Triaging Herpes Zoster Ophthalmicus Patients in the Emergency Department: Do All Patients Require Referral?

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Abstract

**Objectives:** The objective was to assess the predictive value of clinical signs and symptoms of herpes zoster ophthalmicus (HZO) for development of moderate to severe eye disease.

**Methods:** This was a prospective cohort multicenter study of 54 patients referred to the ophthalmology service after presenting to the emergency department (ED) or primary care clinic with a zosteriform rash of less than 10 days’ duration. Upon referral to ophthalmology, easily assessable clinical signs and symptoms were documented. A complete ocular exam was then performed. Patients were followed for 2 months.

**Results:** Twenty-three patients (43%) developed moderate to severe disease as defined by corneal or intraocular involvement. Eye redness and rash in the supratrochlear nerve distribution had a statistically significant association with clinically relevant eye disease. All 23 patients who developed moderate to severe eye disease presented with a red eye. Hutchinson’s sign (nasociliary nerve involvement) was not predictive of clinically relevant eye disease.

**Conclusions:** Eye redness was 100% sensitive for predicting moderate to severe eye disease in this sample of patients and should necessitate immediate referral for ophthalmologic assessment. Patients lacking eye redness, even with a positive Hutchinson’s sign, may not require immediate specialist consultation. All patients not being referred require careful instructions to seek further care should they develop any concerning eye symptoms such as redness, pain, photophobia, or visual disturbance.

**Keywords:** herpes zoster ophthalmicus, prognosis, treatment, risk factors, primary care

Herpes zoster ophthalmicus (HZO) is a common cause of ocular disease with potentially devastating complications. Varying rates of ocular involvement are described in the literature, with most studies reporting between 50% and 80% of patients developing some form of ocular inflammation. Despite the potential for vision-threatening complications such as keratitis, uveitis, retinitis, and optic neuritis, a significant number of patients experience little or very mild ocular involvement. Furthermore, multiple studies have shown that prompt systemic antiviral therapy of HZO significantly reduces the rate and severity of ocular involvement.

Rash involvement in the cutaneous region of the terminal branches of the nasociliary nerve, commonly known as Hutchinson’s sign, has been reported to have positive predictive value for ocular involvement. This clinical sign has rarely been assessed prospectively and, to our knowledge, never with respect to other areas of rash distribution. Figure 1 depicts the peripheral nerve distribution for the nasociliary, supratrochlear, and supraorbital nerve. Although studies have shown Hutchinson’s sign to be significantly associated with eye disease, to our
knowledge, only one study discriminates the severity of eye involvement.\(^8\)

Clearly not all patients with HZO require ophthalmologic care; however, due to the variability of eye involvement and potential for vision-threatening complications, it has been our experience that many primary care practitioners automatically refer all patients with HZO for ophthalmologic assessment. Moderate to severe eye disease is most commonly managed with a combination of systemic antiviral medication and topical cycloplegia and steroids. Some patients require treatment for complications from intraocular inflammation such as glaucoma.

It has been our experience that many patients referred to our service from the emergency department (ED) lack any identifiable ocular inflammatory symptom or sign. In discussions with emergency physicians it is clear that there is no agreed-upon criteria for referral of these patients. The aim of this study was to attempt to evaluate various signs and symptoms associated with HZO, with the assumption that individuals or in combination, certain clinical signs and symptoms are predictive of moderate to severe ocular involvement. We analyzed signs and symptoms that would be easily elucidated by a nonophthalmologic primary care or emergency physician with or without access to a slit lamp (such as Hutchinson’s sign). We attempted to create a clinical decision-making tool for primary care and emergency physicians to identify which patients require ophthalmologic assessment.

**METHODS**

**Study Design**

In this multicentered prospective cohort study, we recruited patients referred to the on-call ophthalmology service at two Canadian university-based residency programs. This study was approved by the institutional review boards of Hamilton Health Sciences and St. Joseph’s Healthcare Hamilton. Informed consent was obtained from all patients. Research adhered to the tenets of the Declaration of Helsinki.

**Study Setting and Population**

All immune-competent patients with a unilateral zosteriform rash in the V1 or V2 distribution presenting within 10 days of rash onset, regardless of antiviral therapy, were recruited upon referral to the ophthalmology service. The study was advertised to the EDs and university-affiliated family medicine clinics that use the on-call ophthalmology services. The following patients were excluded: children under 18 years of age, history of herpes simplex keratitis, previous HZO (on affected eye), or any eye surgery within the past 6 months.

**Study Protocol**

Upon presentation to the ophthalmology clinic, a study questionnaire was administered that recorded visual acuity, diplopia, discharge, prodromal symptoms, rash onset, and rash location. Rash location was recorded in detail by subdividing the cutaneous branches of the trigeminal nerve (Data Supplement S1, available as supporting information in the online version of this paper). The subjective symptom of photophobia was standardized by pointing a pen light at the affected eye and asking if this elicited pain. Other questions included a four-point pain scale and a rash grading scale (Data Supplement S2, available as supporting information in the online version of this paper). Presence of eye redness was defined by any conjunctival hyperemia compared to the contralateral eye. Disease-specific treatments initiated by the referring emergency physician were recorded, including any antiviral therapy. The patient was then examined by one of two authors (RA or MB) and a study form was completed that made specific note of any blepharitis, conjunctivitis, various forms of keratitis (punctate, mucous plaque, dendritiform, interstitial, disciform, or necrotizing), anterior or posterior uveitis, retinitis, or any cranial neuropathy. Treatment was initiated based on the clinician’s discretion.

Numerous studies testing a range of laboratory investigations have concluded that no tests effectively increase diagnostic accuracy compared to the clinical exam in diagnosing various manifestations of varicella zoster disease. We therefore relied on clinical diagnosis and did not perform laboratory testing (such as polymerase chain reaction or enzyme-linked immunosorbent assay).\(^9\)–\(^11\) Determination of immune competency was based on medical history alone, including a functional inquiry, with patients below the age of 50 years referred for systemic evaluation with their primary care physician.

**Measurements**

The primary outcome measure was development of potentially harmful eye disease, defined a priori as any keratitis or uveitis. This was determined at baseline exam, with all patients scheduled to be seen again at 2 weeks and 2 months to detect delayed eye involvement. At each visit, a complete ophthalmologic exam was performed. The 2-month exam included measurement of corneal sensation using a Cochet-Bonnet corneal esthesiometer. Patients with ocular disease requiring treatment were followed more frequently as
needed. All patients were asked to schedule visits if any eye pain or visual disturbance developed between appointments.

Data Analysis
Descriptive statistics were performed. Categorical variables were reported as counts and percentages and were compared using a chi-square test. Continuous variables were reported as means and standard deviations (SD) and compared using logistic regression. Clinically important and potentially harmful eye disease was defined a priori as any corneal involvement or any intraocular inflammation. Explorative analysis in Stata version 11.0 (StataCorp, College Station, TX) across demographics, antiviral therapy, symptoms, and signs was performed to determine which parameters were associated with 100% sensitivity for predicting the development of clinically relevant disease. If no single parameter was identified, parameters were analyzed in combination. In up to three additional iterations, a new parameter or combination of parameters was sought that was 100% sensitive in selecting for more severe disease on the subset of patients positive for the previous parameter(s). This process, similar to classification and regression tree analysis, was used to generate a decision rule and classification tree. A stop-point, which was defined prior to analysis but after the collection phase, was defined as a rule that obtains a sensitivity of 100% and specificity > 70%. This process was limited to a maximum of 10 candidate decision scores and was therefore evaluated at the 0.005 level (adjusted for multiple comparisons using the Bonferroni method). A p-value of 0.05 was considered for statistical significance for all other tests. All tests were two-sided.

RESULTS
We recruited 54 patients during the 2-year study period, of whom 31 (57%) were male. The mean ± SD age was 60.2 ± 17.6 years (range 20–93). There were 42 (78%) patients who received oral antiviral therapy, including 26 (62%) within the recommended 72 hours of rash onset. At least one follow-up appointment was attended by 48 (89%) patients, and 38 (70%) completed all visits including the final 2-month exam. All patients not returning for follow-up examinations were successfully contacted by telephone and stated that they did not want to return because they had no ocular problems.

Of the 54 patients, 14 (26%) did not develop any eye involvement at all, and 17 (31%) had eye involvement limited to blepharitis or conjunctivitis. There were 23 (43%) patients with more pronounced disease. These included various degrees of superficial corneal involvement such as punctuate epithelial erosions, dendritiform keratitis, or mucus plaque keratitis. In addition, 11 of these patients (20% of total) developed anterior uveitis, and two (3.7% of total) of these patients developed immune stromal keratitis. There were no cases of posterior uveitis, retinitis, optic neuritis, or other cranial neuropathy. Corneal sensation was measured in 34 (63%) patients at 2 months, and eight (24%) of these patients developed decreased corneal sensation. Table 1 outlines by visit the distribution of ocular findings.

Only eye redness and rash in the supratrochlear nerve distribution (forehead above nasal bridge) had statistically significant associations with moderate to severe eye disease. These values, and others of interest, are presented in Table 2. All 23 patients who developed clinically relevant eye disease presented with a red eye. Of the 10 patients with a red eye who did not develop more than mild eye disease, classification analysis (p < 0.0001) shows that seven patients would have been referred with a red eye unnecessarily after eliminating three more patients who did not have either photophobia or supratrochlear rash distribution. The classification tree has 100% sensitivity and 77% specificity; it is presented in Figure 2.

Hutchinson’s sign (nasociliary nerve involvement) was not predictive of clinically relevant eye disease (p = 0.18). When analyzed for its predictive value of any eye involvement at all, that is to say a positive Hutchinson’s sign in the setting of even limited blepharitis or conjunctivitis, it was still not a significant predictor (p = 0.067). Photophobia (p = 0.19) and supraorbital (forehead above brow) rash involvement (p = 0.104) did not have statistically significant correlations to eye disease either. Figure 1 depicts the peripheral nerve distribution for the nasociliary, supratrochlear, and supraorbital nerve. The development of more severe eye disease was significantly associated with the development of decreased corneal sensation at 2 months, as shown in Table 2.

Table 1
Ophthalmological Involvement by Visit

<table>
<thead>
<tr>
<th></th>
<th>Number Attended</th>
<th>None</th>
<th>Bleph</th>
<th>Conj</th>
<th>PEE/SPK</th>
<th>DK/MP</th>
<th>Inter K</th>
<th>Nec K</th>
<th>AC Rxn</th>
<th>Post Uveitis</th>
<th>CN</th>
<th>Dec K Sens</th>
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</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>54</td>
<td>16</td>
<td>27</td>
<td>30</td>
<td>11</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Visit 2/3</td>
<td>48</td>
<td>24</td>
<td>12</td>
<td>13</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Visit 4</td>
<td>38</td>
<td>27</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any Visit</td>
<td>54</td>
<td>14</td>
<td>30</td>
<td>31</td>
<td>13</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

None = no ocular findings; Bleph = blepharitis; Conj = conjunctivitis; PEE/SPK = punctuate epithelial erosions/superficial punctate keratitis; DK/MP = dendritiform keratitis/mucus plaque keratitis; Inter K = interstitial keratitis; Nec K = necrotizing keratitis; AC Rxn = anterior chamber reaction; Post Uveitis = posterior chamber uveitis; CN = cranial nerve neuropathy; Dec K Sens = decreased corneal sensation.
DISCUSSION

The rate of ocular disease in our study was consistent with previously published data. We had 74% of patients who developed eye involvement; however, only 43% of patients had disease causing corneal or intraocular pathology. Therefore, more than half of patients with eye involvement developed mild disease such as blepharitis or conjunctivitis. All 23 patients with more pronounced disease requiring intervention presented with a red eye.

Supratrochlear distribution of the rash was significantly associated with development of disease (p = 0.0004). This dermatome covers the glabellar and medial brow regions and represents a terminal branch of the frontal nerve (see Figure 1). Rash in this area predicted 21 of 23 patients with disease with 14 false-positives. Contrary to the findings of Zaal et al., the

Table 2
| Clinically Relevant Eye Involvement Associated with Photophobia; Redness; Supratrochlear, Supraorbital, and Nasociliary Rash Location; and Decreased Corneal Sensation |
|-------------|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|             | Yes       | No        | p-value | Sensitivity | Specificity | NPV   | PPV   |
| Photophobia | 9         | 7         | 0.188   | 0.39       | 0.77        | 0.63  | 0.56  |
| No photophobia | 14       | 14       |         |            |            |       |       |
| Redness     | 23        | 10        | <0.001  | 1.00       | 0.68        | 1.00  | 0.70  |
| No redness  | 0         | 21        |         |            |            |       |       |
| Supratrochlear | 21       | 14        | <0.001  | 0.91       | 0.55        | 0.89  | 0.60  |
| No Supratrochlear | 2       | 17        |         |            |            |       |       |
| Supraorbital | 22        | 25        | 0.104   | 0.96       | 0.19        | 0.86  | 0.47  |
| No supraorbital | 1        | 6         |         |            |            |       |       |
| Nasociliary | 18        | 19        | 0.184   | 0.78       | 0.39        | 0.71  | 0.49  |
| No nasociliary | 5        | 12       |         |            |            |       |       |
| Nasociliary | 25*       | 12        | 0.067   | 0.78       | 0.46        | 0.59  | 0.68  |
| No nasociliary | 7         | 10       |         |            |            |       |       |
| Decreased Corneal sensation | 6        | 2         | 0.014   | 0.46       | 0.91        | 0.73  | 0.75  |
| Not decreased | 7         | 19       |         |            |            |       |       |

p-values <0.05 were considered statistically significant.
Yes = had clinically relevant eye involvement; No = did not have clinically relevant eye involvement; NPV = negative predictive value; PPV = positive predictive value.

*Clinically relevant eye involvement definition expanded to include patients with isolated conjunctivitis and blepharitis for the purposes of comparing results of our cohort with those from other studies.

Figure 2. Categorical tree displaying clinical guideline for referral of patients presenting with HZO. HZO = herpes zoster ophthalmicus.
only other paper to prospectively test Hutchinson’s sign, this study did not find Hutchinson’s sign (nasociliary nerve) to be significant (p = 0.18). However, when eye involvement is defined to also include blepharitis and conjunctivitis, as is the case in most previous studies, Hutchinson’s sign does approach statistical significance (p = 0.067). This is consistent with other studies that find Hutchinson’s sign to be useful, but not infallible in predicting intraocular involvement.2,7,12 Zaal et al.13 also found severity of skin lesions and severity of pain to be associated with development of ocular disease; however, our results did not find such significance.

We aimed to develop a triaging tool that would allow primary care and emergency physicians to more accurately determine which patients required ophthalmologic referral. As previously mentioned, over half of all patients did not develop disease severe enough to warrant any intervention, and it is these patients that we seek to identify to reduce the burden of unnecessary referrals for patients and clinicians. Eye redness proved to be a simple but highly sensitive sign for screening patients. No patient developed severe eye disease during the 2 months of follow-up if he or she did not present with a red eye. Although the specificity was only 68%, the absence of a red eye clearly identifies a large group of patients who can be followed by the primary care physician rather than automatically referred to a specialist simply because they have V1 zoster. Our classification tree suggests that specificity can be improved to 77% by also not referring patients who have a red eye but are found to have neither photophobia nor a supratrochlear rash (p < 0.0001). Referral can always be made should these patients develop ophthalmologic symptoms such as increased redness, pain, or decreased vision. In the ED setting patients can be counseled regarding this possibility and told to return to the ED or present to their primary care physician should they develop such symptoms. Other papers have supported the recommendation that not all patients require immediate referral, and our data provide prospective analysis that helps to identify which patients can be safely observed.13

We did not find antiviral therapy to have a significant correlation to development of clinically relevant eye disease. As our study did not randomize patients to treatment groups, it is not an appropriate construct for drawing conclusions in relation to antiviral use. However, several randomized trials have shown systemic antiviral therapy to reduce the incidence and severity of ocular disease.5,6,14 The high rate of antiviral treatment (78%) in our cohort may help explain our inability to capture several of the rarer but potentially devastating forms of eye involvement such as scleritis, posterior uveitis, retinitis, optic neuritis, and motor nerve palsies.1,2,15,16 Previous studies have shown that ophthalmic localization of herpes zoster is an independent positive predictor for primary care and emergency physicians to prescribe antiviral treatment.17 Consistent with the findings of Zaal et al., we found a significant correlation between decreased corneal sensation at 2 months and more severe eye disease (p = 0.014) as shown in Table 2.18

**LIMITATIONS**

Some limitations of this study include the inherent selection bias of referring physician patterns, an investigator bias that did not mask the clinical examiner to the results of the intake questionnaire, loss to follow-up, and the modest sample size, which could not capture the more rare manifestations of HZO. With respect to the referral bias of primary care physicians, this likely resulted in underestimation of our results, as referred patients are more likely to have disease. Regarding loss to follow-up, although 16 patients did not complete all visits, all patients not returning for follow-up were successfully contacted by telephone and they stated that they did not want to return because they had no ocular problems. With respect to rare but severe ocular manifestations, we presume that patients with scleritis, optic neuritis, or retinitis would present with severe pain and/or visual disturbance such that urgent referral would automatically be undertaken. For many of these entities, a red eye would also be expected.

One final limitation was an oversight in data collection, as the referral source (ED or ambulatory/family medicine clinic) was not charted. However, in our university-based on-call services, our experience dictates that approximately 75% of referrals originate from the ED, and we therefore believe this to be a relatively accurate estimation. The clinical decision-making tool generalizes well to both settings, but some practical differences between the ED and a primary care office do exist. For example, an emergency physician may have access to a slit lamp and could therefore detect keratitis or other relevant eye involvement. By no means should the absence of a red eye negate a slit lamp exam should such instrumentation be available. Similarly, all primary care physicians should examine the globe, including fluorescein application, as part of the assessment of a patient with HZO. The ease of follow-up also differs between primary care settings. We recommend that in both the ED and the primary care office, patients should be counseled regarding the possibility of delayed eye involvement including eye redness, eye pain, photophobia, and decreased vision. In the ED setting, patients can be told to return to the ED or present to their family physician, ophthalmologist, or optometrist should they develop such symptoms. This would be similar to patients with zoster of the torso being cautioned regarding the possibility of postherpetic neuralgia or patients with bacterial conjunctivitis being advised to return for further assessment if their ocular symptoms worsen despite treatment. Opstelten and Zaal13 have recommended that referral to an ophthalmologist is indicated in the presence of visual complaints, a red eye, or Hutchinson’s sign early in the course of disease. Our data provide much needed prospective analysis that helps to identify which patients require immediate referral and which can be safely observed.

**CONCLUSIONS**

Using potential development of corneal or intraocular involvement as the standard to necessitate immediate
referral, data from our sample of patients suggest that eye redness is 100% sensitive for predicting moderate to severe eye disease. We therefore stress that patients with any eye redness must be referred for ophthalmologic assessment. Patients lacking eye redness, even with a positive Hutchinson’s sign, should be counseled regarding the potential for eye involvement with carefully documented instructions to seek further care should they develop eye redness, pain, photophobia, or visual disturbance. These conclusions are the result of explorative data analysis, and it is our hope to conduct a confirmative study in the near future.

References


Supporting Information:

The following supporting information is available in the online version of this paper: Data Supplement S1. Data collection sheet for recording areas of rash involvement. Numbered areas correspond to dermatomal distribution of terminal cutaneous branches of the first and second divisions of the trigeminal nerve. Data Supplement S2. Rash grading scale and pain grading scale. The documents are in PDF format.

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