## Title

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# Practice Patterns in the Initial Management of Herpes Zoster Ophthalmicus in the United States

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## Abstract

**Purpose:** To examine the trends in initial management of herpes zoster ophthalmicus (HZO) in the United States from 2010 to 2018 and compare them to the treatment preferences of cornea specialists.

**Methods:** A retrospective, observational de-identified cohort study was conducted on individuals enrolled in the Optum Labs Data Warehouse (OLDW) who had a new diagnosis of HZO from 1/1/2010 to 12/31/2018. An online survey ascertaining HZO management perspectives was distributed to the Cornea Society listserv. The main outcome assessed was proportion of cases with systemic antiviral prescriptions, eye care provider involvement, and follow-up visits following the initial HZO diagnosis.

**Results:** Approximately 50% of patients received systemic antivirals the day of initial HZO diagnosis or within 7 days (45.6% and 53.7%, respectively). Most initial diagnoses were made by ophthalmologists (45.0%), followed by optometrists (19.2%). Referral rates to ophthalmology within a year of initial diagnosis was 38.6%. 48.7% cases had at least one follow-up visit with any type of provider within 30 days.

Our survey of cornea specialists found 97% would prescribe systemic antivirals to those with ocular involvement, but 66% would prescribe antivirals to those without ocular or eyelid involvement. 70% supported all patients having follow-up with an eye care provider within a month.

**Conclusions:** HZO antiviral therapies appear to be under-prescribed in the US, referral rates to ophthalmology are low, and follow-up is suboptimal, which are not aligned with recommendations from cornea specialists. More research is needed to establish standardized guidelines for treatment, referral, and follow-up with ophthalmology for HZO.

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No conflicts of interest to disclose

**Keywords**

Herpes zoster ophthalmicus; antiviral treatment; clinical practice patterns

## Introduction

Herpes zoster (HZ) occurs when the latent varicella zoster virus (VZV) reactivates along a dermatome.[1–3] More than one million new cases of HZ occur annually in the United States, with one in every three Americans developing HZ during their lifetime.[4,5] Herpes zoster ophthalmicus (HZO) occurs when VZV reactivates in the ophthalmic (V1) division of the trigeminal nerve and makes up 10–20% of all HZ cases.[6,7] HZO may be limited to the periocular region but can have ocular manifestations, including keratitis, uveitis, retinitis, and cranial neuropathies. Patients may suffer permanent vision loss and postherpetic neuralgia (PHN).[6,8,9] The incidence of HZO has continued to increase over the past couple of decades, with an estimated 3.6% increase per year in the US from 1994–2018.[10–12]

The large burden of disease associated with HZO and the rising incidence highlights the need for developing preferred practice patterns. Various specialties have proposed recommendations for the initial management of HZO. A frequent recommendation is that antiviral therapy should be initiated in patients presenting with HZO, even outside of the 72-hour initial rash onset window.[3,13–23] However, recommendations differ with regard to which healthcare provider should be involved and at what frequency. [3,15,16,18–20,22–26] Most recommend follow-up with an ophthalmologist when ocular manifestations are present or if there is indication of nasociliary branch involvment.[3,15,19,20,23–25] Recommendations for follow-up also vary, but follow-up is generally recommended even in cases without ocular complications.[19,20,22,25–27]

The discrepancies in recommendations may contribute to variation in care of patients with HZO. Given the high morbidity associated with HZO, the initial management of HZO is important, particularly implementation of antivirals and assessment by an eye care provider. Research is needed to support the preferred practice patterns for acute HZO.[28,29] The objective of this study was to describe the prevalence of antiviral use, as well as the frequency and specialty associated with follow-up after diagnosis of HZO. Our primary aims were to assess the frequency of systemic antiviral prescription and evaluation by ophthalmology within a week of diagnosis, as well as follow-up care following initial diagnosis. A survey of cornea specialists on their preferences for managing HZO was used to place our findings from the general claims database into context. Understanding the current clinical practice of the initial management of HZO is an important step in identifying areas of practice variation. Ultimately, research that leads to clarity on optimal practice patterns may help formulate evidenced-based guidelines that would improve HZO care.

## Material and Methods

### Guideline Search

We researched recent articles on the management of HZO from the literature (PubMed, Embase, and Google Scholar) to identify recommendations on HZO management to help guide our research questions assessing practice pattern variation. The study did not perform a literature review of all guidelines in the literature.

### Data source

This was a retrospective cohort study using Optum Labs Data Warehouse (OLDW; Optum Labs Inc, Minnetonka, MN, USA), which is a large US healthcare database including enrollment information, de-identified medical and outpatient pharmacy claims for commercial, Medicare Advantage and Medicare Part D enrollees. Individuals from all regions of the United States are represented in OLDW, with a greater proportion from the Central and Southern regions. Medical claims included diagnosis codes (ICD-9 and ICD-10), date of service and provider specialty codes. Pharmacy information included brand name, generic name, quantity, days' supply, drug strength and drug administration route for dispensed medications, and the date the prescription was filled.

### Cohort Selection

The cohort consisted of individuals with medical and pharmacy coverage in OLDW who had at least one healthcare visit with a HZO diagnosis as their primary or secondary diagnosis from January 1, 2010 through December 31, 2018 (identification period). Individuals were required to have at least 2 years of continuous enrollment without a HZO diagnosis code prior to their first HZO diagnosis code within the identification period to increase the likelihood that the first HZO diagnosis was a new diagnosis. Individuals were also required to be continuously enrolled for at least 1 year after the initial HZO diagnosis.

Figure 1 provides cohort selection details. Diagnoses of HZO were attained from physician claims and facility claims from any clinical setting (inpatient hospital, long term care, emergency department, outpatient hospital, office visits, or other unclassified as defined by OLDW), using the International Classification of Disease (ICD) 9$^{th}$ and 10$^{th}$ Edition (ICD-9 053.2x, ICD-10 B02.3x).

### Patient demographics and clinical variables

Patient age, sex (female, male, unknown), race/ethnicity (Asian, black, Hispanic, white, unknown), region (Midwest, Northeast, South, West, unknown), age-adjusted Charlson Comorbidity Index and immunocompromised status were assessed during the baseline period, which was defined as the 1 year prior to the index date (the date of initial HZO diagnosis from January 2010 to December 2018).[30–32] Immunocompromised status was defined as an ICD-9 or ICD-10 code for human immunodeficiency virus, acquired immunodeficiency syndrome, leukemia, or lymphoma (Supplemental Digital Content 1), or a prescription for immunosuppressive medications (Supplemental Digital Content 2).

### Antiviral use

Antiviral prescription fills were identified in pharmacy claims by their generic names. Systemic (oral/IV) antivirals included valacyclovir (Valtrex), acyclovir (Zovirax), and famciclovir (Famvir). Topical antivirals included acyclovir ointment/cream, ganciclovir gel (Zirgan) and trifluridine (Viroptic). Average daily dosage of a prescription fill was calculated using the formula $drug strength \times \frac{quantity}{days' supply}$.

### Provider specialty and HZO visits

Eye care providers consisted of optometrists and ophthalmologists. Non-eye care providers included family practitioners, internists, after hours clinic/urgent care, emergency medicine providers, dermatologists, pediatricians, infectious disease specialists, pathologists and neurologists. For claims associated with the initial HZO diagnosis involving an eye care provider and non-eye care provider on the same date, we assumed these patients were referred to the eye care provider on the same day. If the patient saw both an optometrist and ophthalmologist, we assumed the patient was referred to the ophthalmologist.

**Survey:** A survey consisting of 10 questions was sent through email to the Cornea Society listserv consisting of 1859 members to obtain opinions on the management of HZO by cornea specialists (Supplement 3). The survey was active from February 18, 2021 through March 22, 2021. Descriptive statistics were used to report survey findings.

### Statistical Analysis

The proportion of incident HZO cases receiving any antivirals, any systemic antivirals and any topical antivirals on the same day of HZO diagnosis, within 7 days and within 30 days was determined.

Data was analyzed using R version 4.0.2 (The R Project for Statistical Computing, Vienna, Austria; http://www.r-project.org). Informed consent was not required to gather data on the trends of HZO in OLDW because the database only provides de-identifiable data. The study was granted approval by the Institutional Review Board of the University of California, San Francisco. The survey component of this project was granted an exemption by the Parnassus Committee of the Institutional Review Board of the University of California, San Francisco. The study adhered to the Declaration of Helsinki and all federal and state laws.

**Results:** This study included 17,685 individuals who had a new diagnosis of HZO from January 1, 2010 to December 31, 2018 (Table 1). Median age at the initial HZO diagnosis was 62 years old (CI: 51–74). Most patients were not immunocompromised.

Nearly half (48.2%) of patients received antiviral therapy (topical or systemic) on the day of HZO diagnosis and 57% received antiviral therapy within 7 days. The majority received systemic antivirals, with 45.6% receiving them the day of their HZO diagnosis and 53.7% within 7 days. 5.8% of patients received topical antivirals and 2.6% were exclusively prescribed topical antivirals. The median systemic acyclovir dosage per day was 4000 mg (Q1=2400, Q3=4000), valacyclovir dosage per day was 3000 mg (Q1=3000, Q3=3000), and famciclovir was 1500 mg (Q1=1500, Q3=1500). The most common systemic antiviral

prescribed was valacyclovir, making up 64.7% of all systemic antiviral prescriptions. Table 2 provides more details on antiviral prescription by type and route.

Ophthalmologists made the most initial diagnoses of HZO (7960, 45.0%), followed by optometrists (3390, 19.2%) and family practitioners (1964, 11.1%). Table 3 provides more details on provider type making the initial diagnosis of HZO. Of those diagnosed by an optometrist, 3.6% were referred to an ophthalmologist within 7 days, 6.3% within 30 days, and 9.1% within a year; 25% of patients receiving an HZO diagnosis by a non-eye care provider were referred to an ophthalmologist within 7 days, 27.9% within 30 days, and 29.5% within a year.

Within 7 days of the initial HZO diagnosis, 75.8% of patients saw an eye care provider (optometrist or ophthalmologist), and 70.0% of those eye care providers were ophthalmologists. Of all individuals diagnosed with HZO, 54.7% saw an ophthalmologist within 7 days and 56.2% saw an ophthalmologist within 30 days of their initial diagnosis.

Follow-up was low regardless of provider type; 36.6% of patients were seen within 7 days following the initial diagnosis visit, 48.7% were seen within 30 days, and 52.7% were seen within a year. Of the individuals that were seen by an ophthalmologist, 15.3% had at least one ophthalmology follow-up visit within 7 days, 27.4% within 30 days, and 31.3% within a year. Of the individuals seen by an optometrist, 6.6% had at least one optometry follow-up visit within 7 days, 9.4% within 30 days, and 10.3% within a year.

Our survey of the Cornea Society listserv included 130 responses out of 1895 members. The majority reported seeing more than 10 cases of HZO per year, with one responder seeing around 75 cases. 97% of respondents would prescribe systemic antivirals when HZO presents with ocular involvement. 92% percent (120/130) would prescribe systemic antivirals when the zoster involvement is restricted to the skin regardless of eyelid involvement when the rash onset is less than 72 hours. Outside the 72-hour window, 66% of respondents would prescribe systemic antivirals if the rash did not have eyelid involvement, while 81% of respondents would prescribe systemic antivirals if there was eyelid involvement. Around 70% recommended that patients presenting with HZO skin lesions without eyelid or ocular involvement be seen by an eye care provider (ophthalmologist or optometrist) within 7 days. When eyelid involvement is present, 97% recommended an eye care provider referral within 7 days, with 70% recommending only an ophthalmologist. When ocular involvement is present, 100% believe an eye provider is necessary, with 91% recommending only an ophthalmologist. Regarding follow-up, 70% of respondents recommended follow-up within a month, even for patients presenting with no ocular involvement on their initial exam. About 70% recommended annual check-ups for patients with a history of eye involvement from HZO. Table 4 provides more details on the proportions of respondents that would prescribe antivirals and recommend follow-up for specific clinical scenarios.

**Discussion:** In this claims-based study of practice patterns for the initial management of HZO, nearly 60% of patients were prescribed systemic antivirals within 7 days of a HZO diagnosis. The majority of HZO diagnoses were made by ophthalmologists, followed by

optometrists and general practitioners. Referral by an optometrist or a non-eye care provider to ophthalmology within a year following diagnosis was low. Regardless of the provider who initially diagnosed HZO, most patients did not have a follow-up appointment within 30 days of diagnosis. These findings are not aligned with general recommendations in the literature or with the preferences of cornea specialists from our survey, the majority of whom recommend systemic antiviral treatment and follow-up within a month regardless of presentation type or timeline.

The consensus in the literature for the management of HZO is that systemic antivirals should ideally be given within 72 hours of rash onset to decrease the risk of ocular complications, severity of acute pain, and viral shedding.[33] The Centers of Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) labels for the antivirals approved for treatment of acute herpes zoster (acyclovir, valacyclovir, and famciclovir) recommend initiating treatment at the earliest sign or symptom of the disease.[34–37] The FDA labels also mention that treatment is most effective when initiated within 48 hours of the rash onset, and that the efficacy of treatment when initiated 72 hours after rash onset has not been established.[34–36] These recommendations apply to HZ in the trigeminal nerve distribution.

However, there is no evidence against the benefits of initiating antiviral therapy after 72 hours.[3,15,23] The risk of antiviral side effects is low and DNA shedding of virus is highly variable, detectable up to 34 days from initial rash onset.[27,38] Moreover, a study of oral acyclovir in patients presenting with a HZO skin rash suggest potential benefits in treating beyond the 72 hour window. These benefits included decreased ocular complications, less acute dermatomal pain, and decreased incidence of new skin lesions compared to placebo.[33,39] Due to the favorable side effect profile of antiviral drugs and the serious morbidity associated with HZO, most recommendations favor of antiviral therapy even when patients are outside the 72 hour window.[3,13–23] This is also reflected in our survey results where 66% of respondents would prescribe systemic antivirals in even mild cases, in which patients present with a rash without eyelid or ocular involvement outside the 72-hour rash onset window. A majority of study investigators in the Zoster Eye Disease Study (ZEDS) who responded to a survey also favored the use of antivirals to treat and reduce the complications of HZO.[40] The low rates of systemic antiviral prescriptions and lower than recommended doses in at least 25% of patients prescribed acyclovir in this study suggests suboptimal use of antivirals. Under-prescription and suboptimal doses of antiviral therapies for HZO has also been reported in the UK and Australia.[28,41] Given the good safety profile of systemic antivirals and absence of an appropriate outcome metric, utilization of oral antivirals should not be limited to the traditional 72-hour window. Research, such as the ZEDS clinical trial studying the efficacy of systemic valacyclovir in preventing recurrences of HZO, can strengthen and clarify further recommendations.[29]

Another point of controversy in the initial management of HZO is deciding the specialties responsible for managing the acute care of HZO. Specifically, there is a debate about the role of ophthalmologists, optometrists, and general practitioners. In our study, most patients were acutely seen by ophthalmologists, followed by optometrists and general practitioners. Referrals to ophthalmology within 7 days of an HZO diagnosis from other providers were low. The literature is unclear regarding who should be managing acute HZO episodes,

though most agree that an ophthalmology referral is needed in cases with nasociliary branch or ocular involvement.[3,15,16,19,20,23–26] Some suggest that all possible cases of HZO be referred to ophthalmologists.[18,22] Ambiguity on which provider types should be involved in the acute management of HZO may be due to a lack of studies evaluating outcomes by clinical specialty type. Most respondents in our survey recommended that patients presenting with HZO see an eye care provider, with a strong preference for an ophthalmologist. As a specialty, ophthalmology may want to include recommendations regarding which HZO cases would ideally be managed by our specialty.

Our study also highlights poor patient follow-up for HZO patients regardless of the physician type diagnosing HZO. Although many recommendations highlight the need of follow-up appointments, there is a lack of clarity in terms of follow-up frequency, timing, and/or provider type.[19,20,22,25–27] With HZO, ocular and cranial nerve involvement such as deep stromal keratitis and neurotrophic keratopathy can occur weeks, months, or even years after initial rash onset.[22,33,39] Given that ocular involvement typically occurs 2–4 weeks after disease onset, it would be beneficial to have at least one follow-up within a month and ascertain the necessity of an ophthalmology referral. Future guidelines would ideally address optimal follow-up. The low levels of follow-up may be partially attributable to patient non-compliance as they may be less likely to follow-up after the resolution of visible lesions. If this is true, physicians may need to educate patients about the late-onset ocular complications associated with HZO.

This study has several limitations. First, the study is limited by the quality of ICD-9 and ICD-10 coding. However, our study only included cases where HZO was the primary or secondary diagnosis. In general, the clinical diagnostic accuracy is high for HZO.[42] We chose a two-year look back period in which patients could not have an ICD-9 or ICD-10 code for HZO to decrease the likelihood of classifying a prevalent case as incident. This study may have missed some antiviral prescriptions if patients had secondary insurance not included in OLDW, but this is thought to be minimal. The health status of participants could also differ from the general US population and may represent a more economically advantaged population. However, OLDW is a large database that represents a mixture of ages and geographical regions across the United States.

Another limitation is that we cannot ascertain the severity of disease, the stage of the disease, or intraocular involvement. As such, we could not assess the proportion receiving systemic antivirals or follow-up based on the severity or stage of disease. Lastly, our survey only captured 130 responses from the listserv. Although this is a small proportion of the entire listserv, we assume not everyone in the listserv in an active member. Our goal was to gather opinions from cornea specialists as an ancillary measure to provide a point of comparison to our findings.

Given the lack of established preferred practice patterns, our study aimed to assess the current patterns of HZO management and evaluate how they align with recommendations in the literature and from cornea specialists. Although this study found that there was a strong adherence to recommended antiviral administration route and dose for those prescribed antivirals, there was variation in the management of HZO with regards to systemic antiviral

prescription, physician type managing disease, referrals to ophthalmology, and follow-up. Research is needed to evaluate systemic antiviral therapy after the 72-hour window, clinical outcomes by physician type treating HZO, the cost and benefits of ophthalmology referrals, and frequency and timing of follow-up visits. Research on practice patterns can identify current variations in care and point to areas requiring further research to support the development of evidence-based recommendations and guidelines.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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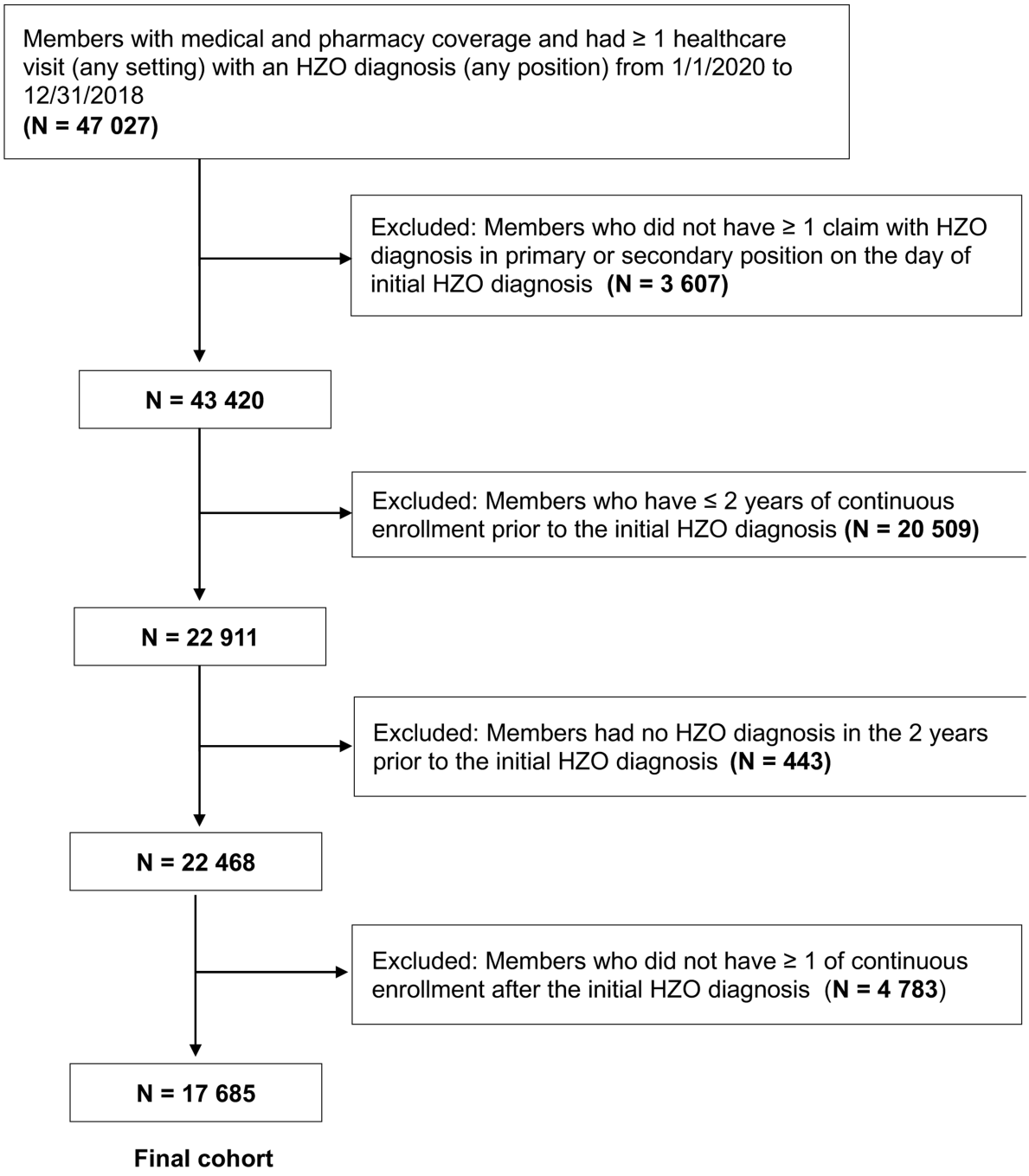


**Figure 1. Cohort inclusion and exclusion flow diagram**

Flow diagram showing inclusion and exclusion criteria for study cohort. HZO = herpes zoster ophthalmicus. Using the International Classification of Disease (ICD) 9th and 10th Edition (ICD-9 053.2x, ICD-10 B02.3x), diagnoses of HZO were attained from physician claims and facility claims from any clinical setting: inpatient hospital, long term care, emergency department, outpatient hospital, office visits, or other unclassified as defined by Optum Labs Data Warehouse.

Flow diagram of study. HZO = herpes zoster ophthalmicus.

**Table 1.**

Characteristics of study population at baseline

| Characteristic[a] | Individuals who had a new episode of HZO from 1/1/2010–12/31/2018 |
|---|---|
| **Age at the Initial HZO Diagnosis** | |
| Median (IQR) | 62 (51–74) |
| **Sex** | |
| Female | 10 379 (58.7) |
| Male/Unknown | 7 306 (41.3) |
| **Race/Ethnicity** | |
| Asian | 628 (3.6) |
| Black | 1 360 (7.7) |
| Hispanic | 1 219 (6.9) |
| White | 13 175 (74.5) |
| Unknown[b] | 1 303 (7.3) |
| **Region** | |
| Midwest | 5051 (28.6) |
| Northeast | 2553 (14.4) |
| South | 7 567 (42.8) |
| West | 2 503 (14.2) |
| Unknown[c] | 11 (0.1) |
| **Charlson Comorbidity Index[d]** | |
| Median (IQR) | 2.0 (1.0–4.0) |
| **Immune Status** | |
| Not Immunocompromised | 15 648 (88.5) |
| Immunocompromised | 2 037 (11.5) |

IQR = Interquartile range.

[a]Values are reported as No. (%) unless otherwise indicated.

[b]The unknown race/ethnicity category includes individuals with either unknown or missing race/ethnicity. As defined in OLDW, unknown race/ethnicity is for individuals who are not in one of the pre-defined categories (Asian, white, black, Hispanic) or who have mixed race/ethnicity.

[c]The unknown region category includes individuals in either unknown or other regions. In OLDW, the pre-defined region categories are (Midwest, Northeast, South, West, Other, Unknown). The Other and Unknown categories were combined given the low prevalence of herpes zoster in each individual group.

[d]Charlson comorbidity index was assessed in the 1 year prior to the index date.

**Table 2.**

Prescribing pattern of antivirals for HZO management[a]

| Type of antiviral | Day of initial HZO diagnosis | Within 7 Days | Within 30 Days |
|---|---|---|---|
| Any antiviral | 8522 (48.2) | 10075 (57.0) | 10717 (60.6) |
| Any systemic antivirals | 8068 (45.6) | 9504 (53.7) | 10177 (57.5) |
| Acyclovir (Oral/IV) | 2141 (12.1) | 2648 (15) | 2992 (16.9) |
| Valacyclovir | 5217 (29.5) | 6138 (34.7) | 6617 (37.4) |
| Famciclovir | 744 (4.2) | 881 (5.0) | 935 (5.3) |
| Any topical antiviral | 1017 (5.8) | 1717 (9.7) | 1936 (10.9) |
| Acyclovir ointment/cream | 172 (1.0) | 263 (1.5) | 300 (1.7) |
| Zirgan/ganciclovir gel | 451 (2.6) | 834 (4.7) | 961 (5.4) |
| Viroptic (1% trifluridine) | 406 (2.3) | 668 (3.8) | 754 (4.3) |

[a]Values are reported as number (%)

**Table 3.**

Provider type involved on the day of initial HZO diagnosis

| | |
|---|---|
| **Eye care provider** | |
| Ophthalmologist | 7960 (45.0) |
| Optometrist | 3390 (19.2) |
| Multiple: Ophthalmologist & non-eye care | 732 (4.1) |
| Multiple: Optometrist & non-eye care | >270 (>1.5)[b] |
| Multiple: Ophthalmologist & optometrist | <11 (<0.1)[b] |
| **Non-eye care provider** | |
| Family practice | 1964 (11.1) |
| Internist | 1113 (6.3) |
| After hours clinic/urgent care | 285 (1.6) |
| Emergency medicine | 248 (1.4) |
| Other non-eye care | 1712 (9.7) |

[a]Values are reported as number (%)

[b]Optum Labs requires cell counts <11 to be reported as <11 rather than reporting true values to protect patient privacy. To prevent back calculation, the value in a corresponding cell of the same subgroup is lowered and reported with a greater than sign to ensure that the total case count within the subgroup stays the same. Each affected subgroup's HZO incidence rate was reported with greater than and less than signs. Numbers are not reported for race/ethnicity subgroups due to the cell suppression policy.

**Table 4.**

Cornea Specialist Listserv Survey Results on Antiviral Prescriptions and Follow-Up Preferences for Different HZO Presentations[a]

| HZO scenario | | % who would prescribe antivirals | | % recommending follow-up with ophthalmologists within 7 days of onset | % recommending follow-up with ophthalmologists or optometrists within 7 days of onset |
|---|---|---|---|---|---|
| Without ocular involvement | Rash restricted to the skin, without eyelid involvement | onset ≤ 72 hours | 92% | 45% | 70% |
| | | onset > 72 hours | 66% | | |
| | Rash restricted to the skin, with eyelid involvement | onset ≤ 72 hours | 92% | 70% | 97% |
| | | onset > 72 hours | 81% | | |
| With ocular involvement | | Regardless of time of onset | 97% | 91% | 100% |

[a]Sample size of 130 respondents