Herpes Zoster: New Insights Provide an Important Wake-Up Call for Management of Nosocomial Transmission

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(See the article by Lopez et al. and the brief report by Mehta et al., on pages 646–53 and 654–7, respectively.)

Two studies in this issue of the Journal illustrate the use of molecular diagnostic and epidemiological approaches that improve our understanding of herpes zoster (HZ) and its management. HZ remains a significant medical problem, occurring in an estimated 600,000 patients per year in the United States [1]. The prompt use of effective antiviral agents has decreased morbidity and mortality from acute HZ, particularly in the immunocompromised host, but has had little impact on the incidence of persistent neuropathic pain [1]. Although an effective vaccine that prevented 51.3% of HZ in vaccinees over the age of 60 years is licensed in the United States, its use is not yet widespread [2]. In the meantime, the combination of an aging population and increased use of immunosuppressive agents are likely to lead to an increase in the incidence of HZ [1]. In a population such as that in the United States, where coverage with the Oka varicella vaccine is high and circulating varicella-zoster virus (VZV) is low, cases of HZ may be an important source of those outbreaks of chickenpox that do occur [1].

The article by Lopez et al. [3] describes one such outbreak of varicella in a long-term-care facility, originating from an elderly patient with HZ. Although virus from the index case patient was not available, samples from contacts and the environment both near to and remote from the index case patient contained identical wild-type viruses. The presence of a unique polymorphism in all of the viruses and the absence of other varicella or zoster cases in the facility provided further evidence for nosocomial transmission. This report highlights a number of intriguing features. First, despite the lesions being covered, virus from the index case patient caused widespread environmental contamination and was transmitted to 3 other residents. Although environmental contamination and putative transmission of airborne virus from patients with HZ to remote contacts has been described previously [4–9], this report is the first to conclusively link the two. The data provide further evidence for HZ as a significant infection control risk, probably more so than varicella in highly immune populations [10]. Covering lesions with gauze and clothing does not eliminate environmental contamination with VZV DNA from patients with HZ, although one report failed to detect VZV shedding if lesions were covered with an occlusive hydrocolloid dressing [9].

Two contacts in this outbreak who developed varicella appeared to have had primary infection, whereas the third had high antibody avidity, indicating reinfection. Primary varicella in adults is often severe, and the fact that all 3 cases were mild is unusual. The virus in this outbreak carried a nonsynonymous single-nucleotide polymorphism (SNP) at position 107252 in open reading frame 62, which codes for a serine to glycine substitution at amino acid position 628 and which previously has been described only in the Oka vaccine strain [11, 12]. The vaccine SNP at 107252 is 1 of only 3 that are consistently present in all Oka vaccine viruses (the so-called fixed vaccine mutations) and hitherto had not been described in wild-type strains, including the parental Oka strain from which the vaccine was derived. The same polymorphism has apparently been described in wild-type strains in the United States [3]. This, together with the fact that the index case patient in this outbreak had zoster (indicating reactivation of a virus that was circulating many years before), makes it extremely unlikely that this virus was a recombinant with the Oka vaccine. However, given the evidence for extensive recombination among strains of VZV [13, 14], more work in this area is needed. Although the virus was clearly transmissi-
ble, the mild nature of the varicella cases raises the possibility that the substitution of a glycine for a serine at position 628 (107252) is associated with attenuated viral virulence. At the same time, it is also possible that all 3 subjects experienced mild recurrent infection. Antibody avidity has been shown to decline in the elderly [15], and there is some suggestion that even some younger individuals sometimes fail to make highly avid antibody (J.B., unpublished data). Reinfection after wild-type varicella has been estimated to occur in 13% of children, but rates are poorly documented in adults [16].

In the second study in this issue, Mehta et al. [17] detected VZV DNA in saliva from all 54 patients presenting with HZ examined and infectious virus in 1 of 2 whose saliva was cultured. Although detection of VZV DNA in the saliva of patients with HZ and Bell palsy has been reported previously, these authors are the first to demonstrate that salivary virus may be infectious [18, 19]. There are no reports that conclusively demonstrate transmission from case patients with HZ before the appearance of a dermatomal rash. However, the finding by this group of viral DNA in the saliva of a young woman with prodromal pain provides a compelling rationale for further investigation. This case also makes less likely the possibility that viral DNA—and indeed live virus—in saliva results from the inhalation of particles shed from the skin, as has been suggested by others [9]. However, since the patient from whom live virus was isolated had upper-body HZ, more data on patients in whom HZ is located distal from the head and neck would be informative. Alternative explanations as to how virus reaches the saliva are proposed by the authors, including local reactivation from head and neck ganglia and viremic spread. Detection of viral DNA in the blood of patients with acute HZ is well recognized [20, 21], but how and when infectious virus is transferred in the blood to oral mucosa is not clear.

Mehta et al. report fascinating data on the association between higher salivary viral load and more severe pain as well as between shedding of virus beyond 15 days and persisting high pain scores. These findings complement previous reports linking the extent of rash with the severity of acute pain [22] as well as others in which high baseline blood viral loads are associated with prolonged pain [21]. Whether ongoing postherpetic neuralgia is related to viral replication and viral load remains unclear. The relationship found by Mehta et al. between the persistence of salivary virus shedding beyond the acute rash and prolonged pain needs further investigation. A simple test at the time of acute disease that could predict poor outcome would be a powerful tool in the management of HZ and postherpetic neuralgia.

So, what lessons can we learn from these cases? First, HZ may be infectious even when lesions are covered. Aerosolised virus from skin, and possibly from the respiratory tract, may cause infections in patients who are not in direct contact with the index case patient. Nosocomial infections in developed countries with childhood infection are more likely to occur from cases of HZ than varicella [10], and this is even more true in a highly immunized population, in which circulation of VZV is low. Although current guidelines recommend the covering of HZ lesions as a means of preventing nosocomial spread and do not recommend the isolation of all affected patients [23], the reports presented here suggest that this advice may need to change. Programs to immunize adults (especially staff or residents of long-stay facilities) against VZV should be ongoing, and evaluation of the benefits of vaccination against HZ in such facilities is urgently needed. Finally, there is much we still do not know about VZV infection and spread. The intelligent use of molecular diagnostics, genotyping, and serology has raised questions about reactivation, viral virulence, and viral shedding. In the absence of easily available animal models of VZV infection, investigations such as those described in this issue of the Journal provide fascinating insights into the natural history and pathogenesis of this virus.

References