ORIGINAL RESEARCH

# What is the True Etiology of "Recurrent Shingles"?

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## ABSTRACT

**Purpose:** To determine the true etiology of cases of putative recurrent shingles referred to a dermatology clinic.

**Methods:** A prospective cohort study of patients aged 15-87 years with reported recurrent herpes zoster was conducted. Vesicular fluid and serology for herpes simplex 1, 2, and varicella zoster virus immunoglobulins were obtained from patients presenting with vesicles. Biopsies were obtained from patients with ambiguous presentations.

**Results:** 44 patients (56%) had evidence of herpes simplex virus infection. 32% of patients had positive herpes simplex virus cultures or polymerase chain reaction sequencing, and 24% additional patients were diagnosed with presumptive simplex infection based on elevated antibody titers. 44% of patients had a diagnosis other than zoster or simplex. One individual had a positive viral culture for varicella zoster virus. 99% of patients who presented with suspected recurrent herpes zoster had no definitive evidence of varicella zoster virus reactivation.

**Conclusions:** The most common diagnosis was herpes simplex infection. Our results suggest that true recurrent shingles in immunocompetent patients is rare.

## INTRODUCTION

Herpes zoster (shingles), caused by reactivation of latent varicella–zoster virus, is characterized by a painful unilateral vesicular rash in a dermatomal distribution. The incidence and severity of herpes zoster increase with age, in association with a decline in cell-mediated immunity.[1] The infection is usually limited to a single occurrence; recurrence is typically characteristic of immune compromise.[1] In immunocompetent persons, recurrent herpes zoster is thought to be rare, with an estimated incidence of 1-3%.[1] However, many immunocompetent persons report being diagnosed with recurrent herpes zoster, and recent studies have suggested that the incidence of herpes zoster recurrences is more frequent than previously reported, typically greater than 6%.[2,3] Moreover, it is reported that immunocompetent patients often experience more than two to three recurrent episodes, particularly in the same dermatome.[2,3] However, the plausibility of recurrent herpes zoster has also been debated, with many clinicians hypothesizing that recurrent zoster in immunocompetent patients is often a

misdiagnosis.[4-8] The purpose of this study was to determine the etiology of cutaneous eruptions that have been previously diagnosed as “recurrent shingles”.

## METHODS

We performed a prospective cohort analysis of 78 patients who were referred to a community outpatient dermatology clinic with “recurrent shingles”. IRB approval was not needed as all patients received the standard of care. Inclusion criteria consisted of a unilateral zosteriform rash, reported recurrence at same anatomical site, and/or recurring pain/discomfort at the same anatomical site. Immunosuppression from illness and/or use of immunosuppressive agents were considered exclusionary. Vesicular fluid was collected for varicella zoster virus / herpes simplex virus 1 and 2 viral culture or polymerase chain reaction (PCR) analysis. For lesions without vesicles or in the absence of primary morphology, herpes simplex-1 and -2 IgG specific antibody assays were obtained. Results were considered positive if IgG titers were elevated. For clinically ambiguous presentations, skin biopsies were performed.

## RESULTS

Subjects were between 15 and 87 years of age; the average age was 54 years with a standard deviation of 19.4. 77% of patients were female (n=60). 32% of patients presenting with recurrent herpes zoster had positive herpes simplex virus cultures or PCR, and 24% additional patients were diagnosed with presumptive simplex infection based on elevated antibody titers. 44% of patients had a diagnosis other than zoster or simplex. One individual had a positive viral culture for varicella zoster. 99% of patients who presented with suspected recurrent herpes zoster had no definitive evidence of varicella zoster virus reactivation. 43 patients (56%) had evidence of herpes simplex virus infection (Table 1).

## DISCUSSION

Our results suggest that true recurrent shingles in immunocompetent patients is rare, as only 1 out of 78 patients had definitive evidence of latent varicella zoster virus reactivation. While population-based studies suggesting that recurrences are common utilize a larger sample size[2,3], their results are confounded by the inclusion of immunocompromised patients and the lack of sufficient laboratory or supporting data. To date, there has only been one large published report of laboratory-confirmed recurrences in immunocompetent patients over age 60: a herpes zoster vaccine study found that in a total of 1646 cases of established herpes zoster, only 5 were deemed recurrences.[9] In immunocompetent patients, recurrent episodes occur in 1% to 6% of cases.[10-13] Our results emphasize the importance of diagnostic validity in classifying cases as true recurrent shingles.

In our study, the most common diagnosis was herpes simplex infection (57%). Herpes simplex virus 2 was attributed to most cases involving the buttocks while herpes simplex virus 1 was most frequently isolated on lesions presenting on the face (Table 2). These anatomical distributions correspond to the sites of latency of herpes simplex virus 1 and herpes simplex virus 2 infection - in the first and second divisions of the trigeminal ganglion and in the sacral sensory ganglia, respectively.[14] Furthermore, the average rate of recurrences reported by patients (monthly for sacral/ herpes

**Table 1.** Final diagnoses and characteristics of patients presenting with putative recurrent herpes zoster.

| | Number (N = 78) | Percentage |
|---|---|---|
| **Final Diagnosis** | | |
| Herpes simplex eruption | 44 | 56% |
| Post-herpetic neuralgia (PHN) | 14 | 19% |
| PHN + Dermatitis | 6 | 8% |
| Folliculitis | 4 | 5% |
| Actinic keratosis | 2 | 3% |
| Contact Dermatitis | 2 | 3% |
| Herpes zoster | 1 | 1% |
| Excoriated ulcer | 1 | 1% |
| Prurigo nodularis | 1 | 1% |
| Fixed drug eruption | 1 | 1% |
| Arthropod assault | 1 | 1% |
| **Anatomic Distribution** | | |
| Head/neck | 19 | 26% |
| Chest/Abdomen/Back | 19 | 24% |
| Anogenital (including buttocks) | 30 | 38% |
| Extremities (including posterior thigh) | 9 | 11% |
| Multiple sites | 1 | 1% |
| **Sex** | | |
| Male | 18 | 23% |
| Female | 60 | 77% |

simplex virus 2 eruptions) and (every 3-4 months for trigeminal/ herpes simplex virus 1 eruptions) are consistent with rates of recurrent simplex infection[14], suggesting that more recurrences of vesicles suggest a much greater possibility of herpes simplex virus. Zosteriform herpes simplex virus infections are encountered in up to 25% of the cases initially diagnosed as herpes zoster on a clinical base, particularly in the facial dermatomes.[15-19] These eruptions occur in both primary and recurrent infections, and are observed in patients of all ages.[15-19] In addition, well-characterized manifestations of herpes simplex infections including herpes gladiatorum (n=2) and genital herpes (n=2) were also referred to our clinic as presumed recurrent shingles (Table 2).

Women have “recurrent shingles” due to herpes simplex virus far more frequently than do men; this is particularly true of recurrent vesicles of the buttocks (Figures 1 and 2), and for reasons unknown. Herpes simplex virus reactivation is triggered by a variety of factors, including stress, UV-irradiation, or immunosuppression, along with menstruation and changes in female sex hormones. However, this does not appear to be sufficient to trigger varicella zoster virus reactivation.[20]

Post-herpetic neuralgia was implicated in many cases of “recurrent shingles” and can be characterized further as post-herpetic neuralgia with overlying unrelated skin conditions and post-herpetic neuralgia without cutaneous manifestations (Table 1). Post herpetic neuralgia was diagnosed in 14 patients (19%) who presented with unilateral recurrent intense pain or pruritus at a site of previous shingles and had no clear clinical or diagnostic abnormalities. Post-herpetic neuralgia is the most common complication of herpes zoster, and a significant cause of morbidity.[9-11] Recognition of post-herpetic neuralgia allows for treatment to be tailored towards analgesic relief.

Overlying skin conditions included folliculitis, actinic keratosis, prurigo nodularis, contact dermatitis, fixed drug eruption, and arthropod assault. In addition, histopathology revealed a variety of nonspecific inflammatory patterns (spongiotic, interface, perifollicular, and perivascular dermatitis). A variety of conditions are known to mimic the

**Table 2.** Characteristics of Herpes Simplex Infection.

| | Gender | Method of Detection | Location | Average Recurrence Rate |
|---|---|---|---|---|
| **HSV-1** | Male: 3<br>Female: 8 | PCR/Viral Culture: 4<br>Serology: 7 | Trigeminal: 4<br>Abdomen: 1<br>Buttocks: 2<br>Thoracic: 1<br>Suprapubic: 1<br>Herpes gladiatorum: 2 | Every 3-4 months |
| **HSV-2** | Male: 5<br>Female: 28 | PCR/Viral Culture: 17<br>Serology: 16 | Buttocks: 22<br>Posterior Thigh: 5<br>Thoracic: 3<br>Trigeminal: 1<br>Genital herpes: 2 | Every 30 days |

**Figure 1.** Recurrent vesicular eruption on the buttock of a female patient

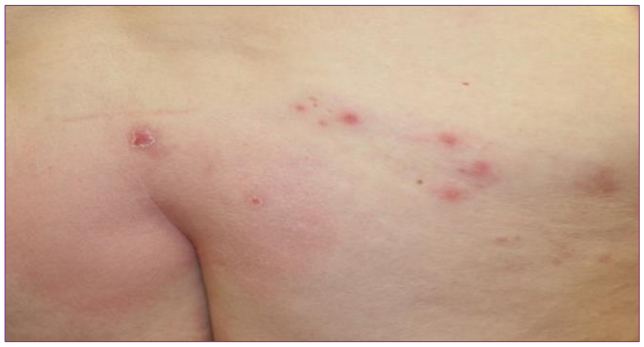
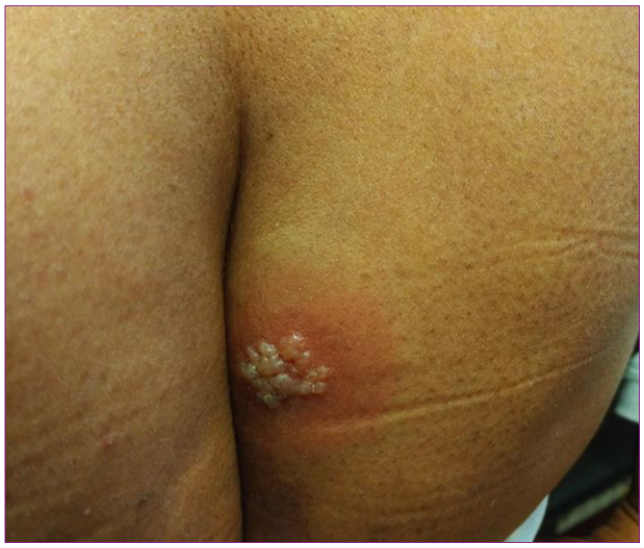


**Figure 2.** Recurrent vesicular eruption on the buttock of a female patient



appearance and distribution of herpes zoster, including Staphylococcal skin infections[21], impetigo[22, 23] bullous lesions[24], and lichen planus[25]. Such entities may be attributed to Wolf's isotopic response, which describes the phenomenon of a cutaneous eruption that develops at the site of a healed, unrelated skin disease - most commonly herpes zoster. Recognition of this phenomenon allows the clinician to treat the primary illness.

Determining the etiology of the "recurrent shingles" has public health implications given the transmissibility of herpes simplex virus in comparison to varicella zoster virus. Approximately 12% of patients aged 14-49 are herpes simplex virus 2 seropositive and 48% are herpes simplex virus 1 seropositive.[26] In comparison, 99% of adults are varicella zoster virus seropositive due to natural infection with wildtype chickenpox or vaccination. Therefore, a person with "recurrent shingles" due to herpes simplex virus may unknowingly transmit the infection.

A limitation of this study is that it cannot establish with certainty a causal relationship between the patient presentation and HSV titers with IgG alone; only a presumptive diagnosis of HSV infection can be made based on serology, which indicates past exposure or recent shedding. Many patients

who are seropositive for herpes simplex virus, especially type 2, were unaware of their symptoms or had subclinical infection and were unlikely to present for culture or PCR analysis.

## CONCLUSION

In this study, laboratory evidence substantiated the clinical observation that the most common sites of suspected recurrent herpes zoster correlate with sites where herpes simplex virus 1 and 2 infections typically present, on orolabial and anogenital skin, respectively. Differentiating between zoster and simplex is critical in reducing transmission of infection. Post-herpetic neuralgia, including cases with superimposed unrelated cutaneous manifestations, was also commonly misdiagnosed as recurrent shingles. Our results support that herpes simplex virus commonly recurs but recurrence of zoster in immunocompetent individuals is rare.

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