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REVIEW ARTICLE

CHARACTERISTICS OF VARICELLA ZOSTER (VZV) VIRUS

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Summary

The evolution of varicella zoster virus lasts more than 400 million years. While primates were the original reservoirs of the virus, subsequently VZV started to circulate in human population and humans have been the exclusive hosts for VZV for more than 45 000 years. VZV is a highly contagious and neurotropic herpetic virus a member of the *herpesviridae* family.

Its primary infection results in typical signs of varicella (chickenpox). After that, the virus establishes lifelong latency in trigeminal and dorsal root ganglia. Endogenous viral reactivation, thought to be associated with waning VZV specific T cell mediated imunity, leads to herpes zoster (shingles), especially in older adults and immunocompromised persons (VZV is the only human herpetic virus exhibiting entirely different clinical picture).

Key words: varicella zoster virus; herpetic viruses; DNA; vaccination; epidemiology; chickenpox; shingles

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INTRODUCTION

Chickenpox is typically a seasonal childhood disease with peaks during late winter and early spring. In the tropical and subtropical regions however, the peak incidence of chickenpox is during the ado-

lescence. The seasonality of this disease does not occur in tropical countries (1-3). In Czech Republic the VZV reporting is in the top rank of the infectious diseases information system Epidat (www.szu.cz). The incidence of chickenpox has been oscillating around 45,000 cases/year. The disease occurs typically during the period from November to June. Table 1 shows absolute numbers of varicella and herpes zoster diagnosis reported in Czech Republic between 2010 – 2015 years.

It is easily transmitted between members of families and school classmates through airborne particles, droplets in exhaled air and fluid from blisters or sores. The virus can be also transmitted indirectly by contact with items exposed to fresh drainage from open sores. Patients are highly contagious days before and days after the date that their rash emerge. When the sores have crusted over, the patient is usually no longer contagious.

Table 1. The incidence of VZV and HZ in czceh republic from 2010 to 2015 (www.szu.cz)

Code	Diagnosis	Year					
		2010	2011	2012	2013	2014	2015
B01	Varicella	48,270	42,785	42,529	40,413	51,617	47,051
B02	Herpes zoster	6,045	6,370	6,409	6,297	6,679	6,451

Clinical symptoms and complications

The typical clinical course of chickenpox is characterized by an incubation period of 11-21 days followed sometimes by non-specific prodromal symptoms such as fever, headache and scarlet fever like exanthema (Fig. 1,2a, 2b, 3).

In adults, headaches, initial vomiting and high temperature could occur. This stage usually lasts from one to four days and, while it is usually missing in children, it may have very serious course in adults. First red spots are presented over the head and the trunk which then develop into thin-walled vesicles from one to three millimeters in size or larger. Vesicles are surrounded by a narrow red halo. The scalp is regularly affected and, often, first lesions are found there. Involvement of mucous membranes of the oral cavity also occurs, particularly on hard palate and buccal mucosa. No intact blisters are present there, rather small erosions with narrow red border and yellowish coating are found. Typically the eruptions are found in the different stages of development and during the last clinical stage they develop into the drying pustules and non-infectious crusts (often brown crusting) called as scutula. No scarring occurs in uncomplicated cases. Complications such as pneumonia, hepatitis, arthritis, bleeding disorders including secondary bacterial infections can develop (4-6).

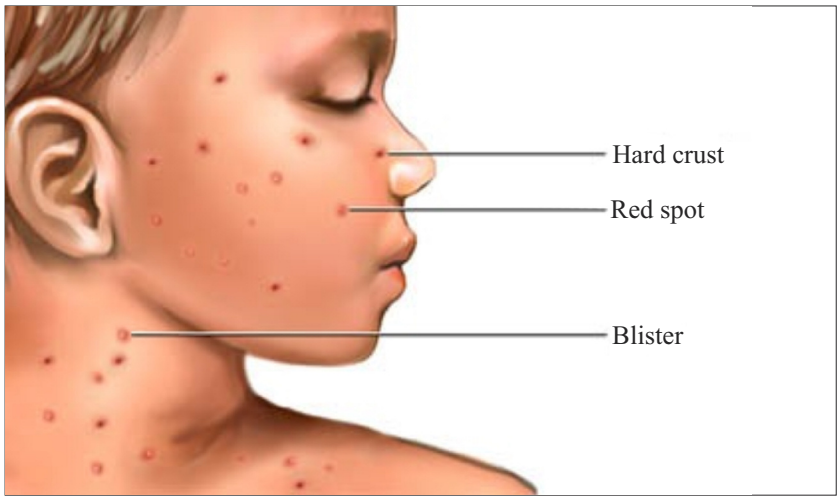

Figure1. The different stages of varicella exanthema (http://nursingcrib.com/wp-content/uploads/chicken-pox1.jpg).

Figure 2a. Child's patient with varicella exanthema (http://www.medbullets.com/step2-3-pediatrics/20582/chicken-pox-varicella).

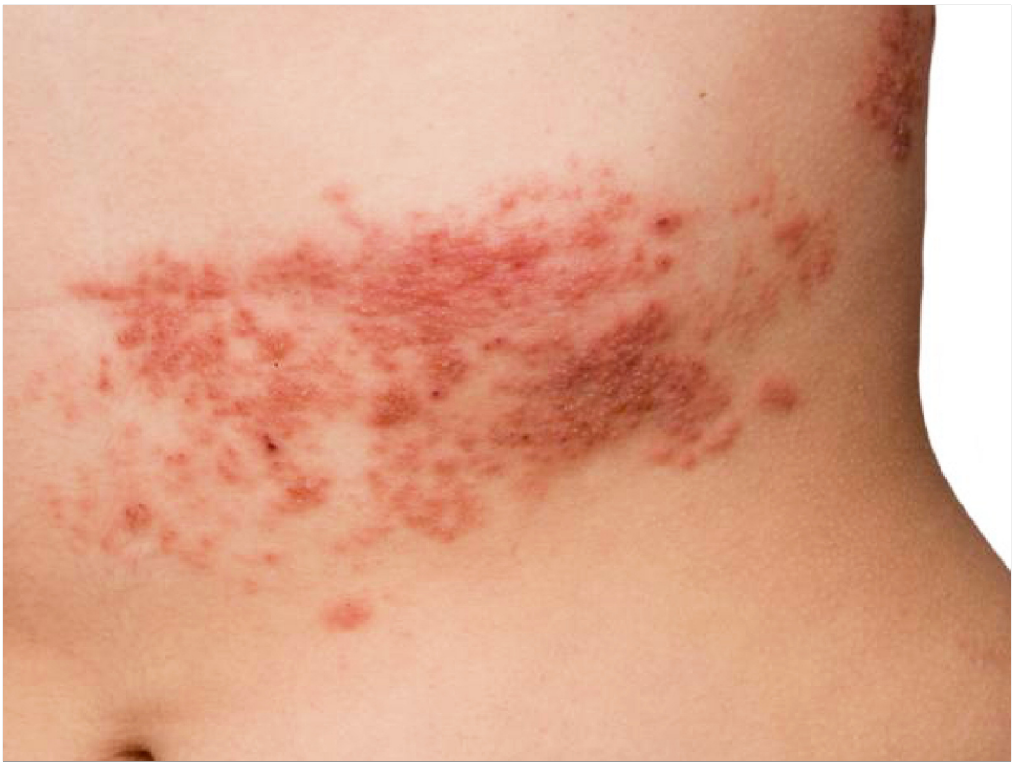

Figure 2b. Child's patient with herpes zoster (http://www.medicalnewstoday.com/articles/154912.php).

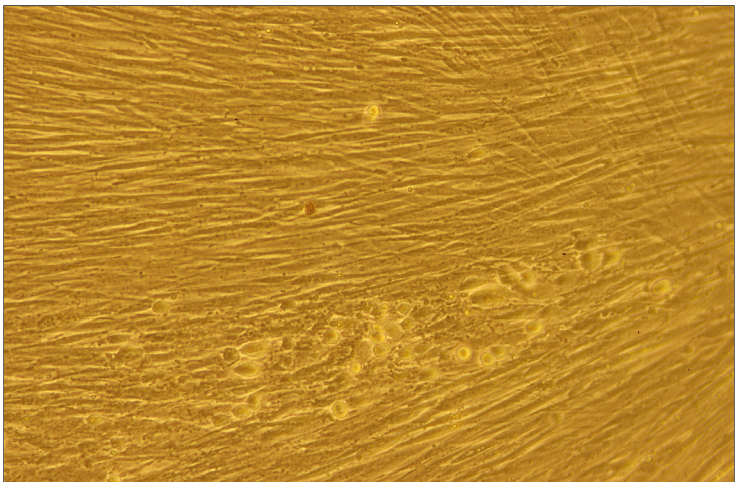

Figure 3. VZV growing on human fibroblasts cell line (sixth day after inoculation of HLF (photo V. Boštíková).

VZV exhibits tropism for neural tissues andneurologic disease can occur before or after the acute infection. Cerebellar ataxia is a possible benign complication that is thought to be due to postinfection demyelination. Resolution occurs within two to four weeks and it is estimated to occur in one in 4,000 cases among those younger than 15 years old. Ataxia, vomiting, altered speech, fever, vertigo and tremor are common symptoms.

Encephalitis occurs in 0.1 to 0.2 % of patients. Mortality has been estimated to range between 5 to 20 % and sequelae has been detected in 15 % of survivors.

Reye's syndrome is described in association with varicella, often with concomitant use of aspirin in children younger than 5 years. It begins in late stages of varicella with vomiting, restlessness, irritability, and progressive decrease in the level of consciousness, associated with progressive cerebral edema.

Immunosuppressed patients are in much greater risk of VZV complications. They may develop high fever and severe skin eruptions with or without hemorrhage. Healing of the cutaneous lesions is three times longer than in the general population. The virus spreads to visceral organs causing hepatitis, pneumonitis, pancreatitis, and encephalitis. Bacterial superinfections (*Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus*) including bacteremia can develop.

Disseminated varicella is more common in children with malignancies and especially in those, where therapy is initiated during the incubation period of VZV infection.

Rarely, varicella in early pregnancy (first 20 weeks) may result in congenital varicella syndrome (CVS). CVS occurs in two percent of infections and is characterized by unusual cutaneous defects, cicatricial skin scars, and atrophy of the extremities. The patients often have microcephaly, cortical atrophy, seizures, mental retardation, chorioretinitis, microphthalmia, or cataracts. Newborns, whose mothers develop varicella close to term, are in risk of neonatal varicella. These babies can be born with varicella lesions or develop lesions after birth, but they typically do not develop serious complications.

In addition herpes zoster could be responsible for wide spectrum of serious health complications. Zoster can affect the cornea and be followed by iridocyclitis with secondary glaucoma (*herpes zoster ophthalmicus*). Postherpetic neuralgia may occur in as many as 25 to 50 % of patients older than 50 years. Almost 50 % of persons older than 50 suffer pain for more than one month. Meningoencephalitis and encephalitis are described in patients with zoster as well.

Immunocompromised patients can experience a more severe form of the disease. Lesions form for up to two weeks after infection and scabbing occurs until three to four weeks into the course of the disease. Patients with lymphoproliferative malignancies are at risk of cutaneous dissemination and visceral involment, including pneumonitis, hepatitis, and menin-

goencephalitis. From 8 to 11 percent of patients with HIV can be infected with zoster. These patients can develop chronic herpes zoster, with formation of new lesions without the healing of the already existing ones (7-9).

Geographic distribution of VZV

Several studies have demonstrated a distinctive geographic distribution of the major VZV clades in temperate versus tropical region on the base of molecular genetics analyses. The regional dominance of specific VZV strains may be dependent on environmental factors, evolutionary conditions, and host-virus interactions, importation of viral strains through immigration or travel. Because live-attenuated varicella vaccines have been used during the last decades in childhood immunization programs, the changes in the picture of distribution of VZV strains both in individual countries and worldwide could occur.

Differences between individual VZV strains are now defined on the base of gene content and sequence similarities and/or differences. VZV is a double stranded DNA virus. Viral genome is 125,000 base pairs of double stranded DNA, contains at least 72 open reading frames (ORF) constituting 71 genes. DNA is extremely stable and contains similar to other *alpha herpes viruses*, two characteristic unique regions flanked by inverted repetitive sequences. The DNA is linear and contains 54 % of adenosine and thymidine pairs. Attempts to improve genotyping methods employed DNA sequencing to screen for SNPs in different ORFs of VZV genome.

The factors affecting the distribution of the individual VZV strains are both the past and current migration of population, as well as the climate in various geographic areas. The geographical distribution of different VZV strains is characterized by three main areas with characteristic distribution, which are separated by the Tropics of Cancer and Capricorn.

Studies of genetic diversity of VZV play an important role in further understanding of the epidemiology and evolution of the virus, and may in future serve as a tool for genetic prediction of virus pathogenicity or re-sistence development (2, 10, 11).

Treatment

Treatment options are based on the patient's age, immune state and symptoms. Antiviral medications such as acyclovir, valacyclovir, and famciclovir are available. Varicella zoster immune globulin (VariZIG) is indicated for administration to high-risk individuals within 10 days of varicella zoster virus exposure, immunocompromised patients without evidence of immunity, newborn infants whose mothers have varicella symptoms between 5 days before and two days after delivery, hospitalized premature infants born at 28 weeks of gestation or later whose mothers do not have evidence of immunity to varicella, hospitalized premature infants born at less than 28 weeks of gestation or who weigh less than 1000 g at birth, regardless of their mothers' evidence of immunity to varicella and pregnant women without evidence of immunity.

Therapeutic choices of herpes zoster generally depend on the host’s immune state and on the presentation of zoster. Conservative therapy includes nonsteroidal anti-inflammatory drugs; and lotions (such as calamine).Medications used include steroids, analgesics, anticonvulsants, and antiviral agents. Surgical care is not generally indicated for the treatment of herpes zoster, though it may be required to treat certain complications (eg, necrotizing fasciitis). Rhizotomy (surgical separation of pain fibers) may be considered in cases of extreme, intractable pain (1,5).

Vaccination

Varicella-associated morbidity and mortality can be effectively prevented by the implementation of uni-versal varicella vaccination. As stated above, the VZV establishes latency after the primoinfection, which precludes its eradication from the host. One polyvalent vaccine is currently available in Czech Republic – Priorix-Tetra from GSK – which offers a protection against measles, mumps, rubella and chickenpox. The other vaccine available is Varilrix, also from GSK, a monovalent live-attenuated vaccine against chickenpox. Zostavax from Sanofi Pasteur is again a monovalent live-attenuated vaccine against shingles. The application scheme varies depending on the vaccine.

In recent years, prevention of chickenpox by vacci-nation has become more significant. Safe and effective live-attenuated varicella vaccine was originally developed in the early 1970s in Japan by Takahashi et al. (17). The vaccine has been licensed for com-mon use in the USA since 1995. To date, universal vaccination has also been used successfully in several other countries such as Canada, Australia,

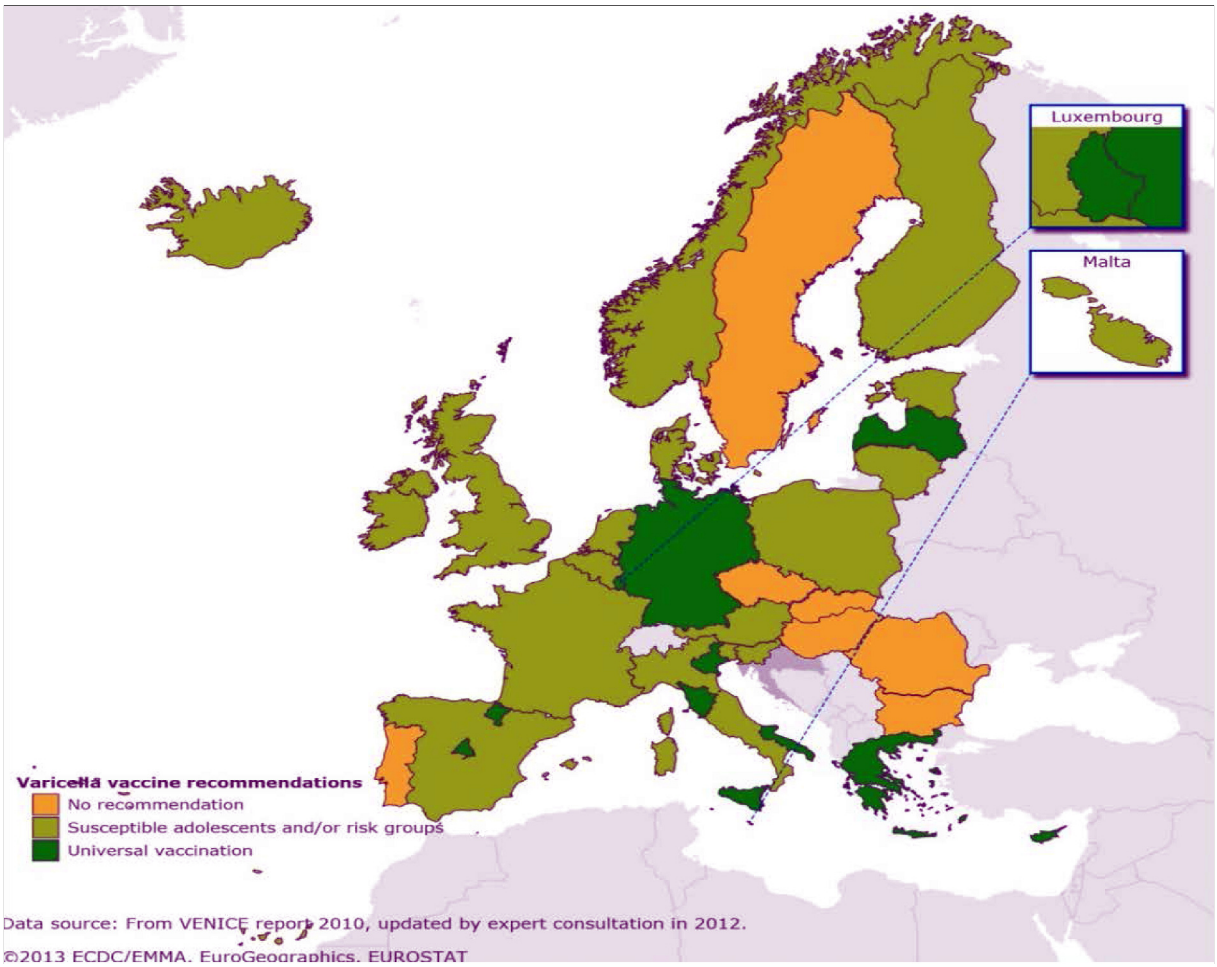

Figure 4. Varicella vaccination recommendations in EU/EEA countries, 2012 (http://ecdc.europa.eu/en/publications/publications/varicella-guidance-2014-consultation.pdf).

Japan and South Korea. More than ten European countries such as UK and Germany currently have targeted vaccination of specific groups at risk of severe chickenpox, e.g. VZV seronegative immunocompromised patients and seronegative women who may be considering pregnancy. All of the currently available varicella vaccines consist of an avirulent virus derived from a Japanese wild-type strain isolated from a boy with typical chickenpox named Oka (p-Oka). All commercially distributed vaccines have been reported to differ only in the number of passage of virus in tissue culture used and in stabilizers, as well as other components of the formulation (12-16). Targeted vaccination of susceptible high-risk patients and/or their household contacts, recommended in many European countries, is an alternative strategy which necessitates a well-organized healthcare system. Figure 4 shows varicella vaccination recommendations for European countries.

Although a slight increase in the peak incidence age of varicella has been observed post-universal varicella implementation, the incidence rates among adolescents and adults have decreased when compared with the pre-vaccination era. To avoid an age shift to older age groups it is necessary to ensure catch-up vaccination and maintain high vaccine coverage. The predicted increase of HZ incidence among naturally immune adults following varicella vaccination has not been observed, possibly because travelling, contact with HZ patients and subclinical reactivation offer greater boosting effects on the cell-mediated immunity than expected.

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