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Herpes zoster – is there a need for new treatment recommendations?

Herpes zoster – da li su potrebne nove preporuke za lečenje?

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Abstract

Background/Aim. The reactivation of the *varicella zoster* virus results in herpes zoster. Acyclovir is currently recommended over 7 to 10 days for herpes zoster treatment and should be started within 72 hours of rash eruption. This study analyses whether a therapy delay and/or shorter courses of treatment are associated with adverse outcomes. **Methods.** We identified 292 patients treated at the Clinic for Infectious and Tropical Diseases in Belgrade for herpes zoster in a five-years period. The data on these patients were analyzed using the descriptive statistics, the χ^2 test, the Mann-Whitney *U*-test and the multiple logistic regression analysis. **Results.** The average time from rash eruption to the first dose of acyclovir was 4.07 ± 2.64 days. The patients received acyclovir for 6.83 ± 2.45 days. Seventy-one patients had disseminated herpes zoster, 100 had cranial nerve involvement, 86 had complications other than postherpetic neuralgia and one patient died. In cases where therapy was delayed there was no significant association with complications (χ^2 = 0.031; p = 0.86). Our logistic regression model was not able to predict who was treated less than 7 days. An association between the HZ complications and abbreviated acyclovir regimens was not demonstrated (χ^2 = 1.109; p = 0.326). We conducted the PubMed search on February 1st, 2017 and found no proof for the need to apply at least 7 days of acyclovir therapy for herpes zoster in the studies that have been published so far. **Conclusion.** We were unable to prove an association between therapy delay and unfavorable outcomes. The same was true for shorter than recommended acyclovir courses.

Key words:
varicella zoster virus infection; recurrence; drug users; treatment outcome.

Apstrakt

Uvod/Cilj. Rektivacija *varicela zoster* virusa dovodi do herpesa zostera (HZ). Prema aktuelnim preporukama terapija ove bolesti podrazumeva 7 do 10 dana primene aciklovira. Terapiju treba započeti unutar 72 časa od pojave ospe. Ova studija imala je za cilj da proceni da li je kašnjenje u započinjanju terapije i/ili skraćeno trajanje terapije aciklovirom povezano sa lošim tokom i ishodom HZ. **Metode.** Sprovedena je analiza 292 bolesnika koji su lečeni zbog herpes zostera u Klinici za infektivne i tropske bolesti u Beogradu u petogodišnjem periodu. Podatke o ovim bolesnicima analizirali smo pomoću metoda deskriptivne statistike, χ^2- testa, Man-Vitni *U*-testa i multiplom logističkom regresijom. **Rezultati.** Vreme od pojave ospe do prve doze aciklovira iznosilo je 4,07 ± 2,64 dana. Bolesnici su lečeni aciklovirom prosečno 6,83 ± 2,45 dana. Sedamdeset jedan bolesnik imao je diseminovanu bolest, kod 100 su bili zahvaćeni kranijalni nervi, a kod 86 su se razvile komplikacije. Jedan bolesnik je preminuo. Slučajevi kod kojih je došlo do kašnjenja u započinjanju terapije nisu bili statistički značajno povezani sa komplikacijama (χ^2 = 0.031; p = 0.86). Logistička regresija nije uspela da predvidi ko je bio lečen aciklovirom više ili manje od sedam dana. Nije dokazana povezanost između komplikacija HZ i terapijskih režima kraćih od preporučenih (χ^2 = 1.109; p = 0.326). Pregledom *PubMed* baze podataka učinjenim 1. februara 2017. godine, u do tada objavljenim studijama nismo pronašli dokaze o tome da je neophodno najmanje sedam dana terapije aciklovirom za herpes zoster. **Zaključak.** Nije dokazano da je kašnjenje u započinjanju terapije aciklovirom povezano sa nepovoljnim ishodima. Isto se može reći i za kraće terapijske kure.

Ključne reči:
infekcija, varičela-zoster virus; recidiv; aciklovir; lekovi, korišćenje; lečenje, ishod.

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Introduction

Reactivation of the *varicella zoster* virus results in a vesiculous rash that follows a dermatomal distribution usually accompanied by pain or itching, and is known as herpes zoster (HZ) or shingles [1].

The incidence rate of HZ is 4 to 4.5 per 1000 person/years. The cumulative lifetime incidence of HZ is 10%–20% [2]. Approximately 50% of 85-year-olds have experienced at least a single episode of HZ in their lifetime [3, 4]. HZ rarely occurs in younger patients [5]. The immunocompromised patients are at a high risk for HZ with a cumulative lifetime higher than 50%. HZ is generally considered to have no gender predilection, although some types demonstrated a higher prevalence of HZ in women [6, 7].

HZ is rarely fatal in the immunocompetent patients, whereas the mortality rate in the immunocompromised patients with disseminated disease is 5% to 15% [3].

HZ involving the ophthalmic branch of the trigeminal nerve is called herpes zoster ophtalmicus (HZO) [3]. The prevalence of HZO was reported to be 8% and 56% among the people with HZ [8]. HZO is important because it often affects the structures of the eye.

The otorhinolaryngology specialists can occasionally encounter HZ that involves the geniculate ganglion of the facial nerve producing earache, external auditory meatus rash, vestibulocochlear dysfunction and even disorders of taste. This clinical entity is called herpes zoster oticus. The Ramsay-Hunt syndrome (RHS) is defined as herpes zoster oticus with a facial nerve palsy. RHS has an incidence rate of 5 per 100,000 person-years [9].

The most common complication of HZ is postherpetic neuralgia (PHN). No clear official consensus exists, but the majority of the authors define PHN as persistent or recurrent pain lasting between one and six, or more months (depending on the author) after the beginning of the eruptive phase of HZ [10, 11]. PHN is recorded in 9% to 45% of those who had a bout of HZ [12, 13].

Other neurologic complications, ophthalmologic complications and bacterial superinfections also occur although they are less common. The neurologic complications other than PHN are aseptic meningitis, encephalitis, myelitis, peripheral neuropathies and the Guillain-Barre syndrome [14].

Immunosuppression carries a greater risk of complications in the patients with HZ. In this setting, the skin lesions may disseminate and cause multiple dermatomes, sometimes crossing over the midline or even taking on a chickenpox-like form. Cases of pneumonia, encephalitis and hepatitis were also reported [15].

The patient should start the antiviral therapy if he/she is 50 years of age, or older, has disseminated HZ, atopic dermatitis, intense pain, involvement of the face or complications of HZ, or immunocompromised [1, 16, 17]. Of the recommended antivirals only acyclovir is available in Serbia.

Shorter rash evolution, reduced duration of viral shedding, shorter pain duration and lower incidence of PHN were all reported in the patients started antivirals within the first 72 hours after the skin lesions first appear [1, 3, 16]. While most experts suggest a 72-hours deadline to start a therapy, others recommend prescribing antivirals even at later stage of the disease, especially if new lesions still form [16, 18, 19].

Intravenous acyclovir (10 mg/kg three times a day over 7 to 10 days) should be administered if the patients are immunocompromised, have disseminated HZ, cranial nerve involvement, or develop certain complications other than PHN [17, 20, 21]. Since intravenous acyclovir should be administered in an inpatient setting, the above mentioned subgroups of patients are also the ones who require hospitalization. In most studies, the hospitalization was found to be warranted in about 3% of patient with HZ [22, 23]. Some authors treated the patients with antivirals until clinical resolution was achieved, or no new lesions observed [24, 25].

In this study, our goal was to answer the question of whether shorter courses of therapy, or therapy delays were associated with the unfavorable outcomes of HZ. Expanding on this query, we tried to find evidence of the need for at least 7 days of antiviral therapy in the research conducted by other authors around the world.

Methods

We conducted a single cohort retrospective study. We searched the paper-based medical records of all the patients treated from January 1st, 2011 to December 31st, 2015 at the Respiratory and Skin Infection Ward of the Clinic for Infectious and Tropical Diseases, the Clinical Center of Serbia in Belgrade. The patients that were treated within that time frame for HZ as a primary diagnosis were included in the study and demographic, epidemiologic, clinical and laboratory data were obtained.

We found that 292 people were treated at our hospital for herpes zoster in the five year period analyzed in the study. The mean age of the patients was 65.07 ± 17.19 years with the youngest patient being 3 years old and the oldest one 94. One hundred and fifty-eight women (54.1%) and 134 men (45.9%) were included in the study. The majority of patients (91.1%) were residents of Belgrade.

We considered the antiviral therapy warranted if the patents had HZ-like rash that lasted less than 72 hours, or HZ-like rash and any of the following: more than, or equal to 50 years of age, disseminated HZ, immunosuppression, atopic dermatitis, involvement of the face and complications of HZ other than PHN.

The severity of pain and the severity of rash could not be determined from the medical histories of the patients, therefore these parameters were not included, although many authors included them [22].

We considered hospitalization justified if any of the following was present: complications of HZ other than PHN, disseminated HZ, immunocompromised state of the patient and cranial nerve involvement.

The patients who had chemotherapy and/or radiotherapy, allogenic hematopoietic stem cell transplant and the solid organ transplant recipients, human immunodeficiency virus (HIV) positive individuals and the patients on chronic corticosteroid or immunomodulatory therapy (e.g., the patients with rheumatologic disorders, inflammatory bowel disease, multiple sclerosis, etc.) were considered to be immunocompromised.

The compiled data were included in the descriptive statistics analysis using the IBM SPSS Statistics version 16.0. Only the patients in whom the hospitalization was objectively indicated were subjected to further analysis. The χ^2 test (categorical variables with more than 5 observations in a single cell) and the Mann-Whitney *U* (MWU) test (continuous variables with a non-normal distribution, or heterogeneous variances) were used in an attempt to assess the possible association between the treatment delay and/or a shorter treatment course and unfavorable outcomes. We used the multiple logistic regression model in order to identify the predictors of abbreviated antiviral treatment.

The research was conducted in accordance with the ethics standards of the Declaration of Helsinki.

Results

The age frequency distribution histogram illustrates a clearly non-normal distribution (Shapiro-Wilk statistic = 0.885; $p < 0.001$) and a negative skew (skewness = -1.392 ± 0.143). One hundred and eighty patients (61.6%) were 65 years of age, or older and 252 (86.3%) were 50 years of age, or older (Figure 1). The women were overrepresented in our study but this was not found to be statistically significant ($p = 0.178$).

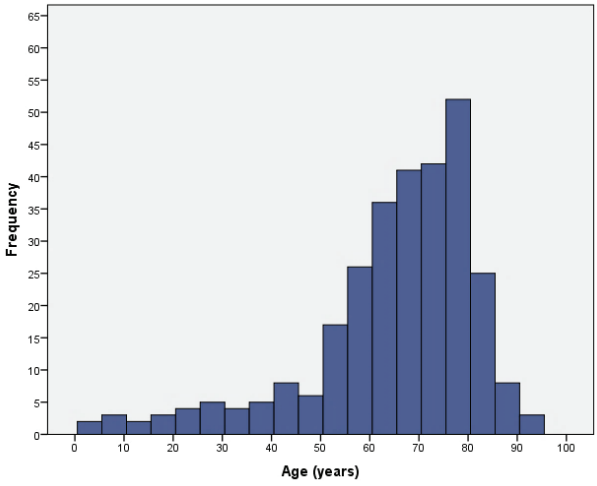

Fig. 1 – Patient age distribution histogram.

Figure 2 illustrates the seasonal variations of HZ. Even though Figure 2 seems to illustrate that the significant seasonal variations of HZ exist, the χ^2 test failed to demonstrate a statistically significant difference ($p = 0.059$).

The clinical characteristics of HZ are presented in Table 1. The cranial nerves were most commonly affected by HZ. The ophthalmologic complications were the most frequent at 18.5%.

Table 1

Clinical characteristics of herpes zoster

Parameters	Patients, n (%)
Affected nerve	
cranial nerves	97 (33.2)
cervical spinal nerves	46 (15.8)
thoracic spinal nerves	96 (32.9)
lumbar and sacral spinal nerves	53 (18.2)
Complications	
HZO with eye involvement	54 (18.5)
neuroinfection	4 (1.4)
impetiginisation	37 (12.7)
pneumonia	2 (0.7)
PHN	12 (4.1)

HZO – herpes zoster opthalmicus;
PHN – postherpetic neuralgia.

The average time from the eruption of the rash to the first dose of acyclovir was 4.07 ± 2.64 days (range 0–15). Some 50.8% received acyclovir even though the rash lasted longer than 72 hours before the initiation of therapy.

Thirty-two patients were immunocompromised (15 were on immunosuppressant drugs, 14 were undergoing chemotherapy or radiation therapy and 3 were organ transplant recipients), 71 had disseminated HZ, 100 had the cranial nerve involvement and 86 had complications other than PHN. A single patient had atopic dermatitis. A single patient died and 5 patients were discharged against medical advice. We found that 5 patients (1.7%) did not require treatment with antiviral drugs at all. The hospitalization had objectively been indicated in 188 (64.4%) patients. The results presented in the subsequent paragraphs concern these 188 patients.

The patients received acyclovir for 6.83 ± 2.45 days (range 1–16 days), with 61 (32.4%) patients treated for less than 7 days (Figure 3). Eight patients (4.3%) were treated for more than 10 days and 48 (25.5%) were treated for more than 7 days. No data on treatment duration was available for 31 (16.5%) patients.

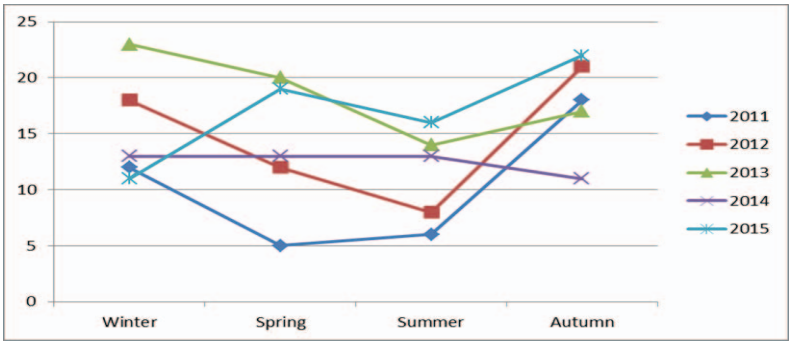

Fig. 2 – Seasonal incidence of herpes zoster spanning 5 years.

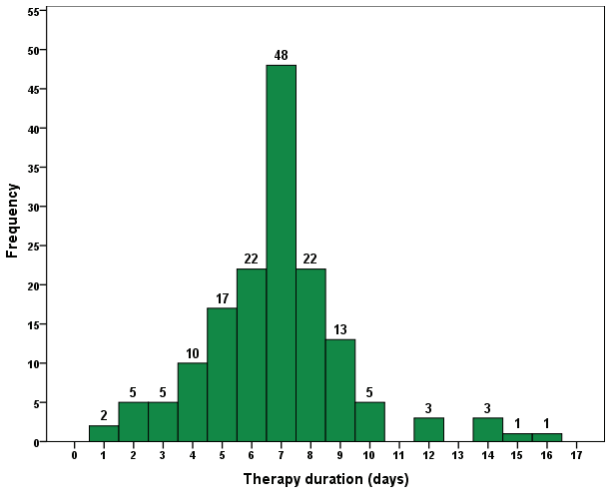

Fig. 3 – Histogram of acyclovir treatment duration (days).

All patients were discharged on the completion of antiviral therapy so the hospital stay was exactly equal to the duration of antiviral therapy.

In cases in which therapy was instituted 72 hours after the HZ rash first appeared, there was no significant association with the complications ($\chi^2 = 0.031$; $p = 0.86$). There was also no association with the overall duration of acyclovir therapy (MWU = 2645; $p = 0.131$).

The gender, patient age, longer than 3 days from the rash eruption to treatment, presence of disseminated disease, immunosuppression and cranial nerve involvement as well as the presence of complications other than PHN were entered into the multiple logistic regression model and it proved not to be able to predict who amongst our patients would be treated for less than 7 days ($\chi^2 = 6.84$, $p = 0.446$).

No association between the HZ complications and an acyclovir therapy regimen, or shorter than 7 days ($\chi^2 = 1.109$; $p = 0.326$) was demonstrated. The therapy duration was not significantly different between the patients with and without the HZ dissemination (MWU = 2780; $p = 0.941$), complications (MWU = 1456; $p = 0.341$), immunodeficiency (MWU = 1456; $p = 0.102$), or the patients with and without the cranial nerve involvement (MWU = 2699; $p = 0.189$). The association with the fatal outcomes in the cases of shorter antiviral treatment regimens was not analyzed due to the rarity of lethal outcomes in our cohort.

No other antivirals beside acyclovir were given to our patients. Local acyclovir ointment was prescribed to 38 (13%) patients. One hundred thirty-one (54.2%) patients received local or systemic antibiotics. The majority of patients, that is, 149 (51%), were treated with nonsteroidal anti-inflammatory drug (NSAID), while 43 patients (14.7%) were prescribed opioids, and another 14 (4.8%) needed antiepileptics in order to achieve an adequate pain control. Diclofenac was most commonly utilized, around the clock, for pain management in our study, with 144 patients (49.3%) receiving the drug.

We conducted a search in the PubMed database on February 1st 2017 using the formula [(day) OR days] AND ["Herpes Zoster/therapy" (Major) AND acyclovir] with the filter set to human. Two researchers independently reviewed the papers that were identified by the search algorithm in the search to prove the need for at least 7 days of acyclovir therapy for herpes zoster. Our search in the PubMed database yielded 190 results. Upon reviewing all the papers we found no evidence of the need for at least 7 days of acyclovir therapy. The oldest study designs even used 5 days of acyclovir therapy as a standard regimen.

Discussion

The majority of the authors have found HZ to be a disease of the elderly and the same is true of this study [3, 4]. Although some demonstrated a predomination of women amongst the patients with HZ, we failed to demonstrate any significant difference between the genders when it comes to HZ [7]. According to the 2011 census, Belgrade has 1,659,440 inhabitants, and our study indicates that the average number of patients hospitalized every year for HZ is 53.2. We can extrapolate that the incidence rate of hospitalization is at least 3.2 patients per 100,000 person-years [26]. This is significantly less than what had been reported by other countries. A possible explanation for this anomaly is the fact that a certain number of patients are hospitalized in other hospitals, or in other wards of our clinic, thereby underestimating the true incidence of HZ related hospitalizations.

Despite the evidence of seasonal variations in the incidence of HZ that are thought to be related to changes in atmospheric temperature and insolation, our study failed to corroborate such claims [27]. Paradoxically, we even demonstrated that the incidence of HZ was lowest in summer months (this was statistically nonsignificant), the opposite of what other authors found to be true [28].

We showed that a number of patients with HZ were hospitalized without the clear indications. The fact that more than half of our patients received acyclovir after more than 72 hours after the rash appearance is also worrisome. Yet, there seemed to be no association between the therapy delay and unfavorable outcomes like the development of complications, or longer hospital stay. A possible association with a lethal outcome could not be reliably analyzed due to the fact that a single patient in our cohort had died.

The frequency of herpes zoster oticus was less than expected in our study [9]. Cases of HZ associated with neuroinfection were also rare, due to the fact that these patients required a treatment by the intensive care specialists and were treated in the ICU ward of our clinic [14, 29].

The researchers in Iceland found that no patients younger than 50 years of age had any serious pain, while 6% of patients older than 60 yeras of age reported the severe pain a month after HZ, and 4% reported the severe pain three months after HZ [30]. The frequency of PHN was lower in our study in comparison with the data published by other authors [10]. We speculate that this is a consequence of the outpatient management of PHN as well as management by a neurologist.

The average length of inpatient acyclovir treatment in our cohort was similar to that reported by other centers [31, 32]. Around a quarter of the patients in our study were treated

longer than one week. Our logistic regression model could not predict which patients would be treated with acyclovir shorter than 7 days. Also, we found no significant differences in acyclovir treatment duration between those with and those without the dissemination, complications, immunodeficiency and cranial nerve involvement. Consequently, we cannot say that we were able to understand the logic that led the treating physicians to prescribe neither longer nor shorter courses of acyclovir therapy. The acyclovir shortages, that were sadly commonplace in the five year period analyzed, were definitely the most important factor that influenced the decision to utilize abbreviated antiviral regiments.

Viewed another way, the lack of association between the presence of complications and abbreviated acyclovir treatment regimens could be interpreted as a proof of safety of therapy courses shorter than 7 days. Therefore, the acyclovir shortages, though unfortunate, offered a chance to observe the outcomes of shortened acyclovir treatment in all, except the most severe cases of HZ. The conclusion we present in the first sentence of this paragraph cannot be generalized to all patients with HZ since those with severe pneumonia requiring the mechanical ventilation, and/or the central nervous system infections were not analyzed.

Even more intriguingly, we were unable to find a conclusive proof that less than 7 days of acyclovir treatment is associated with unfavorable outcomes in any of the 190 papers we reviewed.

We feel that a major limitation of this study was the lack of objective measures of pain intensity and rash severity. There are also no data on the skin lesion progression that could potentially be useful for determining if there is a need for an extended course of acyclovir therapy. Also, on more than one occasion, there was an acyclovir shortage which might have forced the treating physicians to shorten treatment even though they might have not felt this had been justified from a medical perspective. On the other hand, this can hardly be considered relevant since none of these patients had an unfavorable outcome, despite what is considered a subpar therapy. As noted earlier, few patients with the HZ associated neuroinfections were included in the study.

Conclusion

Our study demonstrated that an unacceptably high number of patients with HZ were hospitalized without clear indications pointing to a need for comprehensive guidelines for the HZ management in Serbia. While the majority of authors recommend at least 7 days of acyclovir therapy, we found no proof, both in the published literature and in this study, that this approach is superior to shorter treatment courses. We believe that the new, evidence-based recommendations regarding the HZ management are necessary in order to avoid the unwarranted hospitalizations and unreasonably long treatment courses, thereby cutting down the HZ-related costs and sparing the patients from the psychological stress associated with hospitalization.

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