Episode 39: Identifying Lesion-Causing Viral Pathogens

Andrea Ott-Vasconi:

Hello, I'm Andrea Ott-Vasconi and welcome to QuidelOrtho Science Bytes. In this episode we will talk about a virus that millions of people live with globally, herpes. There are two types of the herpes simplex virus, or HSV: type 1, the main cause of oral herpes, and type 2, the main cause of genital herpes. Although treatable, most HSV infections are often asymptomatic or unrecognized, and the management of HSV infections can be complicated.

Here with me today to talk about the herpes simplex virus and the important role of diagnostic testing is Lori Henderson, Senior Global Product Manager at QuidelOrtho. Lori has a bachelor's degree in biology from Bucknell University and has experience in drug discovery and in multiple disease and therapeutic areas within the life sciences industry. She has served as a key team member in the development and launch of several biomedical innovations. In her current role, Lori is responsible for identifying and helping drive development of products to meet clinical and patient needs. Thank you, Lori, for joining me today.

Lori Henderson:

Thanks very much, Andrea, for having me.

Andrea Ott-Vasconi:

Let's start by discussing the prevalence of herpes virus infections in the U.S. and globally. How common is the virus?

Lori Henderson:

Well, actually, the World Health Organization has estimated that globally 67% of people under age 50, or 3.7 billion, have an HSV-1 infection and 13% ages 15 to 49, or roughly 491 million worldwide, have an HSV-2 infection. In the U.S. specifically genital herpes ranks fifth among all sexually transmitted infections in terms of annual new cases, but overall second in terms of the number of people currently living with and trying to manage the disease.

If we apply the WHO disease models to the U.S., at least 195 million people might have genital herpes based on prevalence estimates for the age group of 14 to 49, of which about 48% is HSV-1 and about 12% for HSV-2. Due to more efficient male-to-female transmission, women end up being infected almost twice as often as men. So as you would expect, with the persistent nature of these viral infections, prevalence increases with age, with the highest number of new infections though in adolescents. CDC estimates that there are roughly 776,000 new cases of genital herpes every year.

But unique factors really confound generating solid estimates of all this. So not everyone who has herpes knows it and not every herpes infection causes symptoms, and if it does, it's not always genital. In addition, there is a latent infection stage, and it can be contagious at that point. So most genital herpes infections are transmitted by persons unaware that they have the infection or who are asymptomatic when transmission occurs. In essence, all of this means that the management of genital HSV really needs to address the chronic nature of the infection rather than focusing solely on treating

the acute lesion episode.

Andrea Ott-Vasconi:

Could you describe the clinical epidemiology of genital herpes?

Lori Henderson:

Yeah, sure. First, I want to highlight that HSV-1 and HSV-2 are not distinguishable by their lesion patterns, so in essence, oral versus genital location. It's also important to recognize that the majority of people with a herpes infection have not been diagnosed. There are several studies that have found that only 10 to 25% of HSV-2 seropositive patients actually reported a history of a genital lesion. So many undiagnosed patients have mild or unrecognized infections, yet continue to intermittently shed virus.

While genital herpes is most often caused by herpes simplex virus type 2, approximately a third of those cases are caused by HSV type 1, the strain historically associated with cold sores as a result of oral-to-genital contact. HSV-1 can be passed orally or genitally via contact by the virus with either body site. So genital herpes is most often commonly spread by direct skin-to-skin contact during sex, with symptoms starting about two to 12 days after viral exposure.

Andrea Ott-Vasconi:

What are some of the considerations to take into account when a patient initially presents with a cutaneous or mucocutaneous lesion?

Lori Henderson:

Well, there's actually a broad range of both non-pathogenic and pathogenic etiologies that may lead to cutaneous, oral or genital lesions, and that could range everything from dermatitis to yeast and fungal infections. While there are a variety of potential diagnoses, three members of the herpesviridae family of DNA viruses are really the most common causes of these lesions, specifically herpes simplex viruses 1 and 2, and varicella zoster virus.

So just to give a little bit of background, the herpesviridae family of DNA viruses is actually quite large. There are 115 different species identified as of 2020. However, really only five members of this family are recognized as very common human pathogens. There's herpes simplex viruses 1 and 2 that are both associated with oral, labial and genital lesions. There's varicella zoster virus, also referred to as HHV-3 that is responsible for chickenpox and shingles. There's Epstein-Barr virus, which is known as EBV for short, or HHV-4, that's implicated in several diseases such as mononucleosis. And human cytomegalovirus, also known as HCMV or HHV-5.

The first three I mentioned, herpes simplex 1 and 2 and varicella zoster, all cause an initial infection, including the development of lesions, followed by a latent phase and potential recurrent lesion outbreaks. In the case of varicella zoster, the initial infection is identified as chickenpox, while recurrence is diagnosed as shingles. And interestingly, it may seem that this type of lesion causing infection is more of a 20th century phenomenon, but actually the prevalence of these herpes viruses can be traced back as far as ancient Greece. Hippocrates and other Greek scholars described, observing

these cutaneous spread of herpes simplex infections and describing it as their "creep or crawl."

So the herpesviridae family name is actually derived from the Greek word "herpian," meaning "to creep." And while varicella zoster also has a long recorded history, confirmation that chickenpox and herpes zoster or shingles were due to the same causal viral agent didn't occur until the 1940s.

Andrea Ott-Vasconi:

That's really interesting that they share the same causal agent. What are the symptoms associated with herpes infections?

Lori Henderson:

Looking at it first from a localized perspective, localized herpes infection symptoms may include genital area pain or itching, small bumps or blisters around the genitals, anus, or mouth that develop into ulcers or lesions when those blisters rupture followed by scab formation as the ulcers heal, painful urination, and urethral or vaginal discharge.

Generalized symptoms during initial outbreak commonly are flu-like, and so that includes fever, headache, body ache, and swollen lymph nodes in the groin. Genital herpes infections are often painful, typically first appearing at the body site where the virus entered. So however, the ulcers can show up anywhere regardless, and the infection can be spread to other body areas by touching the sore, much like the Greek description of their creep.

After the initial outbreak, symptoms often recur. And recurrence rates vary widely, but most subsequent outbreaks are in the first year after infection and may happen less often over time. Symptoms during these recurrent outbreaks may not last as long and may not be as severe as that initial outbreak.

Andrea Ott-Vasconi:

And how is genital herpes diagnosed? Can it be done by visual assessment alone?

Lori Henderson:

No, it can't. It can't be done by visual presentation alone because patients often present with these nondescript lesions. Cutaneous and mucocutaneous lesions may be indicative of other pathogenic conditions, including varicella zoster herpes viral infections, or non-infectious dermatological conditions that I mentioned earlier, such as psoriasis or dermatitis. Because clinical management of these conditions are distinct, a differential diagnosis of the lesion is really critical.

Clinical diagnosis of genital herpes can be difficult because the self-limiting recurrent vesicular or ulcerative lesions classically associated with herpes simplex virus are absent in many infected persons at the time of clinical evaluation. If it happens that genital lesions are present, a clinical diagnosis of genital herpes should be confirmed by type-specific virology testing from the lesion using a molecular testing methodology. CDC guidelines recommend that HSV nucleic acid amplification tests, or NAATs, N-A-A-T-S for short, are used because they're the most sensitive for detection of HSV from genital ulcers or other mucocutaneous and cutaneous lesions. These tests are increasingly available, including multiplexed assays that provide a differential diagnosis between HSV-1, HSV-2, and VZV from lesion swabs.

I wanted to mention that culture is still utilized in some low resource settings, but that sensitivity of these viral cultures can be low, especially among people who have recurrent or healing lesions where the viability of a swab sample can be inadequate for that culture.

Andrea Ott-Vasconi:

Why is it important to get diagnosed and to determine the type of HSV a person has?

Lori Henderson:

Yeah, that's an important question. First, there are effective antiviral treatments for genital herpes that can reduce the severity and duration of an outbreak and sometimes even avert it. But there are treatment regimen differences depending on which herpes virus is present. So it is important to identify the causative viral strain to best manage the patient treatment.

With an HSV-1 infection, drug therapy is generally consistent across initial and recurrent episodic outbreaks with the same dose of one of the three typical antivirals that's available being prescribed in all cases. However, for HSV-2 infections, the treatment regimen for initial and recurrent episode outbreaks is different. So with a recurrent HSV-2 outbreak typically it's treated with a high antiviral dose for a shorter duration of time. Also, in patients with chronic persistent HSV-2 infections, often a daily low dose antiviral therapy is considered because it's been shown to reduce the frequency of these recurrent outbreaks. However, this type of suppressive therapy is currently not recommended for HSV type 1 infections due to a lack of similar clinical evidence showing effectiveness.

Another reason that it's important to obtain a confirmed diagnosis is to aid in reducing the spread of the virus. There is a misconception that herpes cannot spread as long as lesions are not present, and that's just not true. Early diagnosis and appropriate treatment can reduce the risk of transmission. Early diagnosis is really also important in managing sexually transmitted disease co-infection risks and comorbidities. Similar to many other STIs, the presence of a genital herpes infection and genital lesions has actually been linked with an increased risk of HIV acquisition during sex.

CDC 2021 STI Treatment Guidelines concluded that an HSV-2 genital herpes infection can actually increase the risk for acquiring HIV two to threefold. And also, to back this up with the biology that is behind this, research has shown that HIV may be actually stimulated to replicate more than it would otherwise in the presence of an active herpes virus. So what happens is there's increased HIV replication and viral load, which can lead to a compromised immune system and eventually full-blown AIDS.

Conversely, a definitive diagnosis of a genital lesion infection in an HIV patient is important for appropriate therapeutic management since it's more challenging to treat concomitant genital herpes in a confirmed HIV case. In those instances, a higher antiviral drug dosage is often required to treat the recurrent outbreak.

Andrea Ott-Vasconi:

And what molecular diagnostic testing platforms are available for herpes lesion testing?

Lori Henderson:

Well, as I mentioned earlier, the nucleic acid amplification tests, or NAATs, are recommended for definitive identification and differentiation. Currently, there are a number of PCR method platforms available that fit into this category. One that I'll mention is there are a higher complexity test offerings out there that are typically performed in central lab settings geared to running these higher complexity tests on high throughput instrument platforms. In this kind of situation, specimens are collected at the point of care and sent to the central lab for testing, with results turned back to the patient typically in a day or two other.

Other, more recently available options include moderately complex testing solutions. So with these assays, the workflow and test throughput volumes support use in smaller to mid-size healthcare facilities and physician office laboratories.

Andrea Ott-Vasconi:

Where is molecular herpes lesion testing headed next?

Lori Henderson:

Well, interestingly, while there are current commercially available PCR tests that do provide a high degree of sensitivity and specificity to aid in the accurate diagnosis of these cutaneous and mucocutaneous lesions, one of the challenges that remains is patient loss to follow up when test results take days. So a point-of-care testing option that provides a molecular result during an initial patient visit will really enable a true test-and-treat model by supporting immediate initiation of appropriate therapy and patient management. An assay with a turnaround time of minutes, rather than days, would actually provide a result while the patient is still onsite in a physician's office or an STI clinic, so the treatment can be initiated right away.

Also, this kind of assay turnaround time can help support partner notification and testing. While there isn't much perceived stigma around getting a cold sore, patients receiving an HSV-2 diagnosis then can be appropriately counseled by clinical staff in the moment, rather than the patient being told days later and then grappling on their own with the fear and uncertainty of how they're going to manage this situation and disease, and also how they're going to disclose their status to partners. So with a delayed result patients may end up foregoing both antiviral treatment, as well as notifying their partners, as their lesions now start to begin to heal and they pass through that relatively limited timeframe symptom window. The pressure to do so really isn't there any longer, until they have a recurrence or a partner now experiences an initial outbreak.

So really overall, an assay that can deliver a rapid, central lab equivalent molecular result with a user-friendly workflow is going to allow for this testing near-to-patient in decentralized settings that's going to better support overall outcomes and reduce spread of infection.

Andrea Ott-Vasconi:

Thank you, Lori, for this very insightful and comprehensive discussion today on HSV. I hope everyone enjoyed this podcast episode. Make sure to review sections within the podcast description with links to

learn more. Based on today's podcast, I'll leave you with our pop quiz. Why is it important to differentiate between type 1 and type 2 HSV when diagnosing a patient? You can go back and listen again if you'd like some more details.

Thank you for listening today. Please subscribe to QuidelOrtho Science BYTES, our monthly podcast, brought to you by QuidelOrtho Corporation, where we are transforming the power of diagnostics into a healthier future for all. Take care.

References and Reading Materials:

World Health Organization. Herpes Simplex Virus. Herpes simplex virus (who.int)

Centers for Disease Control and Prevention. Sexually Transmitted Infections Treatment Guidelines, 2021. Table of Contents - STI Treatment Guidelines (cdc.gov)

Molecular Diagnostics: https://www.quidel.com/molecular-diagnostics/testing-hsv