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Journal

Cornea, 31(7)

ISSN

0277-3740

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Publication Date

2012-07-01

DOI

10.1097/ico.0b013e31823cbe6a

Peer reviewed

Published in final edited form as:
Cornea. 2012 July ; 31(7): 786–790. doi:10.1097/ICO.0b013e31823cbe6a.

Practice Patterns and Opinions in the Management of Recurrent or Chronic Herpes Zoster Ophthalmicus

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Abstract

Purpose—The objective of this study was to determine current practices and opinions among cornea specialists for treating and preventing recurrences of Herpes Zoster Ophthalmicus (HZO).

Methods—In November 2010, a survey of 15 questions was distributed to the Cornea Society listserv. Questions identified respondents' treatment practices for recurrent HZO and opinions regarding prolonged antiviral prophylaxis and zoster vaccine.

Results—Of 100 respondents, the majority were cornea specialists (83/98, 85%). Eighty-seven percent (84/97) reported treating recurrent or chronic cases of HZO in the last year. The most common choice of treatment in the posed recurrent HZO clinical scenario was a combination of oral antiviral and topical corticosteroid (63/100, 63%), although significant variability existed in the duration of oral antiviral administration. Fifty-four respondents (56%) believed prolonged acyclovir prophylaxis could reduce recurrent signs of HZO; 28% (27/98) believed recurrences of HZO could be reduced after the period of acyclovir administration. For patients with a history of HZO, most respondents reported not recommending the adult zoster vaccine (63/98, 64%), but 46% (43/94) believed the vaccine could reduce recurrent signs or did not know.

Conclusion—Many cornea specialists are managing recurrent or chronic cases of HZO, but there is variability in the use of topical corticosteroids and antivirals. Additionally, no consensus exists on the efficacy of prolonged antiviral therapy or the adult zoster vaccine to reduce chronic or recurrent disease. These results demonstrate the need for further systematic study of treatment and prophylaxis for recurrent and chronic HZO.

Keywords

Herpes Zoster Ophthalmicus; Recurrence; Management; Practice Patterns

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Introduction

Many studies of Herpes Zoster Ophthalmicus (HZO) have focused on the first reactivation of the varicella-zoster virus (VZV) in the ophthalmic division of the fifth cranial nerve. In contrast, chronic or recurrent infectious HZO, although reported and conceptually recognized in case reports and reviews, is not well characterized.[1–3] The majority of existing literature on recurrent or chronic infectious HZO has described it as a disease of the corneal epithelium.[3–8] Although initially thought to be a non-infectious condition, subsequent reports demonstrated that these late corneal lesions harbored VZV DNA and responded to treatment with antiviral medications, both in immune competent and HIV-positive individuals.[3–10] Furthermore, about half of the immune-competent patients in these reports had one or more recurrences of their corneal epithelial disease following successful antiviral therapy.[3, 7] These late corneal lesions occur in 4–13% of eyes that have had HZO, a rate that is very similar to the overall recurrence rate for dermatomal zoster.[5, 6, 11–14]

In contrast, HZO associated interstitial keratitis and iritis have commonly been described as immunologically mediated diseases. However, there is growing evidence that these complications may also be mediated by chronic or recurrent VZV infection. In one report, about 70% of patients with late dendriform keratitis secondary to infectious VZV also had active interstitial keratitis and/or iritis, suggesting that chronic or recurrent VZV infection may have been playing a role in these patients' ongoing anterior segment inflammatory disease.[3] Additionally, studies have found VZV DNA in corneal buttons from patients with a distant history (1–50 years) of HZO, as well as studies VZV DNA and viral antigen in the aqueous of patients with chronic or recurrent iritis.[15–19]

While the treatment for primary HZO has been established through randomized control trials, there is little literature on the management of chronic or recurrent HZO, for either treatment or prevention, and there have been no clinical trials to date.[20, 21] In order to identify the most critical areas of future research, we performed a survey to assess current practices for treating recurrences as well as opinions and experiences with possible prophylactic measures, including prolonged antiviral therapy and the zoster vaccine.

Materials and Methods

In November 2010, an online survey was distributed to all subscribers of the Cornea Society kera-net listserv via the internet-based survey tool, Survey Monkey (Portland, OR). The Cornea Society listserv has approximately eight-hundred members, primarily ophthalmologists and vision scientists. A reminder was sent four weeks after initial distribution, and the survey was closed in January 2011, when 100 responses were collected. All responses were anonymous: specifically, no identifiers of name, gender, age or region were elicited.

The survey consisted of 15 questions and was divided into 4 sections (see Appendix 1). First, respondents were asked to report on their most likely treatments in the clinical scenario of a patient with history of HZO who presents with stromal keratitis and anterior uveitis, consistent with active recurrent disease. Second, respondents were asked their opinions on the effectiveness of prolonged prophylactic acyclovir to prevent recurrent signs of HZO. Third, respondents were asked their opinions, individual practices and experience with the adult zoster vaccine. Lastly, general demographic information was collected, including type of practice setting and number of HZO cases seen in the past year.

Descriptive statistical analyses were performed. Fisher's exact (for categorical variables) and ANOVA tests (for ordered categories) were used to compare consistency of opinions and practices between related questions and to compare opinions and treatment practices

between subgroups of clinicians, including practice setting, location, specialty and number of recurrent cases seen in the last year. Analyses were conducted in STATA version 8.2 (StatCorp, College Station, TX).

Institutional review board exemption was granted by the Mount Zion panel of the Committee on Human Research at the University of California, San Francisco. The study adhered to the Declaration of Helsinki and all federal and state laws.

Results

Demographics

A total of 100 respondents participated in the survey with response rates to individual questions ranging from 94% to 100%. Respondents primarily identified themselves as practicing cornea specialists (83/98, 85%); the remainder were practicing general ophthalmologists (14/98, 14%) or an optometrist (1/98, 1%). The median years of practice was 12 years (IQR 7 to 25 years). The majority of respondents practiced in private group (49/98, 50%) or academic (29/98, 30%) settings; the remainder practiced in private solo settings with one respondent practicing in an HMO. Respondents' practices were most commonly located in the United States (78/98, 80%); other regions represented in the survey include Africa, Australia/New Zealand, Europe, the Middle East, and Central and South America.

All respondents reported treating at least one case of HZO in the past year. The majority of physicians reported treating recurrent or chronic cases of HZO in the last year with 46% (45/97) reporting 1–5 patients, 22% (21/97) reporting 6–10 patients, 15% (14/97) reporting 11–20 patients, and 4% (4/97) reporting greater than 20 patients with recurrent or chronic HZO. Only 13% (13/97) of respondents had not seen any cases of recurrent or chronic HZO in the last year (Figure 1).

Current Practice Patterns

In our clinical scenario of a patient with recurrent signs of HZO, the majority of respondents chose to treat with a combination of oral antiviral and topical corticosteroid (63/100, 63%); the second most common response was topical corticosteroid alone (24/100, 24%) (Table 1). Among respondents who chose to treat with topical corticosteroids, the most common choice of corticosteroid and dose was prednisolone acetate 1% *QID* (55/97, 57%), with prednisolone acetate 1% five times or more daily in second (27/97, 28%) (Table 2). In response to an optional open-ended question asking respondents to describe their protocol for corticosteroid use, most reported very slow corticosteroid tapers (defined as longer than 1 month, 33/35). Among the 81 respondents who chose to treat with oral antivirals, 44% (36/81) chose to treat for 7–14 days, 19% (15/81) for one year or longer, 20% (16/81) for as long as corticosteroids were being administered, and 17% (14/81) some other duration (Table 3).

Opinions on Prolonged Antiviral Prophylaxis

When asked whether they believed prolonged acyclovir prophylaxis could prevent or reduce recurrent signs of HZO while acyclovir was being administered, 56% (54/96) of respondents said yes, 15% (14/96) of respondents said no, and 29% (28/96) of respondents said they did not know (Figure 2). When asked whether they believed recurrences would be reduced after the period of prolonged acyclovir administration, 28% (27/98) said yes, 46% (45/98) said no, and 26% (26/98) said they did not know (Figure 2).

Opinions and Experiences with Zoster Vaccine

The majority of respondents are not recommending the adult zoster vaccine to patients with a history of HZO (63/98, 64%), but 30% (28/94) of respondents believed the vaccine could reduce recurrent signs, and 16% (15/94) said they did not know (Figure 3). Of the 35 respondents who reported recommending the zoster vaccine, 26 responded to an open-ended question inquiring how long they typically waited after the patient's HZO became quiescent before recommending the vaccine. There was a wide range of responses from 1 month to 5 years and no clear majority, with the median response being 6 months.

When asked about their experiences with the adult zoster vaccine, two respondents reported seeing worsening of disease in a patient with a history of HZO who then received the zoster vaccine. Thirty-six percent (34/95) reported seeing no worsening of disease in such patients. The majority of respondents (59/95, 62%) had not seen patients who received the zoster vaccine after having HZO.

Testing for Internal Validity

Cross-checking responses from related questions confirmed internal validity. Specifically, those who believed in acyclovir prophylaxis were more likely to treat with acyclovir, Fisher's exact $p < 0.001$, and for longer treatment courses, Fisher's exact $p = 0.02$. Those who recommend the vaccine are those who believe in its efficacy, Fisher's exact $p < 0.001$, and those who have seen patients safely vaccinated, Fisher's exact $p < 0.001$.

Discussion

Overall, the results of this survey demonstrate that many cornea specialists and ophthalmologists are seeing cases of HZO that they consider recurrent or chronic, but there is no consensus in treatment practices and opinions. The finding that such a high proportion of respondents are treating substantial numbers of recurrent or chronic HZO cases suggests these cases are not uncommon. To our knowledge, there have been no studies investigating the incidence of recurrent HZO, but the rate of recurrent non-ocular zoster appears to be more common than previously thought.[12–14, 22–24]

To our knowledge, there have also been no clinical studies or practice recommendations for the management of recurrent and chronic HZO. Clinical evidence has been limited to case reports and retrospective chart reviews that describe response of recurrent HZO lesions to antiviral therapy of various doses, durations and routes.[3, 7, 10] In the earliest reports, HZO recurrences were only recognized in immunocompromised patients who appeared to respond well to topical antivirals, but subsequent reports have found highly variable responses to antivirals of various formulations (topical, oral, IV).[8, 9] More recently, VZV DNA was identified from recurrent ocular lesions in immunocompetent patients, and lesions were again found to respond to antivirals, generally topical, oral, or both, though no one medication or regimen was found to be most effective.[3, 7, 10, 25]

In a clinical scenario of a patient with recurrent signs of HZO, the majority of respondents in our survey chose to treat with both topical corticosteroids and oral antivirals, but nearly a quarter of respondents chose to treat solely with corticosteroids. Almost all respondents who reported treating with corticosteroids chose to use prednisolone acetate 1%, four or more times daily, reflective of a surprising consensus in formulation, route of administration, dosage and frequency, despite any established protocol. Additionally, it appears that most respondents are using corticosteroids for prolonged periods of time (>1 month), although this is dependent on patient response to corticosteroid. Selection of the appropriate steroid formulation and administration frequency are important to the balance of treatment efficacy versus patient safety.

Antiviral treatment lasting 10 days for primary HZO is supported by randomized control trials[20], but there are no established guidelines for the duration of antiviral treatment in chronic or recurrent HZO. Despite this lack of evidence, many clinicians are using antivirals for chronic or recurrent HZO. Respondents may be basing their practice patterns upon case reports that describe successful treatment of recurrences with antivirals.[3, 7–9, 25] In this survey, the lack of consensus as to the length of treatment with antivirals, with approximately half the respondents opting for a short term course (7–14 days) and the other half for a longer course, clearly reflects the absence of an accepted treatment protocol.

Respondents were highly divided over the efficacy of prolonged antiviral therapy to reduce recurrences of HZO. Slightly more than half the respondents believed prolonged antiviral therapy could reduce recurrences while antiviral therapy was being administered. There was no clear agreement among respondents whether prolonged antiviral therapy could prevent recurrences after antiviral administration was stopped, although the most common response was that it would not be efficacious. In the absence of any prior studies for recurrent or chronic HZO, it is possible that respondents are forming their opinions based on the Herpetic Eye Disease Study (HEDS), a large, randomized controlled trial that found prolonged antiviral therapy reduced recurrences of ocular herpes simplex viral disease during administration, but the effect did not continue after prophylaxis was stopped.[26]

The zoster vaccine (Merck VZV) has been found to reduce the risk and severity of herpes zoster, but its safety and efficacy for preventing recurrences in patients who have a history of HZO is unknown.[27, 28] Most respondents are not recommending the zoster vaccine to patients with a history of HZO; however, nearly half the respondents were not certain or believed the zoster vaccine could effectively reduce recurrences. Several respondents commented that zoster recurrence would likely provide an innate immune boost similar to that induced by the vaccine, thus the vaccine would not offer any additional protection in this population of patients with recurrent HZO. One respondent commented that his or her patients' HZO seemed to improve after vaccination.

Although many respondents have not seen patients with a history of HZO who then received the HZO vaccine, among the 36 who have seen such patients, only two respondents reported an adverse event, suggesting the vaccine may be safe to use in a clinical trial setting. In the Shingles Prevention Study, a randomized prospective trial comparing zoster vaccine to placebo in over 38,000 patients, only 3 patients were found to have recurrent episodes of herpes zoster over a mean surveillance time of 3.13 years; one patient was in the vaccine arm and the other two in the placebo arm, numbers too small to determine any effect of the vaccine.[22] There has been one case report describing a prominent worsening of VZV interstitial keratitis after vaccination.[29] However, the current recommendation from the CDC and Prevention Advisory Committee on Immunization Practices (ACIP) remains administration of the zoster vaccine to adults 60 years and older even if patient has a history of zoster.[27]

The limitations of this survey include recall bias, response bias and predominance of respondents from one geographical area, in this case the US. The response rate for this survey is comparable to other published online surveys.[30–34] This survey also has strengths, including a high absolute number of respondents with cornea expertise, a high completion rate of the survey amongst respondents, and capture of both private and university demographics. Additionally, cross-checking responses from related questions confirmed strong internal validity. Opinions were consistent between questions and responses correlated logically.

There is great uncertainty surrounding treatment and prophylaxis for recurrent and chronic HZO among cornea specialists and general ophthalmologists. This survey was not intended to provide guidelines for practice, but rather to identify areas of discordant opinion where further clinical evidence is needed. The results of this survey identify three such areas: 1) the effect of various regimens of antivirals, with or without corticosteroids, on treatment of HZO recurrences 2) the role of prolonged acyclovir as prophylaxis to prevent recurrences of HZO and 3) the effect of zoster vaccine in patients with a history of HZO.

Acknowledgments

Special thanks to the Cornea Society for their distribution and responses to this survey.

Sources of Support:

Dr. Acharya is supported by a National Eye Institute K23EY017897 grant and a Research to Prevent Blindness Award. Aileen Sy is supported by the Proctor Foundation, a Dean's Research Fellowship from the UCSF School of Medicine, and a Pathways to Careers in Clinical and Translational Research Fellowship (NIH/NCRR/OD UCSF-CTSI Grant Number TL1 RR024129). The Department of Ophthalmology at UCSF is supported by a core grant from the National Eye Institute, EY02162, an unrestricted grant from Research to Prevent Blindness, New York, NY, and That Man May See, Inc, San Francisco, CA.

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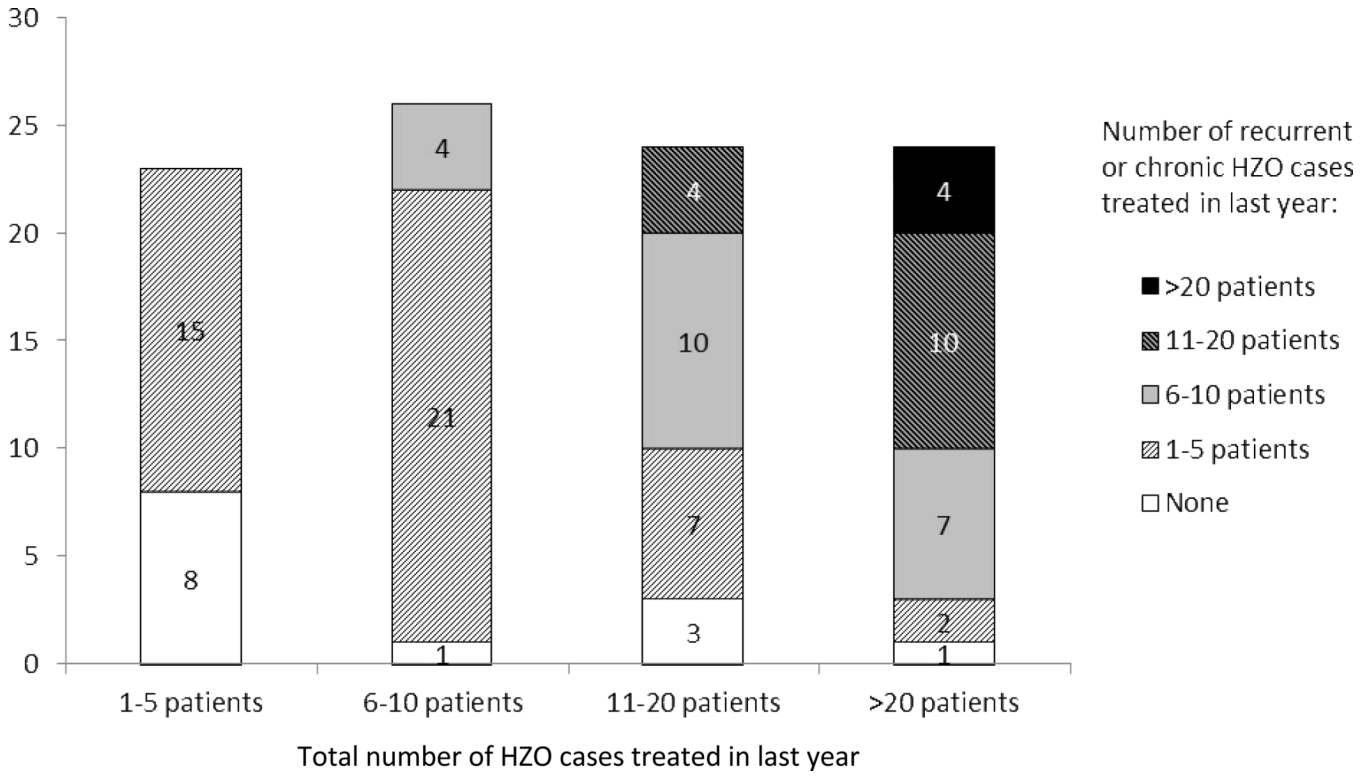

FIGURE 1.

Comparison of total number of HZO cases seen by respondents in the last year with number of recurrent and chronic HZO cases respondents treated in the last year (N=97). Numerical data represent number of respondents. Columns represent distribution of respondents by the total number of HZO cases they treated in the last year. Shading within columns represents subgroup distribution of respondents by total number of recurrent or chronic cases of HZO treated in the last year. All respondents reported seeing at least one case of HZO in the last year.

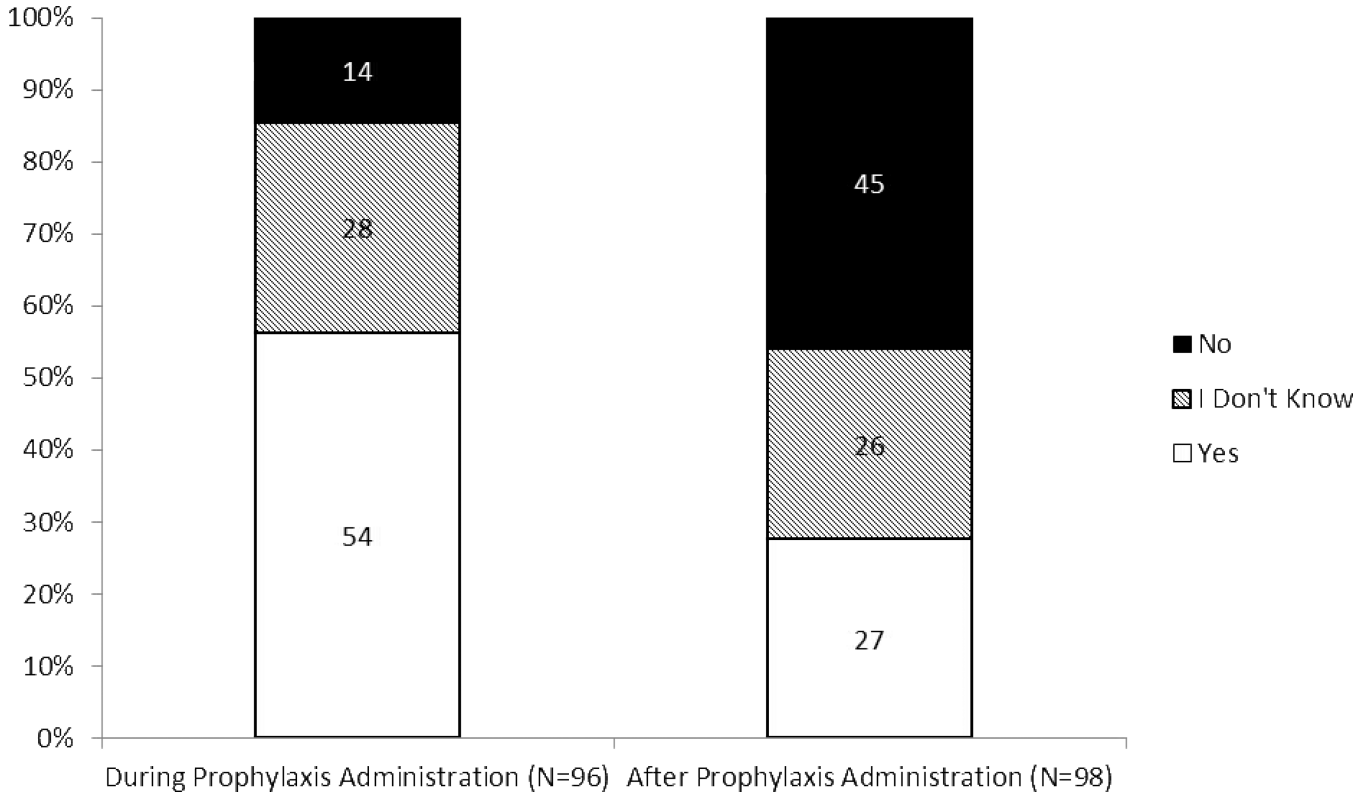

FIGURE 2.

Belief in efficacy of prolonged acyclovir prophylaxis to prevent or reduce recurrent signs of HZO. Respondents reported their beliefs in the efficacy of prolonged acyclovir prophylaxis to prevent or reduce recurrent signs of HZO both during the period of acyclovir administration (left column) and after the period of acyclovir administration (right column). Numerical data represent number of respondents.

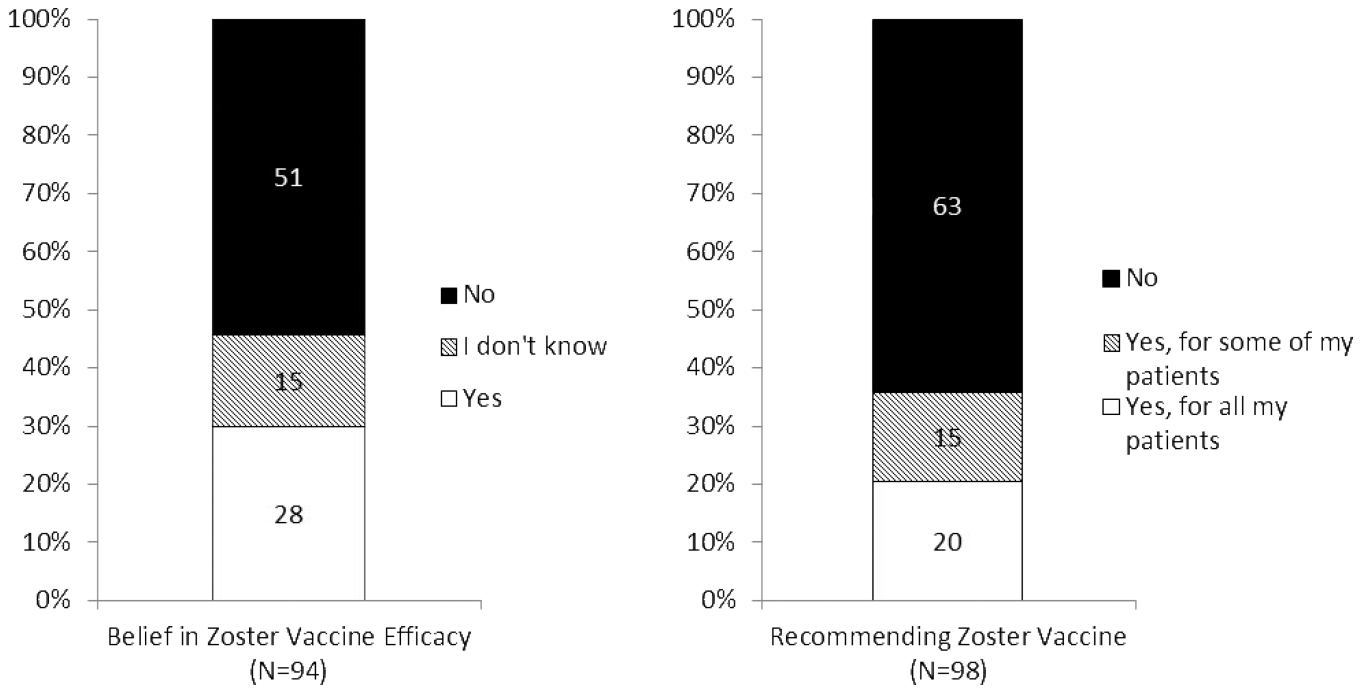

FIGURE 3.

Practice patterns and opinions on efficacy of zoster vaccine to prevent recurrences of HZO. (Left panel) Respondents reported whether they believed the adult zoster vaccine is efficacious to reduce signs of recurrent HZO. (Right panel) Respondents reported whether they are recommending the adult zoster vaccine to their patients. Numerical data represent number of respondents.

Table 1

Choice of treatment in the clinical scenario of a patient with history of HZO who represents with signs of active recurrent disease (N=100).

Treatment Choice	N (%)
Oral antiviral	4 (4)
Topical antiviral	0 (0)
Topical steroid	24 (24)
Oral antiviral + Topical antiviral	1 (1)
Oral antiviral + Topical steroid	63 (63)
Topical antiviral + Topical steroid	1 (1)
Oral antiviral + Topical antiviral + Topical steroid	7 (7)
None of the above	0 (0)

Table 2

Initial choice of steroid and dose for treatment of recurrent HZO scenario amongst respondents who chose to treat with steroids (N=97).

Steroid Choice	Daily N (%)	BID N (%)	TID N (%)	QID N (%)	Five+ Daily N (%)
Prednisolone acetate 1%		1 (1)	3 (3)	55 (57)	27 (28)
Fluorometholone 0.1%	1 (1)		1 (1)	1 (1)	
Loteprednol 0.5%	1 (1)			2 (2)	
Dexamethasone 0.1%			1 (1)	2 (2)	1 (1)
Difluprednate 0.05%[a]				1 (1)	

[a]Difluprednate was not an original option choice in the survey; the respondent chose the answer choice “other” and entered a text response.

Table 3

Duration of oral antiviral administration for recurrent HZO scenario that most closely parallels respondents' practice (N=98).

Treatment Duration	N (%)
Approximately a 10 day course (7–14 days)	36 (37)
One year or longer	15 (15)
As long as steroids are being administered	16 (16)
I would not use antivirals	17 (18)
Other[a]	14 (14)

[a]Respondents entered text responses. Responses most commonly ranged 3–6 months in duration (N=7). Remaining responses described antiviral administration according to clinical course.