Review

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Why Should You Care About Oral Gonorrhea and Oral Human Papillomavirus Infection?

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The incidence of sexually transmitted diseases is increasing with the open-sex culture and as people are having sex at a younger age. Consequently, oral gonorrhea and oral human papillomavirus infections, which are often asymptomatic, result in a high risk of transmission. Oral gonorrhea is symptomatic in less than 20% of patients confirmed by culture for *Neisseria gonorrhoeae* in both men and women. Even if symptoms develop and oral gonorrhea is diagnosed and treated, the cure rate is less than 90%. Hence, oral gonorrhea can lead to antibiotic resistance to gonorrhea. Oral human papillomavirus infections have received more attention because oral human papillomavirus infections play an important role in the development of oropharyngeal cancer. On the other hand, no test for diagnosing human papillomavirus in the oral cavity has been approved by the US Food and Drug Administration. This lack of test makes it difficult to detect oral human papillomavirus infection early, which can further increase the risk of transmission of human papillomavirus infections. Preventing human papillomavirus infections is very important because surgical resection is the only treatment. Vaccination against human papillomavirus-associated oropharyngeal cancers, including tonsil cancer and base of the tongue cancer, has been reported to be effective in reducing the prevalence of oral human papillomavirus infection in middle-aged adults. Human papillomavirus vaccination is essential for protecting against oral human papillomavirus infection.

Keywords: Gonorrhea; Human papillomavirus viruses; Oropharynx

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INTRODUCTION

The incidence of sexually transmitted diseases (STD) is rising with the open sex culture and as people are having sex at a younger age. Globally, more than 1 million STDs occur daily. In 2020, the World Health Organization estimated that 374 million new infections would be caused by one of four STDs: chlamydia, gonorrhea, syphilis, and trichomonas. In 2016, it was estimated that more than 490 million people were living with genital herpes, while human papillomavirus (HPV) infection, the leading cause of cervical and anal cancer (which occurs among men who have sex with men), is estimated to occur in approximately 300 million women. Oral gonorrhea and oral HPV infection are often asymptomatic, so they have a high risk of transmission. Therefore, this review examines why people should be on alert for these two diseases.

MAIN BODY

1. Oral Gonorrhea

1) Symptoms

The most common symptoms of oral gonorrhea are usually sore throat and fever, but it might also present as tonsillitis, gingivitis, or stomatitis [1-4]. Oral gonorrhea, although a rare complication, is also associated with a disseminated gonorrhea infection [5]. Patients with gonococcal pharyngitis are usually infected via the oral-genital route. Therefore, gonococcal pharyngitis is much more common in women and homosexual men. On the other hand, less than 20% of patients diagnosed with *Neisseria gonorrhoeae* based on pharyngeal culture results show symptoms in both men and women [6]. In a physical examination, the oropharynx may be erythematous and have mucous exudate with cervical lymphadenopathy [4]. Nevertheless, even if oral gonorrhea presents symptoms, the possibility of *N. gonorrhoeae* is usually not considered, so a diagnosis of oral gonorrhea is likely to be missed. Therefore, attempts to detect and treat gonococcal pharyngitis early can help reduce the incidence of the disease because gonococcal pharyngitis can serve as a repository for community infection [7].

2) Diagnosis

For mucosal sites, such as the pharynx, sensitivity and specificity are much lower, so a gram stain is not recommended for testing for *N. gonorrhoeae* infection. Culture testing is recommended to confirm an oropharyngeal gonococcal infection. Nucleic Acid Amplification Tests (NAAT) can be performed after collecting a sample using a pharyngeal swab. On the other hand, NAAT can detect symbiotic *Neisseria* species and thus may show low specificity [8]. The US Centers for Disease Control and Prevention (CDC) recommends that patients with oropharyngeal gonorrhea visit the hospital seven to 14 days after initial treatment and perform a culture test or NAAT again to confirm that it is cured. If NAAT is positive or symptoms persist, particularly if a culture test has not been performed, a confirmatory culture test should be performed before re-treatment. An antimicrobial susceptibility test is recommended when performing a cure test [8].

3) Antibiotic resistance

Oral gonorrhea can cause antibiotic resistance [9,10]. A *N. gonorrhoeae* infection in the oropharynx is more difficult to cure than an infection of the urinary tract and anorectum [11], and few antibacterial therapies show a treatment effect of more than 90% for gonococcal pharyngitis [12]. This increases the transmissibility of gonorrhea, which can increase the spread of antibiotic-resistant strains and accelerate the upward movement of minimal inhibitory concentrations (MIC) because there are more opportunities for genetic transfer [13].

The number of antibiotics available for the treatment of gonorrhea has declined. According to the World Health Organization Global Gonococcal Antimicrobial Surveillance Program (GASP), which was convened to ensure adequate surveillance of antibiotic resistance in gonorrhea, high rates of resistance were observed for many antibiotics, including quinolones, azithromycin, and cephalosporins. Several treatment failures with oral cephalosporins have been reported globally, and ceftriaxone-resistant strains have been reported in Japan. For these reasons, antibiotic resistance in *N. gonorrhoeae* is a worldwide public health problem. In 1986, the CDC established the Gonococococcal Isolate Surveillance Project (GISP) as a national surveillance program at 27 sites to monitor the trends in the antibiotic susceptibility of *N. gonorrhoeae*. Monitoring showed that over time, *N. gonorrhoeae* developed resistance to many antibiotics, including penicillin, tetracycline, and ciprofloxacin. In addition, reduced susceptibility to the drug previously used as first-line treatment greatly limited the use of the drug, as evidenced by higher MIC for cefixime compared to before. Furthermore, the treatment guidelines have been modified to halt or at least slow this trend in antibiotic resistance. In 2014, GISP reported that the percentage of reduced azithromycin sensitivity increased from 0.6% in 2013 to 2.5%, and the percentage of decreased cefixime sensitivity increased from 0.4% in 2013 to 0.8% in 2014. Changes in susceptibility occurred even after the exclusion of cefixime as a first-line treatment in a dual therapy combination of ceftriaxone/second-line drug. This trend raises concerns about the potential resistance to the only first-line treatment regimen currently available (ceftriaxone/azithromycin). Therefore, patients with genitourinary or rectal gonorrhea should be checked for oral sexual exposure, and the pharynx should be examined if confirmed [8].

4) CDC guideline: suspected cephalosporin treatment failure

According to the CDC's process for suspected cephalosporin antibiotic resistance, a clinician diagnosing a *N. gonorrhoeae* infection in a patient suspected of cephalosporin treatment failure conducts a culture and antibiotic susceptibility testing of the clinical sample and reports to the CDC after consulting with an infectious disease specialist or STD clinician for guidance on clinical management. Specimens must be sent to the CDC within 24 hours through state and local public health authorities. Health departments should prioritize notification and culture evaluation of the sexual partners of people with *N. gonorrhoeae* infections or reduced susceptibility to cephalosporins that are believed to be associated with cephalosporin treatment failure.

2. Oral HPV infection

Oral HPV infections have attracted increasing attention because the HPV has recently been identified to play an important role in the development of oropharyngeal cancer, and the incidence of HPV-related oropharyngeal cancer is increasing [14]. Sexual experience at an earlier age, a larger number of sexual partners, and changes in sexual behavior, including oral sex, may be associated with an increased prevalence of HPV infection [15]. The main sites of oropharyngeal cancer caused by oral HPV infections are the base of the tongue and tonsils [16]. According to the CDC, approximately 70% of oropharyngeal cancer cases in the United States are caused by HPV. Epidemiologically, HPV-related oropharyngeal cancer occurs more frequently in men younger than 50 years. The prognosis is better than that of non-HPV-related oropharyngeal cancer in terms of clinical response and overall survival [17,18].

Twenty-four types of HPV in the oral cavity (1, 2, 3, 4, 6, 7, 10, 11, 13, 16, 18, 30, 31, 32, 33, 35, 45, 52, 55, 57, 59, 69, 72, 73) are associated with benign lesions, and 12 types (2, 3, 6, 11, 13, 16, 18, 31, 33, 35, 52, 57) are associated with malignant lesions [19,20]. HPV 16 is the most common HPV-related oropharyngeal cancer type, and HPV 33 accounts for up to 10% of HPV-related oropharyngeal cancer types [21,22].

Most HPV infections are self-limiting and asymptomatic and may go unrecognized. Asymptomatic oral HPV infection can spread the virus even with no symptoms. HPV can be spread through genital or anal sex and be transmitted through deep kissing. Therefore, asymptomatic oral HPV infection can increase the risk of transmission of HPV infections. Despite this, there is no test for diagnosing HPV in the oral cavity approved by the US Food and Drug Administration. This makes it difficult to detect oral HPV infection early, which can further increase the risk of transmission of HPV infection. Furthermore, the prevention of HPV is very important because surgical resection is the only way to treat HPV. Vaccination against HPV-related oropharyngeal cancers, including tonsillar and base of the tongue cancers, has been reported to be effective in reducing the prevalence of oral HPV infection in middle-aged adults [23]. Therefore, it is essential to be vaccinated for the HPV to be protected from oral HPV infection [16].

CONCLUSIONS

Oral gonorrhea and oral HPV infections are often asymptomatic, which can increase the risk of disease transmission. In the case of oral gonorrhea, there is a risk of increasing antibiotic resistance to *N. gonorrhoeae*. Oral HPV infections are a major cause of oropharyngeal cancer because of its late symptom onset after infection and difficult early diagnosis before gross lesions are visible. Therefore, efforts should be made to detect patients with oral infections early and prevent transmission. In addition, HPV vaccination is essential to prevent oropharyngeal cancer caused by oral HPV infections.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

J.Y.J. and H.D.J. participated in data collection, designed the study, and wrote the manuscript. S.C. participated in conceptualization coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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