

# The History and Mystery of VZV in Saliva

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(See the article by Nagel et al, on pages 820–4.)

The development and deployment of varicella vaccine in the United States has almost eliminated chickenpox [1], but herpes zoster (HZ), which is due to reactivation of latent varicella-zoster virus (VZV), remains very much with us [2]. Since 2006, the live attenuated zoster vaccine, similar to but 14 times stronger than varicella vaccine, has been used to prevent HZ by boosting cellular immunity to VZV in older individuals [3]. The zoster vaccine, however, has not achieved widespread uptake for complex reasons, including problematic availability and high expense [4]. Simultaneously with VZV vaccination programs, molecular virologic techniques have emerged and have proven extremely useful, in particular polymerase chain reaction (PCR), for diagnosis of diseases caused by VZV [5–7]. These diseases include cases of mild varicella, HZ, cranial nerve palsies, VZV encephalitis/meningitis, various ocular diseases, and zoster without rash (zoster sine herpette). PCR may be used not only to diagnose these diseases but also to determine if the VZV in question is the

wild type or the Oka vaccine strain [8]. PCR for VZV is mostly performed on specimens from skin rashes or cerebrospinal fluid, but recently PCR has been used to diagnose varicella and HZ using saliva.

What is the history of examining saliva for diagnosis of herpesvirus infections? Around the beginning of this century, a transient decrease in normal immune function was demonstrated by scientists at NASA in astronauts following space travel, which was ascribed to stress responses (eg, increased blood cortisol levels) experienced during space flight [9]. Asymptomatic reactivation of Epstein-Barr virus [10, 11] and cytomegalovirus [9] was demonstrated in astronauts, in some instances by examining saliva for viral DNA. Mehta and colleagues then found VZV DNA in saliva in 30% of *asymptomatic* astronauts, both during and after space flights [12]. This impressive observation led to a study of whether VZV DNA was present in saliva of patients with clinical HZ. In a critical diagnostic study on elderly individuals who were not astronauts, salivary VZV DNA was demonstrated in 54 of 54 patients with HZ [6].

In a follow-up study from the Gilden laboratory, included in this issue of the *Journal*, an effort was made to determine if postherpetic neuralgia (PHN) complicating and following HZ might be associated with the prolonged presence of VZV DNA in saliva, suggesting chronic ganglionic infection [13]. The saliva of elderly patients with and

without a history of PHN after HZ, as well as healthy elderly controls with no history of HZ, was tested for VZV DNA. Among HZ patients, 21 of 32 (67%) had VZV DNA in saliva, compared with 2 of 17 (12%) controls ( $P = .001$ ). Perhaps unexpectedly, however, the presence of salivary VZV DNA was similar in patients following HZ, whether they had PHN or not. This suggested that prolonged replication of VZV is unlikely to explain PHN, which has therapeutic implications regarding prolonged antiviral therapy for this often-severe illness. Interestingly, this result was not exactly in agreement with the hypotheses of these investigators; earlier studies had suggested prolonged VZV replication in patients with PHN. On the other hand, the current results provide a clue as to how VZV might stimulate long-term immunity to the virus, by subclinical reactivation with resultant stimulation of specific immune responses.

Like many successful research investigations, the current study raises a number of additional questions. One is why is VZV DNA present in saliva? This finding is understandable if a zoster rash is on or near the face, but even people with a zoster rash on the extremities have VZV DNA in saliva. Does this indicate that reactivation of VZV occurs in distant dermatomes at the same time? If so, why should VZV frequently reactivate simultaneously in the trigeminal ganglion and in a distant ganglion? Might such a phenomenon be related to the VZV latency burden in ganglia in

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various locations? Is asymptomatic reactivation of VZV common, and does it produce VZV in saliva? It would be useful to have additional information on larger numbers of healthy individuals, further refining what percentage of varicella-immune individuals shed VZV DNA in saliva over time. Finally, because VZV DNA is present in saliva after vaccination to prevent HZ [14], is this the result of viremia that leads to VZV DNA in saliva, and how is this mechanism related to what occurs in HZ?

There has been great interest in an illness that has been termed zoster sine herpette, or HZ without rash, for many years. Clinicians are used to rejecting VZV from the differential diagnosis in patients if no rash is present even though the patient may have other symptoms of VZV infection such as unexplained unilateral pain or cranial nerve paralysis. It is becoming clear, thanks in great part to the use of PCR, that VZV can cause disease without rash. Possibly the first recognition of this phenomenon was in patients infected with human immunodeficiency virus who developed VZV encephalitis without rash [15–17]. In these patients, the diagnosis was made by detecting VZV DNA in cerebrospinal fluid. It was then observed that in significant numbers of patients with facial paralysis without rash, VZV DNA was also demonstrable in their saliva [18]. Now one wonders whether individuals who have dermatomal pain in the absence of facial paralysis and rash, true zoster sine herpette, also may have HZ that can be demonstrated by studying their saliva.

Recently, it has been found that VZV DNA is frequently present in saliva and urine in patients with varicella [5]. Interestingly, the time-honored means of identifying VZV disease, measuring antibodies in acute and convalescent serum samples, does not seem to measure up to PCR in either sensitivity or rapidity, and

may be simply outdated for diagnosis of disease [5].

Another question remains regarding detection of salivary VZV DNA for diagnosis. What is the best method to collect saliva? A variety of collectors are commercially available, and some investigators have simply used swabs for this purpose. The most sensitive and specific means to identify VZV DNA in saliva deserves further exploration. In addition, more information on the possible infectiousness of VZV in saliva is necessary and could have utility for infection control.

At present, however, it is clear that identifying VZV in saliva is becoming a useful, rapid, and noninvasive means for diagnosis of VZV infection. Although it does not seem that there is a causal relationship of the presence of VZV DNA and PHN, the persistence of the viral footprint after clinical disease deserves further exploration to uncover its true meaning.

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