Continuing medical education

SEXUALLY TRANSMITTED INFECTIONS: WHAT'S NEW?

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ABSTRACT

Since the beginning of the third millennium the incidence of Sexually Transmitted Infections (STIs) is rising in Europe and in Belgium, and this after a steady decline in the second half of last century. It concerns new or lesser known diseases such as Hepatitis C and Lymphogranuloma venereum (LGV) and 'old' diseases such as gonorrhoea and syphilis, occurring in specific risk groups. In this article we give an update of the diagnostic means and therapeutic challenges that are of interest for the clinician. Besides these (re)-emerging diseases we touch on Human Papillomavirus (HPV) and Herpes Simplex (HSV). This selection of diseases is based on the daily experience of the clinicians working in the STI clinic of the Institute of Tropical Medicine in Antwerp. Data and clinical guidelines are derived from the Scientific Institute of Public Health in Brussels, the European and American Centers for Disease Control and Prevention, and the Guidelines of the Flemish Agency for Care and Health. New evolutions in diagnostics, prevention and treatment options make it necessary to regularly update the knowledge of this group of diseases, especially when they are complicated by HIV co-infection. As the incidence of neither HIV nor STIs seem to decrease in Belgium and Europe, it remains necessary to stay aware of the state-of-the-art management.

Key words: STIs, epidemiology, diagnosis, treatment

INTRODUCTION

Few diseases have so clearly evolved hand in hand with humankind than those that are caused by Sexually Transmitted Infections (STIs). Like any other class of infectious diseases, Sexually Transmitted Diseases (STDs) are prone to epidemiological changes and changes in their medical management. As per definition STIs are referring to a variety of clinical syndromes caused by pathogens that can be acquired and transmitted through sexual activity, changes in human behaviour may lead to changes in the epidemiology. Pathogens can become resistant to existing therapies, or can adapt themselves such that they become fit to be transmitted through sexual practices - or what is commonly understood as such.

In most western European societies fluctuations in STI incidences of the last decades are associated with the Human Immunodeficiency Virus (HIV) epidemic. The emergence of AIDS in the eighties, led to a higher awareness of safe sexual practices among the risk groups, with a resulting decline in STIs (1). Better treatment options and increased life expectancy for HIV patients in the last decade, have led to a general increase of STI incidence, in the same risk groups (2, 3). New patterns of partnerships (multiple partnerships, sequential partnerships, partnerships of the same sexes) have led to an increased risk of the spread of the pathogens (4).

This review is not meant to cover all syndromes that are classically considered as STDs. We will limit ourselves to those syndromes that underwent 'recent changes' in the sense that was described above. Infection by the HIV will neither be discussed, as this is well covered in other publications.

METHODS

The topics for this review are broadly based on the experience and daily practices of the HIV/STI clinicians of the Institute of Tropical Medicine in Antwerp, Belgium. This expertise centre follows a cohort of over two thousand HIV positive persons, who are at the same time an important risk group for other STIs. Beside this cohort the clinic recorded 1347 consultations with HIV negative patients for other STIs in 2010. Evidence is derived from the international literature and from studies presented at the most recent conference of the International Society of Sexually Transmitted Diseases Research held in Québec in July 2011 and at the 13th European AIDS

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Conference of the European AIDS Clinical Society that took place in October 2011 in Belgrade. Treatment guidelines were derived from the Sanford Guide to Antimicrobial Therapy and the Centers for Disease Control and Prevention (CDC) unless mentioned otherwise (5, 6).

Epidemiological data are based on the surveillance reports of the Scientific Institute of Public Health for Belgium and the European Centre for Disease Prevention and Control (ECDC) for Europe (7, 8).

EPIDEMIOLOGY

Trends in STI incidences can only be described if a reliable surveillance system is in place. In Belgium, 3 complementary STI-surveillance systems are applied: two sentinel networks (one based on laboratories, one on clinicians) and one mandatory notification system.

Chlamydia is the most diagnosed STI in Belgium (7). The number of reported Chlamydia cases by the sentinel network of laboratories for microbiology increased from 1064 in 2002 to 3314 cases in 2010, or a mean increase of 16% a year (7). Sixty five percent of the Chlamydia-cases were women, mostly young women with a median age of 24 years. The sentinel network of clinicians indicated multi partnership as the most important risk factor, independent of the sexual orientation. In the same sentinel network of clinicians 10% of the female Chlamydia-cases were reported together with pelvic inflammatory disease (7).

Also the number of gonorrhea cases shows a mean annual increase of 16%: from 289 cases in 2002 to 782 cases in 2010, as reported by the laboratories.

The sentinel network of clinicians pointed out that the most vulnerable group are men (84.2%) and the most vulnerable age group is between 20 and 29 years old. The numbers of Men who have Sex with Men (MSM) increased with 60% while the number of heterosexually oriented gonorrhea patients decreased with one third between 2009 and 2010.

Syphilis cases increased from 155 cases in 2002 to 501 cases in 2010, an annual increase of 13% (sentinel network of laboratories for microbiology). In the sentinel network of clinicians 79% of the syphilis patients were male. The syphilis patient is older than the Chlamydia or gonorrhea patient: 35 to 44 years. Almost all of those patients have a homosexual orientation.

In 2010, twice as many men were diagnosed with human papilloma virus (HPV) than women. The number of female HPV cases diagnosed in 2010 was only half the number of 2009.

Still in 2010, 22 cases of **LGV** were notified, almost exclusively amongst HIV positive MSM. This represents an increase of 23% as compared to 2009.

Of note also is that only 40% of the STI patients in the sentinel network of clinicians are reported to have been vaccinated against hepatitis B virus. Hepatitis A and B are the only STIs against which full, long term protection can be obtained through vaccination (9).

In Europe, the ECDC has been coordinating the enhanced surveillance of STIs since 2009. Diseases under surveillance are syphilis, congenital syphilis, gonorrhoea, Chlamydia and LGV. In their first report (8), covering the period 1990 to 2009, Chlamydia is the most frequently reported STI, with an increasing trend over time, affecting mostly young women (8). This might reflect an increase in testing and screening practices in a number of countries. Less homogeneity is observed for gonorrhoea and syphilis, where marked differences are observed between countries, but men are nearly three times more affected than women for both diseases. Nearly a quarter of all gonorrhoea cases in 2009 (24%) and half of all syphilis cases (51%) were reported in men who have sex with men.

In 2009, 101 cases of congenital syphilis cases have been reported from 23 countries. Only four countries (Belgium, Denmark, the Netherlands and the United Kingdom), report LGV cases, which makes it difficult to comment on possible trends at European level (see further).

ECDC recognises the limitations of its first report: not all countries are reporting yet and different surveillance systems are applied in the respective member states, going from laboratory reporting to sentinel surveillance to comprehensive surveillance systems which makes an interpretation of the international distribution of STIs and its trends very challenging.

NEW EMERGING DISEASES

Hepatitis C

Infection with Hepatitis C (HCV) in Europe is no longer limited to well known risk groups such as intravenous drug users. Since the beginning of this century it has become clear that HIV infection and certain sexual practices can facilitate the transmission of the virus from one person to another (10). Although case control studies are ongoing to identify risk factors that facilitate the transmission, potentially traumatic sexual practices such as fist fucking and inappropriate and common use of sex toys are increasing the risk of infection five to tenfold (10). Moreover illicit drug use other than via the intravenous route (especially nasal drugs) and unprotected anal intercourse have been found to be associated with HCV infection (11). In the ITM cohort of HIV and HCV co-infected patients, more than three quarters had a history of yet another STI 6 months prior to the HCV infection, 50% of them being syphilis (12). A sub-analysis of the same cohort revealed that HIV/HCV co-infected patients had twice as much episodes of laboratory confirmed STIs since the start of follow-up at our clinic than HIV mono-infected patients (13).

Heterosexual transmission of HCV is much less common, and so far no observational study has demonstrated heterosexual transmission among discordant couples (14).

HCV/HIV co-infection leads to faster progression to liver fibrosis and liver cirrhosis. Antiretroviral Treatment (ART) can slow down this evolution but the outcome will remain worse than in the HCV mono-infected patient (15).

The HCV virus can not be cultured in vitro as yet, but a genetically modified variant can (16). A recent study revealed that viable virus of this variant could be obtained from the lumen of diabetes syringes several weeks after being drawn, depending on the temperature at which the syringes were kept. If kept at 4°, the virus remained viable up to 63 days (16). This makes it likely that common use of sex toys, anal douches, and lubricant gel can be possible modes of transmission in high risk settings.

Phylogenetic analyses have revealed the similarity of strains that circulate among MSM: predominantly subtype 1 and to a lesser extent subtype 4 (10). Sustained viral response is less likely in these subtypes (17). HCV strains that are not associated with homosexual transmission (in Belgium: subtype 2 and 3) can be adequately treated with a 48 weeks course of antiviral therapy based on pegylated interferon or pegferon (Peg) and ribavirine (RBV) (18). In HIV co-infected patients, the same drugs are used. Randomised controlled trials have shown that Peg in combination with RBV lead to sustained viral response in an average of 70% of patients (18). Treatment durations differ from 48 to 72 weeks. A comprehensive strategy is offered in the recently launched treatment guidelines for HIV infected people released by the European AIDS Clinical Society in November 2011 (19). Measuring viral load plays a crucial role in the decision if and when to start treatment, and when to stop, but is not easily accessible due to stringent reimbursement rules.

Despite this potentially good clinical outcome – especially when started at still a high CD4+ lymphocyte count level –, the treatment is complicated because of the higher risk of development of resistance, the higher frequency of drug/drug interactions and the overlapping toxicity patterns of HIV-antiretroviral drugs and Peg/RBV. Clinical trials with new protease inhibitors are ongoing – telaprevir and boceprevir being in the furthest stage and already registered since mid 2011 in the US – and are promising in terms of treatment duration, side effects and efficacy (20).

Lymphogranuleum Venereum

LGV traditionally is described as 'a sporadic disease in North America, Europe and Oceania, but highly prevalent in parts of Africa, Asia, and South America' (21). The clinical spectrum comprises of three stages of infection, i.e. a small inconspicuous papule or ulcer with few symptoms, followed by an acute lymphadenitis with bubo formation, eventually followed by an anogenitorectal syndrome with hemorrhagic proctitis, fever and other symptoms caused by systemic spread of infection. In western European countries, it is the last stage that has provoked an epidemic amongst the MSM community during the last decade (22). LGV is caused by the *Chlamydia trachomatis* serovars L1 to L3 that are more invasive than disease caused by the urogenital serovars (D–K) (6). The L2B serovar has been identified as the cause of severe, more invasive and more often chronic inflammation of the rectal mucosa and frequent involvement of pararectal lymph nodes, and it is also significantly associated with HIV positivity (23).

Rectal chlamydial infections are possible in women who indulge in anal receptive sex, but LGV serovars have rarely been isolated (23).

Due to the non-specificity of the symptoms the diagnosis is unfortunately often missed. When the sexual preference is not known or not asked for, the gastro-intestinal symptoms may divert the attention of the clinician. In this context it is also important to mention enteropathogens such as Shigella and Campylobacter as possible causes of dysentery-like syndromes, which can be sexually transmitted (24).

The diagnosis of LGV is based on molecular techniques to detect and identify LGV serovars (23). When LGV is confirmed, standard therapy is doxycycline 200 mg once daily for three weeks, and not azithromycin 1 g monodosis as is given for the urogenital syndrome. Alternatively, erythromycin 500 mg four times a day can be used for three weeks (6).

Species-specific serology can help support the LGV diagnosis when clinical symptoms are present but cannot be used to detect LGV-infected persons who are asymptomatic (23). A seven fold rise in IgA titre against L2 serovar in a patient older than 50 years resulted in a sensitivity of 92% and a specificity of 100% to diagnose LGV proctitis according to multivariable analyses carried out by van der Snoek et al on a cohort of patients in Rotterdam (25). It should be emphasised that serology alone does not suffice to confirm the diagnosis of LGV.

NOT SO NEW BUT RE-EMERGING

Syphilis

The main change of the last decade is its epidemiology: syphilis is re-emerging in Belgium, mainly among MSM, and often as re-infection. The latter can pose problems of diagnosis, in the sense that the only sign of re-infection may be a rising rapid plasma reagin titre (RPR). RPR (or the equivalent VDRL test) is indeed the only parameter of successful treatment: titres should decline fourfold (i.e. two dilutions) within 12-24 months after therapy (6). A rise or decline in RPR titre (or VDRL) can only be confirmed by testing the current and previous blood specimen in parallel. Non-treponemal tests titres might decline more slowly for persons who previously had syphilis (26). Optimal management of persons whose titres do not decline is unclear. They should be re-evaluated for HIV infection if not yet done and retreatment is recommended, certainly when additional clinical and serological follow-up cannot be ensured. Ghanem et al recently assessed the CDC guidelines with regard to the examination of CSF specimens in patients with concurrent HIV infection and syphilis and concluded that the use of criteria based on serum RPR titer (RPR titre of > 1:32) and CD4+ lymphocyte count (< 350 cells/mL), instead of stage-based criteria (latent syphilis with neurologic symptoms or evidence of tertiary syphilis), improved the ability to identify asymptomatic neurosyphilis (27). As in many other infectious diseases, antiretroviral therapy might improve clinical outcomes.

The treatment of syphilis remains intramuscular benzathine penicilline largely based on approximately 50 years of clinical experience. A systematic review of the literature to assess treatment of syphilis in HIV-infected subjects made the authors conclude that little objective data exist to support the guideline recommendations in this population: the available evidence from 23 studies published between 1980 and 2008 is not conclusive with regard to the optimal antimicrobial regimen to treat syphilis in HIV-infected subjects (28).

Gonorrhoea and Chlamydia

"Is *Neisseria gonorrhoeae* (NG) initiating a future era of untreatable gonorrhoea?" That is the alarming title of a recent article by Makoto Ohnishi et al. (29). They found a NG strain that is full-blown resistant against ceftriaxone, an extended spectrum cephalosporin, and one of the last remaining options for empirical first-line treatment.

'Ciproxin has been the first treatment option for a long time been the first treatment option but it can no longer be

used for the treatment of gonorrhoea. The prevalence of resistant strains exceeds 60% in Belgium (figure). The World Health Organization states that an antibiotic should no longer be used for the treatment of gonorrhoea if the prevalence of resistant strains to that antibiotic is above 5%.

In Belgium no ceftriaxion resistant NG has been observed (situation 2010). The first option for NG-therapy in Belgium (2011) is an intramuscular dose of 1 gram ceftriaxone[1]. The Sanford guide to antimicrobial therapy 2010-2011 proposes azithromycin as first therapy option (5). NG-experts however discourage use of azithromycin for NG-therapy. Only 1 single mutation is necessary to obtain full-blown resistance (personal communication Magnus Enemo, Sweden). The NG-reference laboratorium of the Institute of Tropical Medicine found an azithromycin resistance prevalence of 8, 2% in 2010, clearly above the 5%-limit. So it can no longer be used for presumptive therapy (see figure).

Many NG-patients are co-infected with *C. trachomatis*, therefore combination therapy of ceftriaxone and azithromycin is recommended (30).

Although Chlamydia remains the most common STI in the Belgian population, it does not seem to get much attention, maybe because it is easy to treat: azithromycin 1 g as a single dose This statement was challenged by Schwebke and colleagues (31). They organised a clinical trial with 305 male non-gonococcal urethritis-patients in the US and found that doxycycline had significantly better efficacy against *C. trachomatis,* than azithromycin, with cure rates of 95% in the doxycycline and 77% in the azithromycin arm of the study. They conclude that ruling out re-infection is always very difficult in high-risk populations, but that their data could possibly be an indication of a real decrease in response of *C. trachomatis* over the previous 2 decades. However, they did not perform resistance testing for Chlamydia (32). Chlamydia-experts propose to perform a trial comparing azithromycin versus doxycycline and more research on antimicrobial susceptibility testing of *C. trachomatis*. Other research questions that have been put forward are: should doxycycline be the therapy of choice for laboratory confirmed chlamydia-patients, who are willing to take a 7-day regimen? Should we propose a test of cure after azithromycin therapy (>3 weeks after therapy)? Should we reemphasise retesting after 3-6 months?

REMAINING DISEASES: WHAT'S NEW?

Human Papilloma Virus (HPV) infection

Quadrivalent human papillomavirus vaccine against the viral types most likely to cause cervical cancer (types 16 and 18) and genital warts (types 6 and 11) have been licensed (6, 7). The vaccine is 95% to 100% efficacious against cervical intraepithelial neoplasia and adenocarcinoma in situ and 99% efficacious against genital warts caused by serotypes in the vaccine (33).

It has been estimated that genital human papillomavirus (HPV) is the most common sexually transmitted infection in the US. No such estimate exists for Europe because there is no reliable surveillance system for HPV. Nononcogenic types, such as HPV type 6 (HPV-6) and HPV-11, can cause benign or low-grade cervical cell changes, genital warts, and recurrent respiratory papillomatosis. Oncogenic types can cause cervical and other anogenital cancers; oncogenic HPV types are detected in 99% of cervical cancers worldwide (34).

HPV/HIV co-infection requires special attention. HIV patients have a 2- to 6-fold higher risk for anal HPV infection, independent of sex and sexual practices and if infected, the number and variety of HPV subtypes is higher than in HIV negative patients, usually more than ten times (35, 36). Persistent HPV infection may lead to precancerous preliminary stages and is the strongest risk factor for development of cancers. However, evidence is limited concerning the natural history of anal intraepithelial neoplasia.

Fact is that the risk of invasive anal carcinoma in HIV-infected male patients is much higher than in the general population, and appears in the top 3 of the most frequent non-AIDS-defining malignancies among men. Cervical cancer is an AIDS defining cancer in women; HIV-positive women have a nine time higher risk of invasive cervical carcinoma than HIV-negative women (37).

The influence of ART is not clear, although sustained viral suppression and higher CD4+ lymphocyte count reduces the risk of cervical infection with high-risk HPV in HIV–positive women (38). Hoffmann recently described a cohort of 121 men with anal carcinoma, of which the vast majority was on ART, with a well suppressed viraemia and a median CD4 T-cell count of 400/µl (39). This is in line with our own observations.

Although PAP smear is a well known and described tool for early cervical cancer screening, its reliability for screening for anal intraepithelial neoplasia is not yet well documented. Self administered cytobrushes have been suggested as an easy and well accepted screening tool, but the test characteristics are not that convincing (40). Also intra-anal cytology has been suggested, but at this moment evidence is lacking to adopt systematic screening as a programmatic approach in this risk population.

At present CDC recommends that (intra-)anal warts should be managed in consultation with a specialist who is able to do an inspection of the rectal mucosa by standard or high-resolution anoscopy. (6)

With regard to prevention by means of vaccine: bivalent and/or quadrivalent vaccines are widely applied in many countries, given before sexual activity, to prevent cervical cancer. In the US, also males from 9 to 26 years old and MSM are offered the vaccine, the only country so far to apply that policy. According to the CDC, no published data are available on the effectiveness, programmatic requirements, or cost-effectiveness of administering the HPV vaccine in STD clinic settings (6).

Because of the campaigns that accompanied the introduction of the vaccines, many questions may arise amongst the general population with regard to HPV infection, (genital) warts, and the association with cancer. Key counselling messages are that genital HPV infections are very common and in most cases remain unrecognised, asymptomatic or subclinical. Genital warts will not turn into cancer, except in very rare and unusual cases, and correct and consistent male condom use can lower the chances of giving or getting genital warts, although it is not fully protective.

[1] European guidelines propose a dose of 500 mg ceftriaxone IM. In Belgium only 1 gram vials are available. In view of rising MIC's for NG-therapy, it is advisable to use the full gram dose. In Japan NG-experts advice a 1 gram dose intravenously (!).

Herpes Simplex Virus (HSV) infection

HSV infection is less important in terms of risk for complications but important as a source of anxiety and discomfort in many patients. The epidemiology is still poorly understood by researchers let alone by patients who try to inform themselves *on line*, eventually resulting in more anxiety and uncertainty or even in 'cyberchondria' (41).

Two types of HSV have been identified as causing genital herpes: HSV-1 and HSV-2. Most cases of recurrent genital herpes are caused by HSV-2. However, an increasing proportion of anogenital herpetic infections in some populations has been attributed to HSV-1 infection (6). Type specific serologic tests are available, but not indicated in the general population. In the US, about 17% of the population above 12 years, tests positive for HSV-2 infection according to a survey conducted between 1999 and 2004 (42). This is considerably lower than in Africa: a population based cross sectional survey among a rural population in Tanzania for instance revealed that more than one third of the general population was infected with HSV-2, and up to 87% of HIV infected people (43). No figures are available for Belgium (44). Whether it should be part of an STI screening remains controversial, but could be considered for persons with multiple sex partners, persons with HIV infection and MSM at increased risk for HIV acquisition. The subsequent counselling in case of a positive test is not easy. Most individuals who are HSV-2 antibody positive shed virus from the genital tract even in the absence of recognized symptoms (45). In case of discordant couples, the option of suppressive therapy should be discussed (46).

CONCLUSION

This review was by no means meant to be exhaustive. Its purpose was to highlight recent insights in the epidemiology and management of STIs. New evolutions in diagnostic means and prevention and treatment options make it necessary to regularly update the knowledge of this group of diseases, especially when they are complicated by HIV co-infection. As the incidence of neither HIV nor STIs seem to decrease in Belgium and Europe, it remains necessary to stay aware of the state-of-the-art management.

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