 (18)
Ampicillin S, susceptible ≤ 0.125 R, resistant > 2	22 (29)	54 (71)	0
Ceftriaxone S, susceptible ≤ 0.064 R, resistant > 0.5	74 (97)	2 (2.6)	0
Cefixime S, susceptible ≤ 0.064 R, resistant > 0.5	76 (100)	0	0
Ciprofloxacin S, susceptible ≤ 0.032 R, resistant > 0.064	63 (83)	0	13 (17)
Tetracycline S, susceptible ≤ 0.125 R, resistant > 1	6 (7.9)	61 (80)	9 (12)
Spectinomycin S, susceptible ≤ 32 R, resistant > 32	76 (100)	0	0
Erythromycin S, susceptible ≤ 0.5 R, resistant > 4	35 (46)	41 (54)	0
Azithromycin S, susceptible ≤ 0.5 R, resistant > 1	65 (86)	11 (14)	0
Kanamycin S, susceptible ≤ 32 R, resistant > 96	39 (51)	36 (47)	1 (1.3)

MIC, minimum inhibitory concentration.

Key messages

- In Arkhangelsk and presumably many other areas of Russia, penicillins, ciprofloxacin, erythromycin, azithromycin, kanamycin and tetracycline should not be used in the treatment of gonorrhoea if the results of antibiotic susceptibility testing are not available.
- In Russia, optimised, standardised and quality-assured antibiotic susceptibility testing needs to be established in many laboratories.
- Subsequently, continuous local, regional and national surveillance of antibiotic susceptibility is crucial to detect the emergence of new resistance, monitor changing patterns of susceptibility and be able to update treatment recommendations on a regular basis.

for the treatment of gonorrhoea.¹¹ Accordingly, all these antibiotics are widely used in the Arkhangelsk region and in other geographical areas of Russia. This study highlights that ciprofloxacin and ofloxacin can be highly suboptimal, at least in Arkhangelsk, especially if antibiotic susceptibility testing has not been performed. Furthermore, even if ceftriaxone is mainly used as the first choice of antibiotic at the larger medical institutions of the states, the other recommended antibiotics, and many other antibiotics, are used in other institutions and/or in self-medication, mainly because of lower costs and because antibiotics can be bought at pharmacies without a prescription.

Most interestingly, no β -lactamase production was detected among the isolates from Arkhangelsk. In other countries, higher levels of β -lactamase production are usually identified.^{12–15} However, in a previous Russian study, a low level of β -lactamase positivity (2%) was also identified.¹⁶ This may indicate that treatment with β -lactams is no longer widespread in Russia or even that endemic spread of the β -lactamase-producing strains has not been established in Russia during the past few years.

In conclusion, in Arkhangelsk and presumably many other areas of Russia, penicillins, ciprofloxacin, erythromycin, azithromycin, kanamycin and tetracycline should not be used in the treatment of gonorrhoea if the results of antibiotic susceptibility testing are not available. In Russia, optimised, standardised and quality-assured antibiotic susceptibility testing needs to be established in many laboratories. Subsequently, continuous local, regional and national surveillance of antibiotic susceptibility is crucial to detect the emergence of new resistance, monitor changing patterns of susceptibility and be able to update treatment recommendations on a regular basis.

ACKNOWLEDGEMENTS

We thank all the people who contributed at the Dermatologic and Venereologic Dispensary of the Arkhangelsk region, Arkhangelsk, Russia, as well as Line Andreassen, Department of Microbiology, University Hospital of North Norway, for excellent technical assistance. This study was supported by grants from the Barents Secretariat and the Norwegian Ministry of Health and Social Affairs. VV was supported by an exchange programme PhD fellowship from the University of

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Competing interests: None.

VS designed the study and collected the gonococcal isolates in Arkhangelsk, Russia, in collaboration with NF, TA and IL; BCH, MU and VV performed the laboratory examinations of the isolates and analysis of the results; VV, MU and VS wrote the manuscript in collaboration with all the co-authors.

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