American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 11, No 11 (November), 2010: pp 1211-1221
Available online at www.sciencedirect.com

Predictors of Postherpetic Neuralgia Among Patients With Herpes Zoster: A Prospective Study

Mélanie Drolet,[*,†] Marc Brisson,[*,†] Kenneth Schmader,[‡] Myron Levin,[§] Robert Johnson,[‖] Michael Oxman,[¶] David Patrick,[#] Stéphanie Camden,[*] and James A. Mansi[**]

**URESP, Centre de recherche FRSQ du CHA universitaire de Québec, Qc, Canada.*
[†] Laval University, Qc, Canada.
[‡] Center for the Study of Aging and Human Development, Division of Geriatrics, Department of Medicine, Duke University Medical Center; and Geriatric Research, Education and Clinical Center (GRECC), Durham VA Medical Center, Durham, North Carolina.
[§] University of Colorado Denver and Health Sciences Center, Aurora, Colorado.
[‖] University of Bristol and Bristol Royal Infirmary, Bristol, United Kingdom.
[¶] University of California, San Diego and San Diego VA Medical Center, La Jolla, California.
[#] University of British Columbia and BC Center for Disease control, Vancouver, Canada.
***Merck Frosst Canada Ltd., Scientific Affairs, Montréal, Canada.*

Abstract: Postherpetic neuralgia (PHN) is the most common complication of herpes zoster (HZ). The main objectives of this study were to: 1) estimate the severity and duration of PHN; and 2) identify the predictors of PHN. From October, 2005 to July, 2006, 261 outpatients with HZ, aged ≥50, were recruited within 14 days of rash onset during the routine clinical practice of 83 physicians across Canada. Physicians documented HZ characteristics, treatments, general health, functional, and immune status. HZ pain was measured at recruitment and on days 7, 14, 21, 30, 60, 90, 120, 150, and 180 following recruitment. PHN was defined as a worst pain ≥3 persisting or appearing more than 90 days after rash onset. Predictors of PHN were obtained by hierarchical log-binomial regression. Twenty-two percent of 249 immunocompetent subjects with HZ developed PHN. Median duration of PHN was 77 days. Independent predictors of PHN included: older age, limitation in performing usual activities prior to HZ, and pain severity at recruitment. This study confirms that older age and greater acute pain severity are predictors of PHN, while functional status emerges as a novel independent predictor of PHN that deserves further exploration. These findings will contribute to optimal use of the HZ vaccine and testing of new therapies that might prevent PHN.

***Perspective:** This study confirmed that older age and greater acute pain severity are robust predictors of PHN, whereas functional status emerged as a novel predictor. Despite the high proportion of subjects treated with antivirals, the burden of PHN remains considerable, suggesting that prevention and additional early interventions are needed to reduce the burden of HZ.*

***Key words:** Herpes zoster, postherpetic neuralgia, pain, burden of illness, functional status.*

Postherpetic neuralgia (PHN) is the most common complication of herpes zoster (HZ) and one of the most challenging to treat. Estimates of the incidence of PHN vary according to the definition used. When defined as HZ-associated pain persisting more than 30 days after rash onset, PHN develops in 14 to 19% of subjects with HZ.[11,15] However, when defined as HZ-associated pain rated as 3 or more on a scale ranging from 0 (no pain) to 10 (pain as bad as can imagined), persisting or appearing more than 90 days after the onset of rash,[6] PHN develops in 8 to 12% of subjects with HZ.[7,22,24,26] Moreover, the majority of HZ cases occur in older persons, and the incidence of PHN is much higher in older than younger individuals. The risk of developing PHN among subjects with HZ increases from 5% in subjects younger than 60 years old to 10% in those aged 60 to 69 years and to 19% in those older than 70 years old.[35]

Received October 9, 2009; Revised January 8, 2010; Accepted February 22, 2010.
Funded by Merck Frosst Canada Ltd.
Address reprint requests to Marc Brisson, Unité de recherche en santé des populations, Centre hospitalier affilié universitaire de Québec, Hôpital Saint-Sacrement, 1050 Chemin Sainte-Foy, Québec, QC, Canada, G1S 4L8. E-mail: marc.brisson@uresp.ulaval.ca
1526-5900/$36.00

doi:10.1016/j.jpain.2010.02.020

Robust predictors of PHN in patients with HZ are important for several reasons. First, PHN, as with most causes of chronic pain, seriously affects functional status and health-related quality of life.[23,26,31] Second, once PHN has developed, it can last for months to years and be refractory to treatment.[10] Third, a better understanding of the risk factors for developing PHN could direct research on prevention of PHN (eg, early use of antivirals or early control of pain), and could identify specific subgroups of subjects with HZ likely to benefit from novel candidate therapies. These subgroups are likely to be especially valuable for testing new therapies to prevent PHN. Finally, given that an effective and safe vaccine exists against HZ and PHN,[24] identifying sociodemographic, medical, and biological risk factors that increase the risk of PHN could suggest additional candidates for zoster vaccine.

Previous studies do not agree on some of the risk factors evaluated as predictors of PHN.[5,13,17,21,32,34] The use of different PHN definitions and populations, suboptimal statistical methods, and retrospective design may explain, in part, these conflicting results. Nonetheless, older age, greater rash severity, and greater acute pain have been consistently identified as predictors of PHN. Other factors, such as prodromal pain,[17] female gender,[17] affective distress,[29] and ophthalmic localization of HZ rash[21] were identified only in some studies. Recently, Opstelten et al[22] published a comprehensive analysis of predictors of PHN in a consecutive series of 598 subjects with HZ, aged >50, evaluated by general practitioners within 7 days of the rash onset. They concluded that older age, greater acute pain severity, and greater rash severity were strong predictors, and highly recommended that their predictive model be validated. They identified weaknesses in their study, which included the lack of confirmation of HZ and the inability to evaluate the influence of antiviral drugs on the development of PHN, since only patients recruited within 72 hours after the rash onset received antiviral medication.

Given the limitations of previous studies, the need to identify individuals who might benefit the most from vaccination against HZ and its complications, and the recent Cochrane collaboration meta-analysis suggesting that antivirals do not prevent PHN,[19] we used an improved study design to reevaluate the relative contribution of the different risk and preventive factors of PHN. The aim of this study were threefold: 1) estimate the severity and duration of PHN; 2) identify the relative contribution of different potential predictors of PHN; and 3) describe the excess severity of illness experienced by subjects with HZ who developed PHN compared to those who did not.

Methods

Participants

From October, 2005 to July, 2006, 266 subjects with HZ were recruited in MASTER (Monitoring and Assessing Shingles Through Education and Research), a multicenter prospective study with the overall aim of measuring the burden of HZ and PHN from the patient's perspective. Recruitment took place within the clinical practices of 83 general practitioners or specialists across Canada. None of the participants had been previously vaccinated against HZ. Eligible participants were outpatients with a physician-confirmed diagnosis of HZ, recruited within 14 days of rash onset, ≥50 years of age, who were capable of completing study questionnaires in either French or English. Although the diagnosis of HZ is generally straightforward, it can sometimes be confused with herpes simplex. To increase the validity of HZ diagnosis, all recruiting physicians participated in a training session on HZ differential diagnosis offered by HZ experts. Furthermore, physicians collected a sample of the lesion fluid or scab from the rash of their first 3 enrolled patients (corresponding to 41% of all cases recruited). This collected sample was analyzed by PCR for the presence of varicella-zoster virus DNA. HZ was confirmed by this method for 95% (103/108) of specimens; the 5 unconfirmed cases were excluded from the analysis. The study protocol was approved by the Canadian SHIELD Ethics Review Board and all participants signed informed consent.

Data Collection

Physician Assessment

At recruitment, the physician documented the subject's demographics, date of rash onset, dermatome affected, nature and number of lesions, HZ treatment and other concomitant painful conditions. Immune status was determined based on the clinical judgment of physicians. Physicians first had to state whether the immune status was normal, and if not, to specify the cause of immunosuppression among the following possibilities: taking oral corticosteroids at high dose (≥20 mg/day of prednisone or equivalent for an extended period); having invasive cancer or HIV/AIDS; currently receiving or having recently received cytotoxic or immunosuppressive treatment for cancer, organ transplant or other (and specify if other).

Self-Administered Questionnaires

The baseline questionnaire was completed by the subject at the physician's office during the recruitment visit. Follow-up questionnaires were completed at home at days 7, 14, 21, 30, 60, 90, 120, 150, and 180 after enrollment. The baseline questionnaire included detailed socio-demographic information and recorded the presence, severity, and duration of prodromal pain. All 10 questionnaires included questions on HZ pain and health-related quality of life, as measured by the EQ-5D.[28] The EQ-5D measures the level of problems (no problems, some problems, or severe problems) in 5 health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. HZ pain and discomfort were measured by the Zoster Brief Pain Inventory (ZBPI), an HZ-specific modification of the Brief Pain Inventory that includes other discomfort (eg, itch) in the area of the rash in addition to pain.[6] The ZBPI

measures the severity of current, least, worst, and average pain and discomfort within the last 24 hours using an 11-point Likert scale (0–10). The ZBPI also measures, on an 11-point Likert-scale, the interference of HZ pain with 7 activities of daily living: general activity, mood, walking ability, work, relation with others, sleep, and enjoyment of life. This instrument has demonstrated good reliability and validity.[6]

Statistical Analysis

We used the following definition, proposed by Coplan et al,[6] for clinically significant PHN: worst pain ≥3, persisting or appearing 90 days after the rash onset. This definition was also used in the Shingles Prevention Study[24] and the study of Opstelten et al[22] of PHN predictors. In the sensitivity analysis, we examined the impact of defining PHN as a worst pain ≥3 persisting or appearing 30 days after rash onset. To allow for comparison of our results with previous studies assessing the predictors of PHN,[5,8,17,20,22,32] our main analyses were restricted to immunocompetent subjects. However, sensitivity analysis was also performed including immunocompromised subjects.

We used log-binomial regression to identify the predictors of developing PHN. This analysis was preferred to logistic regression since it provides an exact relative risk (RR) rather than odds ratios.[27] Furthermore, when the incidence of an outcome is higher than 10%, the estimation of the relative risk by logistic regression (odds ratio) is a poor approximation.[27] We used the SAS GENMOD procedure with a log link and a binomial distribution for the error. We first examined the univariate association of all characteristics with the risk of developing PHN, and then, all characteristics with *P* value <.15 were considered for the multivariate analysis. We used a hierarchical modeling strategy in order to appreciate the relative contribution of the different categories of potential predictors. Three blocks of different categories of potential predictors were entered into the model in a nested fashion. After the first block of variables related to demographics and general health was entered in the model, we reduced this model by deleting the variables one by one until only those with a *P* value <.15 remained. A variable with a *P* value >.15 was kept in the model only if it increased considerably the predictive value of the model. Next, we entered the second block of variables related to the characteristics of HZ at recruitment, and among these new variables we again deleted one by one those with a *P* value >.15. The final block assessed the effect of initial treatment of HZ. We verified that collinearity was not an issue using condition indices and variance inflation.[2] At each step, the calibration of the model was evaluated with measures of goodness-of-fit (Hosmer-Lemeshow Chi-square statistic) and discrimination (area under the Receiver Operating Characteristics [ROC] curve). The area under the ROC curve reflects the model's ability to correctly identify cases that developed PHN and varies from .5 to 1, with 1 representing perfect discrimination. The added predictive value of each new block of variables was determined by comparing the ROC curves while taking into consideration their correlation.[12]

To compare the burden experienced by subjects who developed PHN during the study with those who did not, we used the HZ Severity-of-Illness score (HZSOI), a severity-by-duration measure of total pain and discomfort associated with HZ. This measure was developed by Coplan et al[6] for use in the Shingles Prevention Study.[24] The HZSOI was estimated by calculating the area under the curve of the worst pain scores measured for a specified time period following rash onset (either 90 days or 180 days). Scores less than 3 after 30 days were considered as zero.[6] The $HZSOI_{0\text{-}180\ days}$ scores can range from 0 for an individual experiencing no pain for the total duration of the follow-up to 1,800 for an individual experiencing a pain scored as 10 for 180 days. The $HZSOI_{0\text{-}180\ days}$ for subjects who developed PHN was calculated from rash onset until 180 days. In this way, we captured the overall severity-of-illness experienced by cases that developed PHN throughout the different phases of HZ and PHN.

We used ANOVA with post hoc Student t-test to compare the HZSOI scores between subjects who developed PHN and those who did not. Because of the slightly skewed distribution of the scores, we validated our results with nonparametric tests. We also used spline curves to illustrate the difference in the evolution of pain severity over time between subjects who developed PHN compared to those who did not. Spline curves are a nonparametric extension of traditional linear models that are used as a smoothing technique to explore data in the case of nonlinear associations. All analyses were conducted using SAS v.9.2 (SAS Institute, Cary, NC).

Results

Between 89% and 98% of participants completed the questionnaires at each time point, and 82% completed all 10 questionnaires. Twelve subjects were immunocompromised and were excluded from our main analyses. Mean age at diagnosis was 65 (±11) years, 58% were women, and one-third were working (Table 1). Thoracic dermatomes were the most frequently involved (49%). The great majority of subjects (73%) experienced prodromal pain before rash onset. Almost 90% of subjects were initially treated with antiviral medication.

When PHN is defined as pain ≥3 persisting or appearing 90 days after rash onset,[6] 22% (n = 56) of immunocompetent subjects with HZ recruited within 14 days of rash onset developed PHN. None of the patients had pain appearing after 90 days. Median duration of PHN was 77 days after the first 90 days of acute and intermediate pain (ie, total median duration of pain since rash onset = 169.5 days). Moreover, 48% of subjects who developed PHN still reported clinically significant pain 180 days after rash onset. At the beginning of the PHN period, the majority of subjects with PHN (69%) reported moderate pain (3–6) and 15% reported severe pain (≥7). At the end of study follow-up (180 days), these proportions were respectively 70% and 6%.

Table 1. Characteristics at Recruitment of Immunocompetent Subjects With HZ According to Whether They Developed PHN During the Study Follow-Up or not

	Total		Developed PHN During Study Follow-Up		
	N = 249*		Yes N = 56*	No N = 193*	
Characteristics	(%)	(N)	% (N)	% (N)	P Value†
Socio-demographic and general health					
Age at rash onset					.01
49–60	38.6	(96)	25.0 (14)	42.5 (82)	
61–70	29.3	(73)	26.8 (15)	30.0 (58)	
71–96	32.1	(80)	48.2 (27)	27.5 (53)	
Mean age ± SD	65.6	± 10.8	70.3 ± 11.1	64.2 ± 10.4	.001
Gender					
Men	41.4	(103)	37.5 (21)	42.5 (82)	.51
Women	58.6	(146)	62.5 (35)	57.5 (111)	
Education					
Elementary	15.0	(37)	25.0 (14)	12.1 (23)	.04
High school	40.7	(100)	37.5 (21)	41.6 (79)	
College / University	44.3	(109)	37.5 (21)	46.3 (88)	
Working	33.6	(83)	17.8 (10)	38.2 (73)	.008
Income					
<$20,000	25.3	(63)	37.5 (21)	21.7 (42)	.02
$20,000–$39,999	27.3	(68)	33.9 (19)	25.4 (49)	
$40,000–$49,999	11.7	(29)	14.3 (8)	10.9 (21)	
≥$50,000	24.5	(61)	7.1 (4)	29.5 (57)	
Missing	11.2	(28)	7.1 (4)	12.4 (24)	
Has another pain condition	47.4	(118)	57.1 (32)	44.6 (86)	.10
Reported problems before having HZ in:					
Mobility	10.8	(26)	22.6 (12)	7.4 (14)	.0005
Self-care	3.7	(9)	9.4 (5)	2.1 (4)	.002
Usual activities	12.5	(30)	22.6 (12)	9.6 (18)	.007
Having pain or discomfort	34.8	(84)	45.3 (24)	31.9 (60)	.07
Being anxious or depressed	23.3	(56)	27.8 (15)	22.0 (41)	.37
EQ-5D index score before having HZ					
<.50	5.5	(13)	9.4 (5)	4.3 (8)	.02
.50–.74	18.1	(43)	30.2 (16)	14.6 (27)	
.75–.99	23.1	(55)	16.9 (9)	24.9 (46)	
1.00	53.4	(127)	43.4 (23)	56.2 (104)	
VAS score before having HZ					
0–49	10.8	(26)	16.7 (9)	9.1 (17)	.05
50–79	23.6	(57)	31.5 (17)	21.4 (40)	
≥80	65.6	(158)	51.8 (28)	69.5 (130)	
Characteristics of HZ at recruitment					
Delay between recruitment and rash onset‡					
0–3 days	37.7	(90)	49.0 (25)	34.6 (65)	.09
4–7 days	33.5	(80)	21.6 (11)	36.7 (69)	
8–14 days	28.8	(69)	29.4 (15)	28.7 (54)	
Primary dermatome affected‡					
Trigeminal	5.0	(123)	7.8 (4)	4.3 (8)	.57
Cervical	20.1	(48)	25.5 (13)	18.6 (35)	
Thoracic	48.9	(117)	45.1 (23)	50.0 (94)	
Lumbar	20.1	(48)	15.7 (8)	21.3 (40)	
Sacral	5.8	(14)	5.9 (3)	5.9 (11)	
Number of lesions‡					
1–10	39.1	(93)	35.3 (18)	40.1 (75)	.77
11–20	20.2	(48)	17.6 (9)	20.9 (39)	
21–50	23.1	(55)	27.4 (14)	21.9 (41)	
>50	17.6	(42)	19.6 (10)	17.1 (32)	

Table 1. Continued

Characteristics	Total N = 249* (%)	Total N = 249* (N)	Developed PHN During Study Follow-Up: Yes N = 56* % (N)	Developed PHN During Study Follow-Up: No N = 193* % (N)	P Value†
Worst pain					
No / Mild pain (0–2)	16.7	(41)	7.1 (4)	19.5 (37)	.001
Moderate (3–6)	39.8	(98)	26.8 (15)	43.7 (83)	
Severe (≥7)	43.5	(107)	66.1 (37)	36.8 (70)	
Had prodromal pain‡	73.1	(174)	82.4 (42)	70.6 (132)	.01
Duration of prodromal pain§					
1–2 days	32.8	(56)	31.7 (13)	33.1 (43)	.93
3–4 days	29.8	(51)	26.8 (11)	30.8 (40)	
5–7 days	26.9	(46)	29.3 (12)	26.2 (34)	
≥8 days	10.5	(18)	12.2 (5)	10.0 (13)	
Worst prodromal pain§					
Mild (1–2)	14.4	(25)	0.0 (0)	18.9 (25)	.96
Moderate (3–6)	40.2	(70)	45.2 (19)	38.6 (51)	
Severe (≥7)	45.4	(79)	54.8 (23)	42.4 (56)	
Reported pain interference score ≥5 in:					
General activity	40.6	(101)	55.4 (31)	36.3 (70)	.06
Mood	34.5	(86)	48.2 (27)	30.6 (59)	.04
Walking ability	22.5	(56)	35.7 (20)	18.7 (36)	.004
Normal work	34.5	(86)	42.9 (24)	32.1 (62)	.03
Relations with other people	23.3	(58)	30.4 (17)	21.2 (41)	.06
Sleep	49.0	(122)	64.3 (36)	44.6 (86)	.007
Enjoyment of life	44.2	(110)	57.1 (32)	40.4 (78)	.006
Global score of pain interference ≥5	29.1	(72)	39.3 (22)	26.2 (50)	.05
Reported problems in EQ-5D health domains:					
Mobility	27.5	(67)	43.6 (24)	22.8 (43)	.002
Self-care	13.5	(338)	23.6 (13)	10.6 (20)	.008
Usual activities	47.9	(117)	67.9 (38)	42.0 (79)	.001
Having pain or discomfort	86.9	(213)	92.9 (52)	85.2 (161)	.16
Being anxious or depressed	43.2	(105)	55.4 (31)	39.6 (74)	.04
EQ-5D index score					
<.50	19.9	(48)	27.3 (15)	17.7 (33)	.03
.50–.74	36.1	(87)	47.3 (26)	32.8 (61)	
.75–.99	34.0	(82)	20.0 (11)	38.2 (71)	
1.00	9.9	(24)	5.4 (3)	11.3 (21)	
VAS score					
0–49	20.9	(51)	36.4 (20)	16.4 (31)	.003
50–79	43.0	(105)	40.0 (22)	43.9 (83)	
≥80	36.1	(88)	23.6 (13)	39.7 (75)	
Initial treatment of HZ					
Has taken antiviral medication	88.4	(220)	82.1 (46)	90.2 (174)	.08
Type of antiviral‖					
Acyclovir	5.9	(13)	2.2 (1)	6.9 (12)	.55
Valacyclovir	45.0	(99)	45.7 (21)	44.8 (78)	
Famciclovir	49.1	(108)	52.2 (24)	48.3 (84)	
Adequacy of the antiviral treatment ‖,¶					
Optimal start time, optimal prescription	26.6	(58)	31.1 (14)	25.4 (44)	.54
Optimal start time, sub-optimal prescription	26.1	(57)	17.8 (8)	28.3 (49)	
Optimal start time, missing prescription	21.1	(46)	26.7 (12)	19.6 (34)	
Sub-optimal start time, optimal prescription	8.3	(18)	11.1 (5)	7.5 (13)	
Sub-Optimal start time and prescription	9.6	(21)	8.9 (4)	9.8 (17)	
Sub-optimal start time, missing prescription	8.3	(18)	4.4 (2)	9.3 (16)	

Table 1. Continued

	Total		Developed PHN During Study Follow-Up		
	N = 249*		Yes N = 56*	No N = 193*	
Characteristics	(%)	(N)	% (N)	% (N)	P Value†
Has taken other medication:					
NSAID / Analgesic	10.8	(27)	14.3 (8)	9.8 (19)	.33
Opiates / Narcotics	22.1	(55)	26.8 (15)	20.7 (40)	.32
Antidepressant	14.5	(36)	16.1 (9)	14.0 (27)	.69
Anticonvulsant	7.2	(18)	8.9 (5)	6.7 (13)	.57
Anxiolytics / Hypnotics	.8	(2)	1.8 (1)	.5 (1)	.26
Corticosteroids	1.6	(4)	1.8 (1)	1.6 (3)	.90
Ophthalmics	2.8	(7)	7.1 (4)	1.6 (3)	.005
Topicals	14.1	(35)	14.3 (8)	14.0 (27)	.95

Abbreviations: HZ, herpes zoster; VAS, visual analog scale.

NOTE. 12 subjects were immunocompromised and excluded from these analysis. Reasons for impaired immune status were high dose corticosteroids for extended period (n = 2), cancer (n = 4), HIV (n = 1), and drug for cancer or organ transplant (n = 10).

*Because of missing data, the number of individuals does not always add to the total.

†*P* values were obtained by univariate log-binomial regression (Wald test) and represent the global level of significance of the variable. *P* values were adjusted to take into consideration missing values when 10 or more missing values were observed.

‡Information on the rash is missing for 10 cases.

§Percent calculated among the 186 cases who reported prodromal pain.

‖Percent calculated among the 232 cases who received antiviral medication.

¶Adequacy of antiviral treatment was determined as follows: Optimal start time: antiviral started within 3 days of rash onset.[9,16] Optimal prescription: duration of 7 days or more and recommended dose (Acyclovir: total of 4000 mg/day, Valacyclovir: 3000 mg/day, and Famciclovir: 1500 mg/day).[9,16]

When considering simultaneously the socio-demographic and general health characteristics, older age and reporting problems with usual activities before having HZ increased significantly the risk of developing PHN (Table 2, model 1). When adding the characteristics of HZ at recruitment, only higher pain severity at recruitment increased significantly the risk of developing PHN and added predictive value to the previous model (Table 2, model 2). The initial treatment of HZ was not significantly associated with the risk of developing PHN (*P* value for antivirals = .30) when the socio-demographic, general health and the HZ severity were already considered. When including the 12 immunocompromised subjects in this analysis, the same predictors of PHN remained, and being immunocompromised also emerged as a final independent predictor of PHN (Model 1: RR =1.98 95% CI (1.14–3.45), *P* value = .02; Model 2: RR = 1.66 95%CI (.95–2.91), *P* value = .08.

Sensitivity analysis using 2 different definitions of PHN resulted in a greater proportion of subjects that developed PHN, with 41% having pain ≥3 persisting more than 30 days compared with 33% having pain of any intensity persisting more than 90 days. Older age and severity of pain at recruitment remained significantly associated with PHN in both sensitivity analyses. The only difference associated with these alternate definitions was that limitations in usual activities at recruitment emerged as a final predictor for both sensitivity analyses instead of limitations prior to HZ.

Finally, subjects who developed PHN during follow-up experienced a substantially greater $HZSOI_{0\text{-}180days}$ score compared to those who did not (688 vs 152, *P* value < .0001) (Table 3). This excess HZSOI experienced because of PHN was as important in younger as in older adults and resulted not only from the longer duration of pain, which followed from the definition of PHN, but also from higher pain severity during the first 90 days after rash onset (Fig 1).

Discussion

Our results indicate that 2 socio-demographic and general health characteristics (older age and reporting problems in usual activities before having HZ) and 1 characteristic of HZ at recruitment (pain severity) were associated significantly with the risk of developing PHN. Our results suggest that impaired immune status may also be associated with the risk of PHN. This study quantified the burden of illness caused by PHN in terms of patient suffering. From our initial cohort of subjects seeking care for HZ within 14 days of rash onset, 22% still reported clinically significant pain 90 days after rash onset, which was defined as PHN. The median duration of pain during the PHN period was 77 days. In addition, these subjects experienced considerable pain severity throughout the study follow-up.

Functional status is a critically important aspect of health in older adults, but analysis of functional status as a risk factor for greater burden of illness has been lacking in HZ research and in infectious-diseases research in general.[14] We assessed whether the functional status before having HZ or the extent that HZ pain interfered with activities of daily living at recruitment increased the risk of PHN. Although many indicators of functional status prior to HZ and at recruitment were significantly associated with an increased risk of PHN in univariate analysis, most of these effects were no longer significant in the multivariate model. Interestingly, functional status prior

Table 2. Hierarchical Model of the Predictors of Developing PHN Among Immunocompetent Subjects

	Model 1		*Model 2*	
Potential predictors	*RR*	*P Value* CI 95%*	*RR*	*P Value* CI 95%*
Socio demographic and general health				
Age at rash onset (years)		*.005*		*.05*
	1.03	(1.01–1.05)	1.02	(1.00–1.04)
Income†		*.04*		*.25*
≥50,000	1.00		1.00	
$40,000–$49,999	5.23	(1.54–17.84)	2.24	(.98–5.13)
$20,000–$39,999	4.01	(1.25–12.87)	1.77	(.87–3.63)
<$20,000	5.15	(1.63–16.30)	1.85	(.89–3.83)
Had problems in usual activities before HZ		*.007*		*.05*
No	1.00		1.00	
Yes	1.92	(1.20–3.09)	1.66	(.99–2.79)
HZ characteristics at recruitment				
Worst pain severity				*.03*
No pain (0) / mild (1–2)			1.00	
Moderate (3–6)			1.22	(.56–2.67)
Severe (≥7)			2.06	(.98–4.35)
Area under the ROC curve	.74	(.67–.82)	.78	(.71–.86)
P value for the added predictive value of the block compared to the previous model		—		*.11*

*The *P* values in italic refer to the global level of statistical significance of the variable.
†Adjusted for missing data. Income was kept in model 2 because: 1) it increased the predictive value of this model; 2) some categories were statistically significant; and 3) it allowed a valid assessment of the predictive value of adding pain severity to model 1 as both models include the same variables.

to developing HZ (as measured by limitation of usual activities) remained statistically significant in our main analysis of PHN predictors while limitations in functional status at recruitment emerged as a predictor when using different PHN definitions. Only 1 previous study observed a relationship between functional status during acute HZ and the risk of PHN.[18] The authors hypothesized that functional impairment in cases developing PHN reflected their response to HZ rather than premorbid functioning limitations. Our results rather suggest that premorbid functional status, possibly as a marker of poor health or immune function, might also independently increase the risk of developing PHN. This is a novel finding in HZ and PHN research that deserves further exploration.

Although the number of immunocompromised subjects in this study was small and their identification was solely based on the recruiting physician's clinical judgment, to our knowledge these results are the first to suggest an independent effect of immunosuppression on the risk of developing PHN. It is generally recognized that subjects with disorders of cell-mediated immunity are at increased risk of developing HZ and that their HZ can be more severe than typical cases.[9] However, data is scarce regarding the risk of developing PHN according to the immune status of patients with HZ. Most studies that have assessed predictors of developing PHN using multivariate analysis were restricted to immunocompetent subjects,[5,8,17,20,22,32] while the few studies that included immunocompromised subjects had several limitations leading to inconsistent results.[1,4,25] Additional studies with more immunocompromised subjects and a detailed assessment of the causes of immunosuppression are needed to confirm these observations and fully understand the role of immune status in the development of PHN.

Although our study was neither designed nor powered to assess the efficacy of antiviral treatment to prevent PHN, we examined the association between initial treatment of HZ and the risk of developing PHN. Antiviral therapy did not emerge as a final independent predictor, whereas a nearly significant association was observed in univariate analysis ($P = .08$), and previous results from the MASTER study indicated that antiviral treatment significantly reduced the severity of illness (ie, severity by duration) of HZ and PHN (Drolet, unpublished material, 2009). These observations suggest that the severity of illness (ie, magnitude of pain over time) might be a measure more sensitive to the preventive effect of antivirals. The authors of a recent Cochrane collaboration on the efficacy of antivirals for the prevention of PHN also concluded that pain severity, in addition to pain duration,

Table 3. Herpes Zoster Severity-Of-Illness (HZSOI) Experienced by Immunocompetent Subjects Who Developed PHN During the Study Follow-Up Compared to Those Who Did Not

	Developed PHN During Study Follow-Up		
	Yes (N = 63*) Mean (95% CI)	No (N = 198†) Mean (95% CI)	P Value ‡
$HZSOI_{0\text{-}30\ day}$	176.4 (157.8–195.1)	112.4 (102.8–121.9)	<.0001
49–60 yrs	153.2 (117.9–188.5)	103.2 (88.7–117.6)	.01
61–70 yrs	187.7 (152.4–223.0)	128.0 (110.9–145.0)	.003
>70 yrs	188.4 (162.9–213.8)	105.9 (87.9–123.9)	<.0001
$HZSOI_{0\text{-}90\ days}$	432.9 (395.9–469.8)	154.7 (136.9–177.0)	<.0001
49–60 yrs	330.2 (260.3–400.1)	130.1 (100.4–159.8)	<.0001
61–70 yrs	492.4 (422.5–562.3)	179.4 (144.4–214.3)	<.0001
>70 yrs	476.0 (425.6–526.4)	154.6 (118.6–190.6)	<.0001
$HZSOI_{0\text{-}180days}$	687.7 (638.7–736.7)	152.3 (125.4–179.1)	<.0001
49–60 yrs	542.1 (448.1–636.1)	126.5 (85.1–167.9)	<.0001
61–70 yrs	733.4 (642.9–824.0)	180.7 (132.8–228.6)	<.0001
>70 yrs	787.5 (719.8–855.3)	149.6 (99.6–199.5)	<.0001

*Age distribution of the 63 cases who developed PHN: 49–60 yrs, n = 14; 61–70 yrs, n = 15; >70 yrs, n = 27.
†Age distribution of the 198 cases who did not developed PHN: 49–60 yrs, n = 824; 61–70 yrs, n = 58; >70 yrs, n = 53.
‡The HZSOI of subjects who developed PHN or not was compared with ANOVA and the *P* values were obtained from post hoc Student t-test.

should be used as efficacy measures in future randomized trials of antivirals for the prevention of PHN.[19]

Our results were generally consistent when using different definitions of PHN, but were slightly different from those of Opstelten et al.[22] The final predictors in the Opstelten study were older age, greater acute pain severity, greater rash severity, and shorter duration of rash prior to consultation. Although a shorter duration of rash prior to consultation correlated significantly with the risk of developing PHN in our univariate

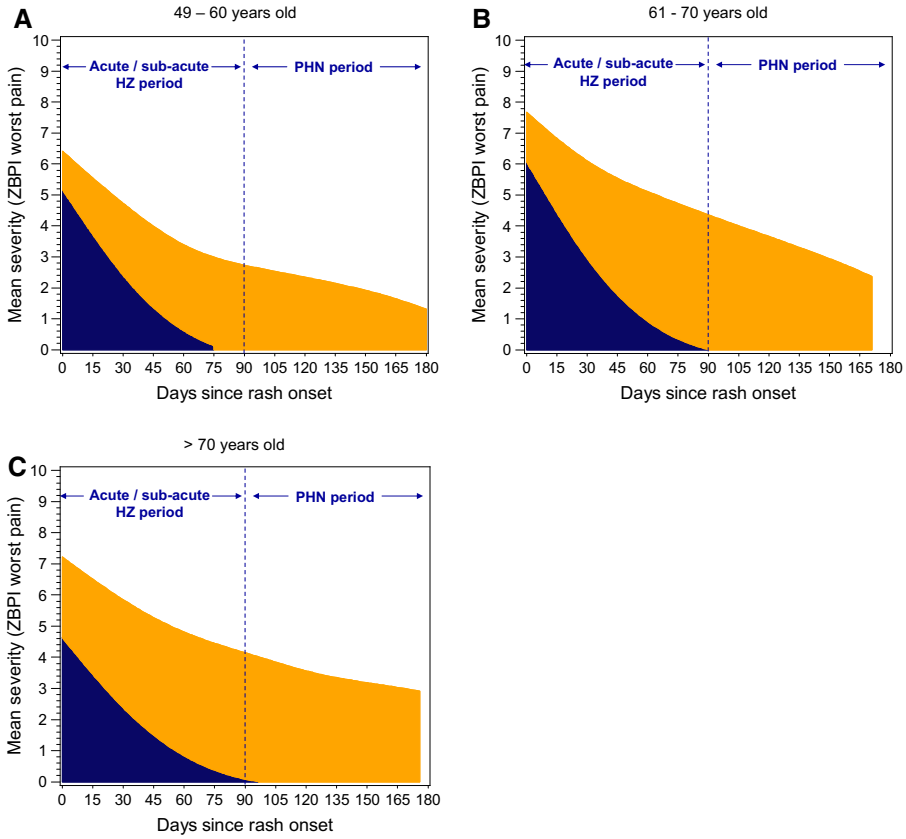

Figure 1. Did not develop post-herpetic neuralgia; Developed postherpetic neuralgia; Excess severity associated with developing post-herpetic neuralgia. HZ, herpes zoster; PHN, postherpetic neuralgia (defined as a worst pain ≥3 persisting or appearing 90 days after the rash onset); ZBPI, Zoster Brief Pain Inventory.

analysis, this was not observed in the multivariate model. One hypothesis could be that shorter duration of rash prior to consultation reflects more severe pain, which is a stronger predictor of PHN. In addition, rash severity was not predictive of PHN in the univariate and multivariate analyses. These differences may be due to sample size. Previous results from our study indicated that the number of lesions was associated with severity of illness (Drolet, unpublished material, 2009). It is thus possible that our sample size was not sufficient to detect an effect of the number of lesions on the risk of PHN (a categorical variable) but was sufficient to detect an effect on the severity-of-illness score (a continuous variable, thus more sensitive).

Our study has several strengths compared to previous studies assessing the predictors of PHN. First, we tested a sample of 41% of our subjects for the presence of the varicella-zoster DNA by PCR and confirmed that the diagnosis of HZ was correct for 95% of the tested cases, while most previous studies did not have such diagnosis confirmation.[22] Sensitivity analysis revealed that our conclusions on the main predictors of PHN were very similar when the analysis was restricted to subjects with a confirmed HZ diagnosis. Second, we used an optimal multivariate statistical strategy to assess the relative contribution of different categories of risk factors. Third, we assessed the effect of antiviral treatment on PHN while controlling for all the other risk factors. Fourth, we used an informative measure capturing simultaneously the burden caused by pain duration and severity to illustrate the excess burden of illness suffered by subjects with PHN throughout the study follow-up.

To make large-scale recruitment feasible and to reproduce clinical conditions, we imposed minimal additional workload on recruiting physicians, beyond that needed to treat their patients. For this reason, participation was not necessarily offered to all eligible patients and the proportion of eligible patients who declined the invitation was not documented. However, our participants compared favorably with other populations of subjects with HZ previously studied[3,22,30,33] in terms of proportion of subjects reporting prodromal pain, distribution of the dermatomes affected, and pain severity at recruitment. Another limitation attributable to the large-scale clinic-based recruitment is that 122 participants were recruited while already taking antivirals (mean of 5 days of treatment). Although antiviral treatment could alleviate the initial symptoms, the severity of HZ at recruitment was very similar between cases already taking medication and the other cases (ie, proportion reporting prodromal pain, dermatome affected, number of visible lesions [crusted or active], and pain severity). Nonetheless, it remains possible that pain at recruitment might be slightly lower than pain at rash onset in this study, as a result of antivirals or natural evolution of the disease, since cases were recruited up to 14 days after rash onset. However, we still observe a highly significant association between pain severity at recruitment and the risk of PHN.

In conclusion, this study confirms that older age and greater acute-pain severity are predictors of PHN. In addition, we show that the health state of an individual before having HZ correlates with an increased risk of PHN. More than 20% of our initial cohort developed PHN and experienced considerable burden as a result of both pain severity and long duration of pain. Finally, although the incidence of PHN increased with age, once PHN developed, younger and older patients were equally likely to suffer considerable severity of illness.

Acknowledgments

We thank JSS medical research inc. for gathering the study data. All authors have contributed significantly to the design and the publication phases of this research. They have reviewed and approved the final manuscript. The authors would like to thank the MASTER investigators:

Claudius Che, Ronald Cox, Chikkahanumaiah Devaraj, Tommy Hong, Shelendra Joshi, Douglas Mah, Altaf S.T.Mawji, Salim H. J. Sunderji, Jim Tsang, R. Ian Metcalfe, Allan L. Bailey, Allan J. Kelly, Sarjiwan K. Khullar, Robin Côté, Pierre Dauth, Jacques Desroches, Pierre Meunier, Gilles Morin, Alain Tremblay, Mark Kazimirski, Sheilagh McGrath, Jacqueline Verge, André Beauchesne, Rock Lambert, Charles Taschereau, Bruno Tremblay, Camil Vallières, Robert Bissonnette, Celine Gaudet, Robert Lagarde, Hélène Laporte, Marcel Leclair, Thanh Phi Luu, Thi Ngoc Lan Nguyen, Simon Nigen, John M. Bartlett, Carl Bertrand, Selwyn De Souza, Roderick Rabb, Lucy Rabb, Daryl Sokolon, James Ying, Paul Ziter, Gayle Climpson-Kennedy, Martin L. Kates, Darren Larsen, Lenny Alladin, Gary Barrs, Jean, Bouthillier, Alain Brassard, Christian Leduc, Francine Lampron, Michel Lynch, Pierre Payer, Albert Prossin, Eric St-Amour, Christos M. Tsoukas, Pierre Varvarikos, Louis Chung, David H. Cram, David J.Crawford, Clement Lang, Grazyna Lipinski, Pravinsagar G. Mehta, Praful Patel, Jayshree Patel, Victoria Taraska, John H. G. Atherstone, Rosemary M. Atherstone, Craig L. Bergstrom, Ronald S. Collette, Andrew Hosie, Alkarim N. K. Karmali, Philip Kelly, Geoffrey W. Killick, Cilliers Marais, Johannes M. B. Wagenaar, Geeta Achyuthan, Susanne Arndt, Sy Lam, Edmond K. H. Liu, Parshottam Mathur, Sol Baum, Kin L.Chung, Aneel Kaushik, Matthew Kim, Claire Nunes-Vaz, Howard Rudner, James Vavougios, Daniel Yim, Robert Nelson Baker, Kenneth M.C. Cho, Chantal Haussmann, Ian L. Mitchell, Ernest Jacob Pauls, Danny Wong, Jacques Charbonneau, Hélène Cormier, Philippa Keegan, Andrew Kuchtaruk, Wayne Olsheski, Yves Poulin, Agnes Reicher, Sandra Simon, Bruce H. Wheeler, Philip Wong, Michelle Young, David A. Henry, Ginette Barrière, Paul Nunn, Serge Tremblay, Ted J. Jablonski, Pierre Juneau, Peter Cameron, Lyn Guenther, Roman Jovey, Ian Landells, Francisco Diaz-Mitoma, Charles Lynde, Gil Faclier, Jason Rivers, Janet McElhaney.

This study was funded by Merck Frosst Canada Ltd. and was conducted under a collaborative research agreement between Merck Frosst Canada Ltd. and the MASTER study scientific steering committee consisting of Drs Brisson, Levin, Schmader, Oxman, Johnson, Patrick and Mansi. The scientific steering committee was responsible for the development of the protocol and for the direction of the study. Dr Brisson has received an unrestricted

research grant from Merck Frosst Canada to conduct the analysis and publications under the direction of the scientific steering committee. The study data set is housed in the Centre hospitalier affilié universitaire de Québec, Hôpital Saint-Sacrement, Québec, Canada. Merck Frosst does not have any ownership rights to the findings and results. The scientific steering committee has absolute discretion and the final decision over the contents and authorship of all publications or presentations.

Potential Conflict of Interest

Dr Drolet, no conflict. Dr. Brisson was an employee of Merck Frosst Canada Ltd. from 2003 to 2006; within the past 5 years, Dr Brisson has consulted for Merck Frosst and has received reimbursement for travel expenses from GlaxoSmithKline. Dr Schmader has received grant support from Merck and Wyeth and has consulted for Merck and GlaxoSmithKline. Dr Levin has consulted for Merck Frosst and has received research funds and/or consultation fees from Merck & Co. Dr Oxman has consulted for Merck Frosst and is National Chairman of VA Cooperative Study #403, "The Shingles Prevention Study" and its Substudies, which has been supported, in part, by grants from Merck and Company, Inc to the VA Cooperative Studies Program, the VA San Diego Medical Research Foundation, and the VA Connecticut Research and Education Foundation. Dr Johnson has consulted and has received honoraria for public speaking from Merck Frosst, Merck Inc (US), Sanof Pasteur Merck, Astellas, Novartis and GlaxoSmithKline. Dr Patrick, no conflict. S Camden, no conflict. Dr Mansi is an employee of Merck Frosst Canada Ltd, and Merck is the developer and distributor of the HZ vaccine.

References

1. Balfour HH Jr: Varicella zoster virus infections in immunocompromised hosts. A review of the natural history and management. Am J Med 85:68-73, 1988

2. Belsley D, Kuh E, Welsch R: Regression diagnostics: Identifying influential data and sources of collinearity, 1st ed. New York, NY, John Wiley & Sons, 1980

3. Beutner KR, Friedman DJ, Forszpaniak C, Andersen PL, Wood MJ: Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. Antimicrob Agents Chemother 39:1546-1553, 1995

4. Choo PW, Galil K, Donahue JG, Walker AM, Spiegelman D, Platt R: Risk factors for postherpetic neuralgia. Arch Intern Med 157:1217-1224, 1997

5. Coen PG, Scott F, Leedham-Green M, Nia T, Jamil A, Johnson RW, Breuer J: Predicting and preventing postherpetic neuralgia: Are current risk factors useful in clinical practice? Eur J Pain 10:695-700, 2006

6. Coplan PM, Schmader K, Nikas A, Chan IS, Choo P, Levin MJ, Johnson G, Bauer M, Williams HM, Kaplan KM, Guess HA, Oxman MN: Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: Adaptation of the brief pain inventory. J Pain 5:344-356, 2004

7. Dworkin R, Schmader K: The epidemiology and natural history of herpes zoster and postherpetic neuralgia. Herpes zoster and postherpetic neuralgia, 2nd ed. Amsterdam, NL, Elsevier, 2001, pp 39-65

8. Dworkin RH, Boon RJ, Griffin DR, Phung D: Postherpetic neuralgia: Impact of famciclovir, age, rash severity, and acute pain in herpes zoster patients. J Infect Dis 178(Suppl 1):76-80, 1998

9. Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, Betts RF, Gershon AA, Haanpaa ML, McKendrick MW, Nurmikko TJ, Oaklander AL, Oxman MN, Pavan-Langston D, Petersen KL, Rowbotham MC, Schmader KE, Stacey BR, Tyring SK, van Wijck AJ, Wallace MS, Wassilew SW, Whitley RJ: Recommendations for the management of herpes zoster. Clin Infect Dis 44(Suppl 1):1-26, 2007

10. Dworkin RH, Schmader KE: Treatment and prevention of postherpetic neuralgia. Clin Infect Dis 36:877-882, 2003

11. Edmunds WJ, Brisson M, Rose JD: The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Vaccine 19:3076-3090, 2001

12. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 143:29-36, 1982

13. Helgason S, Petursson G, Gudmundsson S, Sigurdsson JA: Prevalence of postherpetic neuralgia after a first episode of herpes zoster: Prospective study with long term follow up. Bmj 321:794-796, 2000

14. High KP, Bradley S, Loeb M, Palmer R, Quagliarello V, Yoshikawa T: A new paradigm for clinical investigation of infectious syndromes in older adults: Assessment of functional status as a risk factor and outcome measure. Clin Infect Dis 40:114-122, 2005

15. Hope-Simpson RE: Postherpetic neuralgia. J R Coll Gen Pract 25:571-575, 1975

16. Johnson RW, Wasner G, Saddier P, Baron R: Herpes zoster and postherpetic neuralgia: Optimizing management in the elderly patient. Drugs Aging 25:991-1006, 2008

17. Jung BF, Johnson RW, Griffin DR, Dworkin RH: Risk factors for postherpetic neuralgia in patients with herpes zoster. Neurology 62:1545-1551, 2004

18. Katz J, McDermott MP, Cooper EM, Walther RR, Sweeney EW, Dworkin RH: Psychosocial risk factors for postherpetic neuralgia: A prospective study of patients with herpes zoster. J Pain 6:782-790, 2005

19. Li Q, Chen N, Yang J, Zhou M, Zhou D, Zhang Q, He L: Antiviral treatment for preventing postherpetic neuralgia. Cochrane Database Syst Rev 2009;(2):CD006866

20. Nagasako EM, Johnson RW, Griffin DR, Dworkin RH: Rash severity in herpes zoster: Correlates and relationship to postherpetic neuralgia. J Am Acad Dermatol 46:834-839, 2002

21. Opstelten W, Mauritz JW, de Wit NJ, van Wijck AJ, Stalman WA, van Essen GA: Herpes zoster and postherpetic neuralgia: Incidence and risk indicators using a general practice research database. Fam Pract 19:471-475, 2002

22. Opstelten W, Zuithoff NP, van Essen GA, van Loon AM, van Wijck AJ, Kalkman CJ, Verheij TJ, Moons KG: Predicting postherpetic neuralgia in elderly primary care patients

with herpes zoster: Prospective prognostic study. Pain 132(Suppl 1):52-59, 2007

23. Oster G, Harding G, Dukes E, Edelsberg J, Cleary PD: Pain, medication use, and health-related quality of life in older persons with postherpetic neuralgia: Results from a population-based survey. J Pain 6:356-363, 2005

24. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, Arbeit RD, Simberkoff MS, Gershon AA, Davis LE, Weinberg A, Boardman KD, Williams HM, Zhang JH, Peduzzi PN, Beisel CE, Morrison VA, Guatelli JC, Brooks PA, Kauffman CA, Pachucki CT, Neuzil KM, Betts RF, Wright PF, Griffin MR, Brunell P, Soto NE, Marques AR, Keay SK, Goodman RP, Cotton DJ, Gnann JW Jr., Loutit J, Holodniy M, Keitel WA, Crawford GE, Yeh SS, Lobo Z, Toney JF, Greenberg RN, Keller PM, Harbecke R, Hayward AR, Irwin MR, Kyriakides TC, Chan CY, Chan IS, Wang WW, Annunziato PW, Silber JL: A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 352:2271-2284, 2005

25. Rusthoven JJ, Ahlgren P, Elhakim T, Pinfold P, Reid J, Stewart L, Feld R: Varicella-zoster infection in adult cancer patients. A population study. Arch Intern Med 148: 1561-1566, 1988

26. Schmader KE: Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain 18:350-354, 2002

27. Skov T, Deddens J, Petersen MR, Endahl L: Prevalence proportion ratios: Estimation and hypothesis testing. Int J Epidemiol 27:91-95, 1998

28. Szende A, Williams A: Measuring self-reported population health: An international perspective based on EQ-5D, 1st ed. Budapest, HU, Springmed Publishing, 2004

29. Thyregod HG, Rowbotham MC, Peters M, Possehn J, Berro M, Petersen KL: Natural history of pain following herpes zoster. Pain 128:148-156, 2007

30. Tyring SK, Beutner KR, Tucker BA, Anderson WC, Crooks RJ: Antiviral therapy for herpes zoster: Randomized, controlled clinical trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. Arch Fam Med 9:863-869, 2009

31. van Seventer R, Sadosky A, Lucero M, Dukes E: A cross-sectional survey of health state impairment and treatment patterns in patients with postherpetic neuralgia. Age Ageing 35:132-137, 2006

32. Volpi A, Gatti A, Pica F, Bellino S, Marsella LT, Sabato AF: Clinical and psychosocial correlates of post-herpetic neuralgia. J Med Virol 80:1646-1652, 2008

33. Whitley RJ, Weiss H, Gnann JW, Jr., Tyring S, Mertz GJ, Pappas PG, Schleupner CJ, Hayden F, Wolf J, Soong SJ: Acyclovir with and without prednisone for the treatment of herpes zoster. A randomized, placebo-controlled trial. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Ann Intern Med 125: 376-383, 1996

34. Whitley RJ, Weiss HL, Soong SJ, Gnann JW: Herpes zoster: Risk categories for persistent pain. J Infect Dis 179:9-15, 1999

35. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS: A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc 82:1341-1349, 2007