

CLINICAL REPORT

Survey of Diagnostic Services for Genital Herpes in Fourteen Countries in Eastern Europe

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This paper reports survey-based data on the diagnosis and management of genital herpes simplex virus (HSV) infection in 14 countries of the Eastern European Network for Sexual and Reproductive Health (EE SRH). Only 43% of the countries could provide the number of genital HSV cases recorded at national level. Eighty-six percent of countries employed syndromic management in cases of genital ulcer disease. Most countries performed type-specific and/or non-type-specific enzyme immunoassays to detect HSV antibodies. Non-type-specific serology for diagnostic purposes should be actively discouraged. Direct detection methods for HSV, such as PCR, antigen detection and culture, are available in the region, but their usage was extremely low. Their use in Eastern European countries should be actively promoted. The availability of laboratory services must be improved, and countries in the region should implement consensus recommendations for the laboratory diagnosis of genital HSV infections in order to improve clinical practice. Key words: genital herpes infection; diagnosis; Eastern Europe.

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Although healthcare in Eastern European countries has undergone substantial changes during the past two decades, issues related to the diagnosis and management of sexually transmitted infections (STIs) remain largely neglected by local health authorities. We have previously reported the establishment of the

international collaboration group, the Eastern European Network of Sexual and Reproductive Health (EE SRH) (1), a project supported by the Swedish International Development Cooperation Agency (SIDA). The EE SRH currently includes representatives from 15 participating countries. The main objective of this network is to facilitate improvement in reproductive healthcare in Eastern Europe, firstly via the improvement, harmonization and assurance of quality of diagnostic testing and management of STIs and other reproductive tract infections (RTIs).

Genital herpes simplex virus (HSV) infection is one of the most prevalent life-long incurable STIs. Data on the laboratory methods used by both public and private section services in the region have not been available previously.

The aim of this study was to collect data regarding the availability of diagnostic services and diagnostic tests used, as well as the relative importance of genital HSV infection in 14 EE SRH countries, in order better to understand the diagnostic needs of Eastern Europe.

METHODS

In May 2009 a questionnaire was sent to country representatives of the EE SRH. The questionnaire enquired about the diagnosis of genital HSV infection in each country, including: (i) the availability and number of samples tested and morbidity due to genital HSV infection in the country; (ii) the occurrence of genital ulcer disease (GUD) in clinics providing services for STIs; (iii) the aetiology of GUD in patients attending clinics; (iv) the main diagnostic tests used for genital HSV infection and their manufacturers; (v) the use of syndromic management for GUD; (vi) the availability and use of laboratory confirmatory testing; and (vii) the populations tested (mandatory). Where further clarification was needed, telephone interviews and personal interviews during the annual meeting of the EE SRH were held subsequently.

RESULTS

Representatives from 14 of the 15 EE SRH Network countries completed the questionnaire. Only six countries (43%) recorded the number of new cases of genital HSV infection each year. Among those reporting, the incidence per 100,000 inhabitants ranged from 3.1 (Georgia) to 81.1 (Kyrgyzstan) (Fig. 1). However, the rates of infection do not distinguish between primary and recurrent genital herpes.

Estimates of the proportion of genital ulcerations that are either syphilis or genital HSV infection are shown in Table I.

Syndromic management principles in GUD were reported by all countries, except Estonia and Russia. However, all countries, with the exception of Armenia, used some laboratory testing in order to establish a definitive diagnosis in at least some clinics (Table II).

Virus detection

Only Lithuania had a few laboratories performing isolation and typing of HSV (distinguishing HSV-1 and HSV-2) for routine diagnosis. Anti-viral susceptibility testing was not undertaken in any country.

Antigen detection using direct immunofluorescence (DIF) was used in 33% of participating countries surveyed, but only in a minority of clinics, i.e. approximately 3.5% in Belarus, 5% in Tajikistan, 8% in Kyrgyzstan, 10% in Ukraine and 50% performing testing for HSV in Estonia. Antigen detection of HSV by enzyme-linked immunosorbent assay (ELISA) was used only in Estonia and was available at all laboratories performing any test for HSV.

Polymerase chain reaction (PCR) was available for detection of HSV in 2/3 of countries, i.e. in laboratories in Georgia (unknown), Belarus (3.5%), Kyrgyzstan (7%), Estonia (20%), Kazakhstan (30%), Hungary

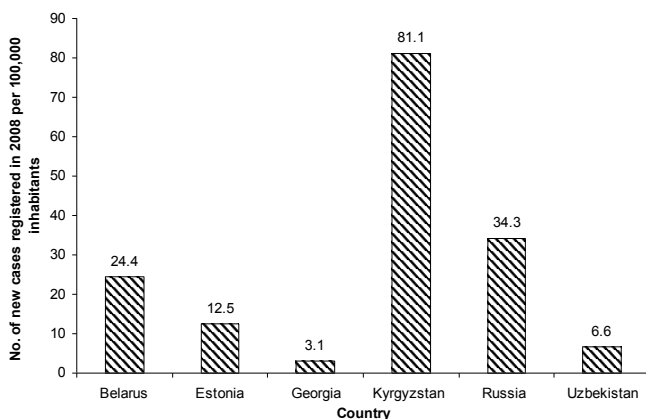


Fig. 1. Number of newly registered genital herpes simplex virus (HSV) infection cases per 100,000 inhabitants in Eastern European Network for Sexual and Reproductive Health (EE SRH) countries that reported having data on HSV morbidity in 2008.

Table I. Approximate percentage of patients attending dermatovenereology clinics in Eastern Europe with genital ulcer disease (GUD), and percentage of patients with GUD with a confirmed diagnosis of syphilis and herpes simplex virus (HSV) infection

Country	GUD (%)	Syphilis (%)	Genital HSV (%)
Armenia	30	10	90
Azerbaijan	20	55	45
Belarus	1.5	40	60
Bulgaria	25	10	90
Estonia	2	35	65
Georgia	5–10	30	70
Hungary	5–7	50	50
Kazakhstan	20	3	97
Kyrgyzstan	32	40	60
Lithuania	5	10	90
Russia	2	30	70
Tajikistan	3–5	30	70
Ukraine	10	10	90
Uzbekistan	30	20	80

(50%), Lithuania (unknown), Russia (unknown) and Ukraine (unknown).

Herpes simplex virus serological testing

ELISA testing for detection of non-type specific HSV antibodies was available in 2/3 of countries, namely Belarus, Estonia, Georgia, Hungary, Kyrgyzstan, Lithuania, Russia, Tajikistan and Ukraine. Most countries applied serological tests aimed at detection of either IgM and/or IgG antibodies. In Bulgaria, a complement-fixation test was occasionally used.

Type-specific serological testing was available in 86% of countries, excluding Armenia and Hungary.

Populations mandatorily tested for genital herpes

Of 14 countries surveyed, seven (50%) had initiated mandatory testing for genital herpes in specific patient groups. The groups targeted varied from country to country. For example, Georgia targeted HIV-positive individuals; Hungary targeted pregnant women (in early first semester and late trimester); Kazakhstan targeted pregnant women at the first antenatal visit, and women who had had spontaneous abortions; Kyrgyzstan and Tajikistan targeted pregnant women during the first, second and trimesters of pregnancy; Ukraine targeted men who have sex with men, and HIV-positive patients; and Uzbekistan targeted pregnant women during the first semester of pregnancy. For testing purposes, depending on the test availability, either type-non-specific or type-specific serological tests or PCR were employed.

Reagents/test kits

Participating countries in the European Union (EU) and Georgia used a broad selection of diagnostic systems produced in the West. However, in-house, non-commercial reagents were often used, particularly for the direct

Table II. Availability of laboratory tests used for the laboratory diagnosis of genital herpes simplex virus (HSV) infection in 14 Eastern European Network for Sexual and Reproductive Health (EE SRH) countries

Country	Use syndromic approach	Use laboratory confirmation	Virus isolation	Antigen detection			Detection of antibody		
				DIF-Ag	EIA-Ag	NAATs	ELISA HSV 1/2 Abs	ELISA type-specific Abs	CFT
Armenia	+								
Azerbaijan	+	+						+	
Belarus	+	+		+		+	+	+	
Bulgaria	+	+					+	+	+
Estonia		+			+	+	+	+	
Georgia	+	+				+		+	
Hungary	+	+				+	+		
Kazakhstan	+	+				+	+	+	
Kyrgyzstan	+	+		+		+	+	+	
Lithuania	+	+	+			+	+	+	
Russia		+				+		+	
Tajikistan	+	+		+			+	+	
Ukraine	+	+		+		+	+	+	
Uzbekistan	+	+				+		+	

+: approach or assay available; DIF-Ag: detection of virus antigen using direct immunofluorescence test; EIA-Ag: detection of virus antigen using enzyme immunoassay; NAATs: nucleic acid amplification tests; ELISA HSV 1/2 Abs: enzyme-linked immunosorbent assay for detection of antibodies to both HSV type 1 and type 2; ELISA type specific Abs: ELISA for detection of HSV-type-specific antibodies; CFT: complement fixation test.

detection of HSV. Non-EU countries mainly used tests (both for the detection of virus and antibodies) manufactured in Russia. Additionally, Ukraine and Belarus also used locally manufactured HSV test systems. In a small number of cases laboratories in non-EU countries used ELISA kits produced in the West.

DISCUSSION

This study was designed to investigate the availability of diagnostic services and diagnostic tests used, as well as the relative importance of genital HSV infection in 14 of the EE SRH countries, of which four are part of the EU.

The results clearly showed that genital HSV infection is a presumed major cause of GUD and that, in the vast majority of cases, a definitive diagnosis is not established using laboratory testing, even if facilities exist. It should be remembered that both *Treponema pallidum* and HSV might coexist in the same lesion (2). Because of the diversity of the signs and symptoms of genital HSV infections, a laboratory confirmed diagnosis should be made whenever possible (3). The reported incidence figures varied considerably between the different countries surveyed. However, these exact figures must be interpreted with caution. Accordingly, completely reliable incidence figures and figures of relative percentage of HSV and syphilis in GUD may not be available due to the inadequacy of the diagnostic services available (use of inappropriate diagnostic tests and reagents), uneven access to the point-of-care sites (where tests for HSV are performed), and suboptimal systems for case reporting and epidemiological surveillance.

Viral isolation, HSV DNA detection by PCR and HSV antigen detection by enzyme immunoassay or DIF, all could be used for direct virus detection. However, PCR

techniques have higher sensitivity and are less dependent on transport time and some other variables (4). Viral isolation was available only for routine diagnostics in one of the 14 EE SRH countries surveyed, while direct detection of viral DNA was available in a further nine countries. In Tajikistan viral detection is achieved solely using DIF, while in Bulgaria, Azerbaijan and Armenia no direct detection of HSV in lesions was available. Clearly, there is a need to reinforce the regional capacity for the direct detection of HSV, preferably using validated PCR techniques. Furthermore, HSV typing to distinguish HSV-1 and HSV-2 has important prognostic consequences, since the recurrence rate is significantly lower in HSV-1 compared with HSV-2 genital infection, and typing also needs to be encouraged in the region.

Although type-specific HSV serology may be a useful tool for the diagnosis and management of genital HSV infection in selected cases, generally it is not of high diagnostic value. Serology is necessary for staging of genital herpes as either primary or recurrent disease (in combination with culture or PCR). In addition, type-specific serology can identify discordant couples, which might reduce transmission risk and the risk of congenital disease (5). Unfortunately, nine (64%) of the 14 countries surveyed indicated that they used HSV antibody tests that cannot differentiate between infections caused by HSV-1 and HSV-2. These tests are of little diagnostic value for genital HSV infection, especially in impoverished communities, where oral-labial HSV-1 infections are commonly acquired during childhood.

In general, many of the surveyed countries had modern diagnostic tools necessary to provide a definitive diagnosis of this infection. However, for several different reasons these tests were not widely used: firstly, the number of testing and/or point-of-care sites providing such testing varied and in the majority of the countries

was limited, which made access to those services uneven between the countries and even within the same country; secondly, health services lacked resources to cover costs for such testing, so it was up to the physician to motivate the patient to pay for this relatively expensive diagnostic testing; and thirdly, it was also up to the physician to identify the need for testing, knowing that this virus infection is incurable and rarely treated even if properly diagnosed.

Although bacterial STIs remain a significant public health problem and are a main focus in many East European countries, the relative importance of HSV in GUD has increased globally (6–8). It is unlikely that Eastern Europe is any different, bearing in mind the recent reduction in cases of primary and secondary syphilis (9). Furthermore, the differentiation between genital HSV infection and other infectious or non-infectious aetiologies of genital ulceration is difficult, and laboratory confirmation of the infection should always be sought. Diagnosis based only on clinical symptoms has been shown to have a low sensitivity, even in carefully monitored populations. False-positive clinical diagnoses also occur frequently (10).

The recent important advances in the laboratory diagnosis of genital HSV infection, the decrease in cost of acyclovir and the emerging importance of genital herpes as a cofactor in transmission of HIV (11) indicate that more attention should be paid to HSV as a cause of genital ulceration. There is clearly a need to improve access to high-quality diagnostics for HSV infection in many Eastern European countries.

In order to improve the present situation, consensus guidelines aimed at optimizing the laboratory diagnosis of HSV infections in the region have been developed (12) and, it is hoped, will soon be adopted and implemented in the EE SRH countries.

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