Vericella Zoster Virus: Structure, Mode of Transmission and Treatment

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Abstract: Herpes zoster cause severe viral disease or infection that shows painful vesicular outbursts with superficial reddening of the skin (erythema) as well as rashes in dermal layer also called as shingles. This condition is occur when virus reactivate itself. Due to this virus, approximately 1 million people suffer every year. It mostly affects the elder people that have a weak immune response. If this condition is not treated in early stage it can result into morbidity. The most important problem is the post herpetic neuralgia that includes neuropathic pain. Valacyclovir Gabapentin phenytoin, carbamazepine are used for the reduction of pain of post herpetic neuralgia. The review article provides an over view about the VZV virus and the disease cause by this virus and its treatment.
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Introduction

Varicella-zoster virus is a virus that causes an infection in humans. There are two diseases that are caused by this virus, Varicella (chickenpox) and zoster (shingles). Virus infects the dorsal root ganglia on the spinal cord. As cell meditated immunity tends to declines, virus reactivates itself in the adulthood, patients with and immunocompromised patients, and cause the skin surface infection called shingles (Chow, Tipples, & Grose, 2013). This disease is associated with vesicles and painful vesicular dermatomal skin rash usually in a striped fashion (Forbes, Thomas, & Langan, 2012). Some rare complications such as encephalitis, conjunctivitis, transverse myelitis and other eyes problems can also be caused by zoster virus. Varicella infections are mild in nature and are not transformed into serious illness unless they are accompanied by some bacterial infections (Schmid & Loparev, 2006).

Genome

The genome of VZV is basically linear molecule that contains up to 125,000 of base pairs (Zerboni & Arvin, 2016). Herpes virus has the smallest genome in the Herpes family. The VZV genome has a G+C content of 46% (Rahaus, Desloges, & Wolff, 2006). The molecular weight of VZV genome is 80×10^6 (Dumas, Geelen, Maris, & Van der Noordaa, 1980; Dumas, Geelen, Weststrate, Wertheim, & Van der Noordaa, 1981). The genome consists of 71 ORFs and promoter sequences. Two covalently linked regions are present in the genome. Both contain distinctive sequences. These regions are flanked by inverted repeat sequences. One of them is unique long region (UL). The UL regions contain 105,000bp. The second region is called unique short region (US) that have up to 5,232bp. The other two regions are (IR) internal repeat region and (TR) terminal repeat region. Unpaired bases at each end of the genome help to circularize the VZV genome. In the repeat region, the origin of replication is present. ORF63, ORF62, ORF70, ORF71, ORF69, and ORF64 gene are duplicated in the genome (Zerboni, Sen, Oliver, & Arvin, 2014).

Five clades of virus are present. There are two forms of genome in the infected cells(Chow *et al.,* 2013).

For in vitro replication of VZV, two thirds of ORFs are required. Most of ORFs are among ~40 genes. These genes include eight glycoprotein (gB, gC, gE, gH, gI, gK, gL, gN) that are conserved in all herpes viruses. These eight proteins are involved in various types of function like DNA replication, DNA cleavage, capsid assembly (Zhang *et al.,* 2010). The proteins involved in replication process have small and large subunits of viral ribonucleotide reductase (ORF18 & ORF19). It also contains two subunit of DNA polymerase (ORF16 & ORF28), ssDNA-binding protein (ORF29), Ori of DNA replication binding protein (ORF51), two kinases (ORF47 & ORF66) and other DNA replication enzymes are dUTPase (ORF 8), thymidylate synthetase (ORF13), DNAse (ORF48) and uracil DNA glycosylase (ORF59) (Mallory, Sommer, & Arvin, 1997) (Niizuma *et al.,* 2003). There is directed mutations of coding and non-coding sequences and deletion of ORFs if the VZV genome (Fig. 1) is cloned in BAC or four to five overlapping

fragments in cosmids (Cohen & Seidel, 1993) (Tischer *et al.,* 2007).

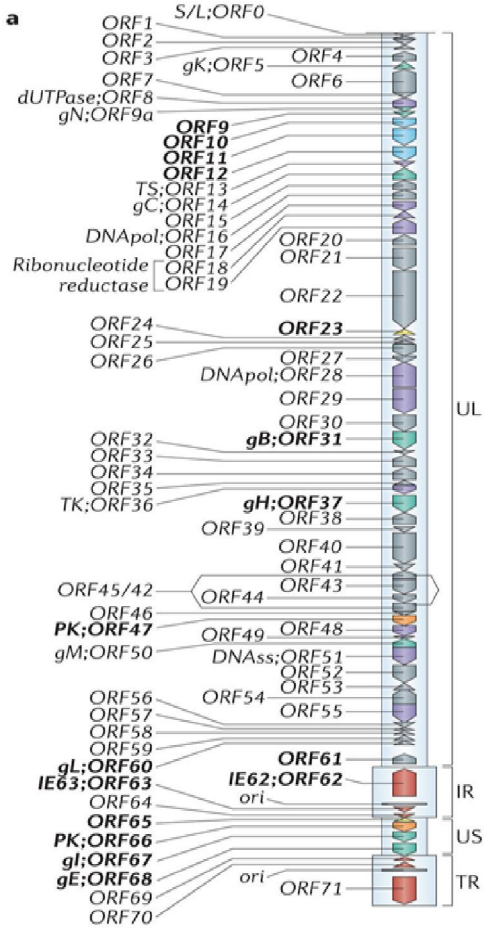

Fig. 1 Genome structure of VZV

Morphology

On the basis of morphology (Figure 2) and its chemical and physical properties Varicella Zoster Virus (VZV) belongs to the family of Herpes virus (Herpesviridae) and it is also known as Human Herpes virus (HHV3). There are three subfamilies of Herpes virus family. These three subfamilies are Alphaherpesvirinea, Betaherpesvirinea and Gammaherpesvirinea (Rahaus, Schünemann, & Wolff, 1999). VZV and HSV (1 & 2) both were grouped into the same subfamily Alphaherpesvirinea on the basis of their host spectrum, length of their replicative cycle, there in vitro cytopathic effects and their latency. But depending on their genome organization, they were classified into different genus. Genus of VZV is varicellovirus and that of HSV is simplex virus. Since their morphology and biological properties are the same but they strongly differ in their symptoms of infection. VZV has a very limited range of infectable host cells like cells of simian origin or the exclusive cells of human.

Size

Vericella Zoster Virus has a size ranges from 150-200nm and enveloped polyhedral structure. It contains four main structural components:

1. Envelope

It is the outermost layer of the virus which is actually made up from the modification of host cell membrane and has atrilaminar appearance with different membrane elements captured during transport(Tortora, Funke, & Case, 2007). The viral envelope also contains many glycoproteins that are encoded by genome (gb, gc, ge, gh, gi, gk and gl) and other alleged glycoproteins (gm & gn). The viruses with the envelope have a diameter ranging from 180-200nm and their shape may be from pleomorphic to spheric.

2. Tegument

The next layer underneath the envelope is tegument. It is actually the part of virus between capsid and envelope. It contains many viral enzymes that are important in taking control over the host cell metabolism. It also contain proteins which are encoded by the open reading frames (ORF) 4, 10, 47, 62 and 63 (Besser *et al.,* 2004).

3. Capsid

The tegument surrounds the capsid that is actually the protein coat surrounding the nuclear material. The capsid ranges in diameter from 100-110nm and has an icosahedral shape (Chen, Zhu, Gershon, & Gershon, 2004). It is made up of 162 capsomers and they all occur in 5:3:2 axial symmetry. The vertices of an 80-120nm icosahedrons are made up of pentameric proteins and facets are composed of hexameric envelope containing different IE proteins produced by open reading frames (ORF) 20, 23, 33, 33.5, 40 and 41(Kuhn, Desloges, Rahaus, & Wolff, 2005).

4. Core

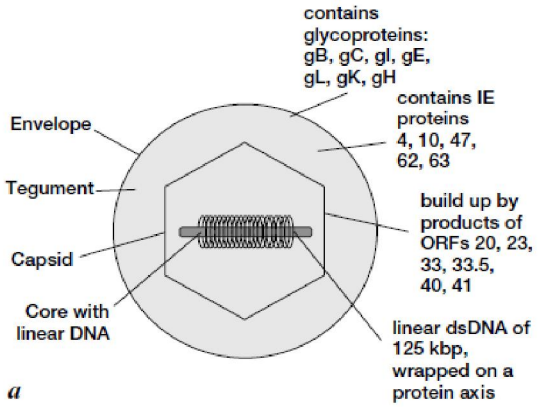

Fig. 2 Morphological structure of VZV

This is the innermost part of the virus containing genetic material. The genome is linear double stranded DNA and it is wrapped on a protein axis in the core. The genome size is 125kb (Ito *et al.,* 2003).

Replication

The replication of VZV has three phases (Fig. 3). The first phase is the adsorption of virus on the host, this phase also includes the entry of virus, its uncoating, capsid transport into the nucleus and viral DNA release. Transcription and translation of viral DNA occurs in the next phase along with viral DNA synthesis. Assembly and enveloping of new virons occurs in the third phase (Chen *et al.,* 2004).

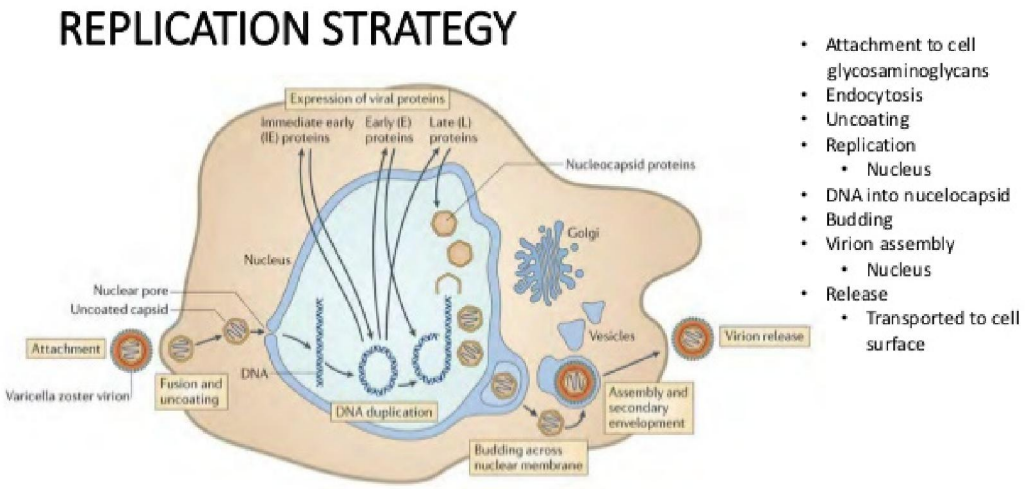

Fig. 3 Replication strategy of VZV

The start of the replication occurs with the attachment of the virus with the specific receptors present on the surface of target cells (Kuhn *et al.,* 2005). The glycoproteins of the virus plays important role in the adsorption phase but the nature of the receptors has not yet been identified. The recent data suggested that at least four VZV glycoproteins present in the envelope of the virus contains mannose-6-phosphate. So, the mannose-6-phosphate receptors are important for attachment (Yang, Hay, & Ruyechan, 2004). Attachment of the virus with the host is followed by the release of tegument and capsid proteins into the cytoplasm and capsid transport to nuclear pores and DNA release in the nucleus (Rahaus & Wolff, 2000). Recent data suggested that there is a significant role of cellular filament system in the transport of virus because there was mutations in the host cell cytoskeleton system after the infection both microtubules and microfilaments undergo reorganization but intermediate filaments remains unaffected (Rahaus, Desloges, & Wolff, 2005).

The viral genes express themselves in a very specific manner. Within a few hours of infection Immediate early (IE) genes are initially transcribed followed by the transcription of early (E) genes and late (L) genes. Expression of these genes are controlled by different factors (Sato, Callanan, Pesnicak, Krogmann, & Cohen, 2002). After the expression of all the genes, the protein core is involved in the wrapping of newly replicated genomes, and in the freshly synthesized capsids packaging occurs and then transported outside the host cell (Di Valentin *et al.,* 2005).

Transmission

VZV is transmitted through droplets (nuclei) inhaled. Aerosolzation can occur by vesicular epidermal lesions or through air tract (Lopez & Marin, 2008). Primary varicella and HZ both have been found to be associated with aerosolization (Sawyer, Chamberlin, Wu, Aintablian, & Wallace, 1994) (Suzuki, Yoshikawa, Tomitaka, Matsunaga, & Asano, 2004) Contact of secondary varicella with a patient is also reported with herpes zoster (J. A. Johnson, Bloch, & Dang, 2011) (Cholongitas & Ilonidis, 2010). Blood and saliva after being exposed to HZ virus become other ways of transmission (Nagel *et al.,* 2011) (Quinlivan *et al.,* 2011) Environment also plays an important role in the transmission of disease and the infection is most common when the patient is in proximity (Walther & Ewald, 2004).

This virus is highly spreadable which occurs through close contact with abrasion or by air tract droplets. Localized and disseminated viruses transmit by different means i.e by direct contact or respiratory droplets respectively. Guidance is needed to handle the VZV affected patients in ICU. They undergo

immunosuppression so they need to be isolated as early as possible. To stop the virus from invading different body parts, proper antiviral treatment is required. If two patients are admitted at the same operation theater and they don't cross contaminate, because the admission period was not the same and non-overlapped (Hagiya, Kimura, Miyamoto, & Otsuka, 2013). VZV can spread from PNS to CNS tissues in both immunocompromised and immunocompetant patients but the spread cases are seen more in the immunocompetant patients which have less than normal range of immune response towards an antigen (43-48). VZV has the ability to spread in either centrifugal or centripetal pattern. It can move in both directions to infect skin and brain/ spinal cord. It becomes very difficult to suspect and recognize the complication when the route is centripetal or CNS because the rash does not appear.

Latency

In PNS, VZV persists the whole life span of the affected individual when the chickenpox resolves. It infects the ganglia present all along the dorsal roots of spinal cord along with cranial ganglia located at the base of skull. During the latent phase, VZV does not undergo transcription and hence remains unrecognized and cleared by the immune system. Research is being carried out to identify the cells that inhabit the VZV to affect the ganglia and also the measure of viral transcription and translation (Kennedy, Grinfeld, & Gow, 1998). PCR result has shown existence of VZV in ganglionic cells i.e 6 to 31 copies/ 100,000 cells (ganglia). During latency, VZV behaves as a non-infectious particle and is extrachromosomal unlike many other viruses which attack nucleic acids. Studies have shown that VZV precisely resides the neurons of ganglia. In the latent phase, VZV shows no change in its morphology and no inciting response. Four genes i.e. 21, 29, 62 and 63 undergo transcription but it is still not understood that which of these genes get translated into proteins during the latent phase.

Viral reactivation can be inhibited by knowing the genes undergoing transcription and translation during latent phase (Mahalingam et al., 1990). When VZV moves to CNS or if the patient exposes to postherpetic neuralgia, treatment becomes difficult. Vaccine consists of a live attenuated virus which undergoes latent phase after vaccination which prevents chickenpox.

Pathogenesis of VZV infection begins with inoculation of mucosal surface with virus and continues till the resolution of acute form, establishing and maintaining dorsal root ganglia latency, reactivation of Varicella Zoster Virus and then skin transport through axon during HZ. During primary infection, to increase the viral load from inoculation point to cellular site and to assist transport to skin, immune evasion is required. This results in prolonged incubation period (10-21 days). During this incubation, primary cell associated viremia is caused by the entrance of virus to local lymphoid tissues and followed by the transport to liver reticuloendothelial cells. During late incubation, transport of VZV to skin is mediated by secondary cell associated viremia and before and after the appearance of rash it can be detected. At some point during primary infection latency is established as VZV reaches the sensory ganglia. VZV also persists in the non-neuronal cells that possess MHC-I. When VZV activates, there is a widespread of virus in ganglia and extensive neurons and glial cells necrosis occurs. VZV along axonal pathways spreads to skin during reactivation and causes skin rash, neuropathic pain and acute sensory disturbances (Kleinschmidt-DeMasters & Gilden, 2001).

Post herpetic neuralgia

In immunocompetent patients, VZV (mostly) resolves showing no consequence of previous disease/injury. Adults experience a prolonged pain which weakens and infirms them. The pain is very hard to deal with and persists for months to years. If the pain persists more than 4 to 6 weeks after the resolvation of rash, the disease is confirmed (Head & Campbell, 1900). Age is the most important factor as the risk of disease is 45% high in patients after 60 years who get affected by VZV. Steroids and pain killers are available for patients but no permanent treatment is present up to date. Pathogenesis of postherpetic neuralgia is in the process to be focused. Two patients with this disease were analyzed and swelling, abrasion was observed around the ganglionic neurons. Smith observed cystic deformation of thoracic sensory ganglia when removed surgically. The severe pain related to this ailment is characterized by the changed structure of neurons. Zacks found no change in structure of neurons in normal and patient of postherpetic neuralgia but epidermal nerve endings loss was recorded in the patients of this complex disease (Kleinschmidt-DeMasters & Gilden, 2001).

Vaccination

In 1995, for healthy children less than 1 year, varicella vaccine was endorsed in USA (Forbes *et al.,* 2012). Another vaccine which was derived from Oka strain of VZV was recommended by FDA in 2006 for HZV prevention and complications (David *et al.,* 2017). The vaccine is non-toxic, cost-effective and competent because a decrease of 90-95% of VZV infection was observed among children between 1-9 years of age (Shapiro *et al.,* 2011). FDA has recommended HZV vaccine for people greater than 50 years even if they have previously suffered from HZ infection. Vaccination coverage should be monitored if another vaccine is being given with VZV vaccine.

Transportation and storage has also been approved by FDA (Willison, Morrison, Mendoza, & Tyring, 2010).

Treatment

The objectives of treatment are to reduce the duration and severity of pain, reduce complications and shorten the episodes of Shingles. Whereas Postherpetic neuralgia often requires symptomatic treatments (Tyring, 2007). People affected by Shingles having moderate pain can be treated by topical lotions containing Calamine. Severe pain may require morphine, capsaicin cream (zostrix) can be used once lesions have crusted (Baron, 2004). Duration and severity of Shingles can be controlled by administration of Antivirals (Bader, 2013). The standard treatment is Aciclovir drug but similar or superior efficacy, tolerability and safety is provided by new drugs valaciclovir and Famciclovir (Tyring, 2007). Intravenous acyclovir is effective to reduce the complications of Shingles in immunocompromised individuals. Furthermore five times daily oral dosage of acyclovir is effective for people who are at high risk of frequent attacks of Shingles (R. W. Johnson & Dworkin, 2003). A study suggested to prescribe acyclovir due to its antiviral activity to Varicella zoster encephalitis patients despite the low level of evidence (De Broucker, Mailles, Chabrier, Morand, & Stahl, 2012). Valacyclover and acyclovir have been approved to treat herpes zoster ophthalmicus (Schuster, Harder, Schlichtenbrede, Jarczok, & Tesarz, 2016). Another manifestation of Varicella Zoster virus is Mollaret's meningitis. Acyclovir can also be used to cure it whereas modern anti herpetic drugs like Valacyclovir and famcyclovir has also shown good results. 25 mg Indomethacin three times daily has reported to be faster source of recovery in patients (Shalabi & Whitley, 2006).

Another study has shown the effectiveness of Famciclovir a well absorbed drug having 7h half-life in virus effected cells for HZ treatment in immunocompetent individuals when given thrice a day (Shafran *et al.,* 2004). A drug Valacyclovir is similar to Famciclovir for the treatment of herpes zoster in immunocompetent patients. The treatment is efficient in resolution of zoster associated pain whereas Valacyclovir is more cost effective (Tyring, Beutner, Tucker, Anderson, & Crooks, 2000). Valacyclovir has also shown efficacy in reducing the incidents of postherpetic neuralgia when conjugated with Gabapentin (Rullán *et al.,* 2017). Acute pain due to postherpetic neuralgia can also be treated with phenytoin, carbamazepine and gabapentin (Francis, Subramanian, Sankari, Potluri, & Prabakaran, 2017). In order to reduce the intensity of postherpetic neuralgia following advanced approaches can be used such as electrical stimulation of thalamus, intercostal nerve cryotherapy, anterolateral cordotomy, spinal cord stimulation, pulsed radiofrequency ablation and botulinum toxin injection (Nagalaxmi V *et al.,* 2014). Brivudine and cidofovir are effective for treating herpes zoster in immune compromised patients (Bandral, Chidambar, Japatti, Choudary, & Dodamani, 2010).

According to a study in 2016, efficiency of cupping, surrounding acupuncture and bloodletting pricking for herpes zoster was shown to be positive. The number of lymphocytes was lowered and number of neutrophils was increased in local blood after the treatment, which is one of the antivirus mechanism (Hao, Yang, & Guan, 2016). The therapeutic effect of acupuncture in treatment of herpes zoster as compared to medicine has reported to be superior and effective (Yu, Zhu, Chen, Fang, & Chen, 2007). Wet cupping is another effective treatment for herpes zoster (Cao, Zhu, & Liu, 2010). Another approach to alleviate the pain and motor weakness due to herpes zoster is psoas compartment block (PCB) that can be used with local anesthetic and steroid (Kim, Kim, Park, & Jeon, 2017).

Discussion

Herpes zoster is a viral infection characterized by painful skin rash usually in striped manner caused by varicella zoster virus. About 15% of people suffer from this virus during their life time (Forbes *et al.,* 2012). Chances of this disease can be reduce by vaccination but as (Chow *et al.,* 2013) reported that this disease is common in immunocompromised patients so, for these patients live attenuated vaccines are not recommended. Researches should be conducted to analyze the effect of inactivated vaccines in immunocompromised patients. Since there is a decline in cell mediated immunity reported by Chow *et al.,* 2013 so, there is an upgrade in cell mediated immunity by vaccine that not only decreases the occurrence of shingles but also reduces the incidence of PHN. Burden of illness is also reduced. Some contradictions still exist for the use of vaccine in special cases like HIV patients with CD4 count more than 400, patients undergoing radiotherapy/immunotherapy, pregnant and breast feeding females (Singh & Scholand, 2011).

Conclusion

Although HZ is a resolvable disease causing agent but serious consequences can be experienced if the disease is left untreated. Post herpetic neuralgia is the complicated and complex disorder thus damaging all the viral body organs. Oral physicians are well known for the recognition of all the symptoms appear in this disease and then diagnosis is done but for the effective patient management and treatment, dentists are consulted. Age factor plays a major role as disease

risk and age share a directly proportional relation. However, antiviral treatment lessens the threat of PHN but still it remains a challenging disease to overcome. Even with the aid of specialists and treatments, pain relieving goal cannot be achieved but with the development of HZ vaccine, prevention is now possible.

Author's Contribution

The authors AA, IA, MM and SM wrote initial draft of manuscript under the supervision of KM. The authors MA and ZH make necessary correction in the manuscript. The final editing and corrections were carried out by QA. Each author has proof-read the manuscript before submission of manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Bader, M. S. (2013). Herpes zoster: diagnostic, therapeutic, and preventive approaches. *Postgraduate medicine, 125*(5), 78-91.
2. Bandral, M. R., Chidambar, Y., Japatti, S., Choudary, L., & Dodamani, A. (2010). Oral complications of herpes zoster infection-Report of 3 cases. *International Journal of Dental Clinics, 2*(4).
3. Baron, R. (2004). Post‐herpetic neuralgia case study: optimizing pain control. *European journal of neurology, 11*(s1), 3-11.
4. Besser, J., Ikoma, M., Fabel, K., Sommer, M. H., Zerboni, L., Grose, C., & Arvin, A. M. (2004). Differential requirement for cell fusion and virion formation in the pathogenesis of varicella-zoster virus infection in skin and T cells. *Journal of virology, 78*(23), 13293-13305.
5. Cao, H., Zhu, C., & Liu, J. (2010). Wet cupping therapy for treatment of herpes zoster: a systematic review of randomized controlled trials. *Alternative therapies in health and medicine, 16*(6), 48.
6. Chen, J. J., Zhu, Z., Gershon, A. A., & Gershon, M. D. (2004). Mannose 6-phosphate receptor dependence of varicella zoster virus infection in vitro and in the epidermis during varicella and zoster. *Cell, 119*(7), 915-926.
7. Cholongitas, E., & Ilonidis, G. (2010). Transmission of varicella-zoster virus originating from a patient with localized herpes zoster: Implications for infection control? *American journal of infection control, 38*(8), 669-670.
8. Chow, V. T., Tipples, G. A., & Grose, C. (2013). Bioinformatics of varicella-zoster virus: single nucleotide polymorphisms define clades and attenuated vaccine genotypes. *Infection, Genetics and Evolution, 18*, 351-356.
9. Cohen, J. I., & Seidel, K. E. (1993). Generation of varicella-zoster virus (VZV) and viral mutants from cosmid DNAs: VZV thymidylate synthetase is not essential for replication in vitro. *Proceedings of the National Academy of Sciences, 90*(15), 7376-7380.
10. De Broucker, T., Mailles, A., Chabrier, S., Morand, P., & Stahl, J.-P. (2012). Acute varicella zoster encephalitis without evidence of primary vasculopathy in a case-series of 20 patients. *Clinical Microbiology and Infection, 18*(8), 808-819.
11. Di Valentin, E., Bontems, S., Habran, L., Jolois, O., Markine-Goriaynoff, N., Vanderplasschen, A.,... Piette, J. (2005). Varicella-zoster virus IE63 protein represses the basal transcription machinery by disorganizing the pre-initiation complex. *Biological chemistry, 386*(3), 255-267.
12. Dumas, A., Geelen, J., Maris, W., & Van der Noordaa, J. (1980). Infectivity and molecular weight of varicella-zoster virus DNA. *Journal of General Virology, 47*(1), 233-235.
13. Dumas, A., Geelen, J., Weststrate, M., Wertheim, P., & Van der Noordaa, J. (1981). XbaI, PstI, and BglII restriction enzyme maps of the two orientations of the varicella-zoster virus genome. *Journal of virology, 39*(2), 390-400.
14. Forbes, H. J., Thomas, S. L., & Langan, S. M. (2012). The epidemiology and prevention of herpes zoster. *Current Dermatology Reports, 1*(1), 39-47.
15. Francis, M., Subramanian, K., Sankari, S. L., Potluri, V. L. A., & Prabakaran, A. (2017). Herpes Zoster with Post Herpetic Neuralgia Involving the Right Maxillary Branch of Trigeminal Nerve: A Case Report and Review of Literature. *Journal of Clinical and Diagnostic Research: JCDR, 11*(1), ZD40.
16. Hagiya, H., Kimura, M., Miyamoto, T., & Otsuka, F. (2013). Systemic varicella-zoster virus infection in two critically ill patients in an intensive care unit. *Virology journal, 10*(1), 225.
17. Hao, P., Yang, Y., & Guan, L. (2016). Effects of bloodletting pricking, cupping and surrounding acupuncture on inflammation-related indices in peripheral and local blood in patients with acute herpes zoster. *Zhongguo zhen jiu= Chinese acupuncture & moxibustion, 36*(1), 37-40.
18. Head, H., & Campbell, A. W. (1900). The pathology of herpes zoster and its bearing on sensory localisation. *Brain, 23*(3), 353-362.

19. Ito, H., Sommer, M. H., Zerboni, L., He, H., Boucaud, D., Hay, J.,... Arvin, A. M. (2003). Promoter sequences of varicella-zoster virus glycoprotein I targeted by cellular transactivating factors Sp1 and USF determine virulence in skin and T cells in SCIDhu mice in vivo. *Journal of virology, 77*(1), 489-498.
20. Johnson, J. A., Bloch, K. C., & Dang, B. N. (2011). Varicella reinfection in a seropositive physician following occupational exposure to localized zoster. *Clinical infectious diseases, 52*(7), 907-909.
21. Johnson, R. W., & Dworkin, R. H. (2003). Treatment of herpes zoster and postherpetic neuralgia. *BMJ: British Medical Journal, 326*(7392), 748.
22. Kennedy, P. G., Grinfeld, E., & Gow, J. W. (1998). Latent varicella–zoster virus is located predominantly in neurons in human trigeminal ganglia. *Proceedings of the National Academy of Sciences, 95*(8), 4658-4662.
23. Kim, S. Y., Kim, D. G., Park, Y. M., & Jeon, Y. H. (2017). Psoas compartment block for treatment of motor weakness and pain following herpes zoster. *The Korean Journal of Pain, 30*(1), 62-65.
24. Kleinschmidt-DeMasters, B., & Gilden, D. H. (2001). Varicella-Zoster virus infections of the nervous system: clinical and pathologic correlates. *Archives of pathology & laboratory medicine, 125*(6), 770-780.
25. Kuhn, M., Desloges, N., Rahaus, M., & Wolff, M. H. (2005). Varicella-zoster virus infection influences expression and organization of actin and α-tubulin but does not affect lamin A and vimentin. *Intervirology, 48*(5), 312-320.
26. Lopez, A. S., & Marin, M. (2008). Strategies for the Control and Investigation of Varicella Outbreaks Manual; 2008. *National Center for Immunization and Respiratory Diseases Center for Disease Control and Prevention, Atlanta, GA*.
27. Mahalingam, R., Wellish, M., Wolf, W., Dueland, A. N., Cohrs, R., Vafai, A., & Gilden, D. (1990). Latent varicella–zoster viral DNA in human trigeminal and thoracic ganglia. *New England Journal of Medicine, 323*(10), 627-631.
28. Mallory, S., Sommer, M., & Arvin, A. M. (1997). Mutational analysis of the role of glycoprotein I in varicella-zoster virus replication and its effects on glycoprotein E conformation and trafficking. *Journal of virology, 71*(11), 8279-8288.
29. Nagel, M. A., Choe, A., Cohrs, R. J., Traktinskiy, I., Sorensen, K., Mehta, S. K.,... DiGiorgio, C. (2011). Persistence of varicella zoster virus DNA in saliva after herpes zoster. *Journal of Infectious Diseases, 204*(6), 820-824.
30. Niizuma, T., Zerboni, L., Sommer, M. H., Ito, H., Hinchliffe, S., & Arvin, A. M. (2003). Construction of varicella-zoster virus recombinants from parent Oka cosmids and demonstration that ORF65 protein is dispensable for infection of human skin and T cells in the SCID-hu mouse model. *Journal of virology, 77*(10), 6062-6065.
31. Quinlivan, M., Ayres, K., Kelly, P., Parker, S., Scott, F., Johnson, R.,... Breuer, J. (2011). Persistence of varicella-zoster virus viraemia in patients with herpes zoster. *Journal of Clinical Virology, 50*(2), 130-135.
32. Rahaus, M., Desloges, N., & Wolff, M. H. (2005). ORF61 protein of Varicella–zoster virus influences JNK/SAPK and p38/MAPK phosphorylation. *Journal of medical virology, 76*(3), 424-433.
33. Rahaus, M., Desloges, N., & Wolff, M. H. (2006). Molecular Biology of Varicella–Zoster Virus *Herpes zoster* (Vol. 26, pp. 1-8): Karger Publishers.
34. Rahaus, M., Schünemann, S., & Wolff, M. H. (1999). Morphological and biological characteristics of varicella-zoster virus *Varicella-Zoster Virus* (Vol. 3, pp. 1-9): Karger Publishers.
35. Rahaus, M., & Wolff, M. H. (2000). Transcription factor Sp1 is involved in the regulation of varicella-zoster virus glycoprotein E. *Virus research, 69*(1), 69-81.
36. Rullán, M., Bulilete, O., Leiva, A., Soler, A., Roca, A., González-Bals, M. J.,... Llobera, J. (2017). Efficacy of gabapentin for prevention of postherpetic neuralgia: study protocol for a randomized controlled clinical trial. *Trials, 18*(1), 24.
37. Sato, H., Callanan, L. D., Pesnicak, L., Krogmann, T., & Cohen, J. I. (2002). Varicella-zoster virus (VZV) ORF17 protein induces RNA cleavage and is critical for replication of VZV at 37°C but not 33°C. *Journal of virology, 76*(21), 11012-11023.
38. Sawyer, M. H., Chamberlin, C. J., Wu, Y. N., Aintablian, N., & Wallace, M. R. (1994). Detection of varicella-zoster virus DNA in air samples from hospital rooms. *Journal of Infectious Diseases, 169*(1), 91-94.
39. Schmid, D. S., & Loparev, V. (2006). Varicella-zoster virus *Manual of Molecular and Clinical Laboratory Immunology, 7th Edition* (pp. 631-636): American Society of Microbiology.
40. Schuster, A. K., Harder, B. C., Schlichtenbrede, F. C., Jarczok, M. N., & Tesarz, J. (2016). Valacyclovir versus acyclovir for the treatment

of herpes zoster ophthalmicus in immunocompetent patients. *The Cochrane Library*.
41. Shafran, S. D., Tyring, S. K., Ashton, R., Decroix, J., Forszpaniak, C., Wade, A.,... Candaele, D. (2004). Once, twice, or three times daily famciclovir compared with aciclovir for the oral treatment of herpes zoster in immunocompetent adults: a randomized, multicenter, double-blind clinical trial. *Journal of clinical virology, 29*(4), 248-253.
42. Shalabi, M., & Whitley, R. J. (2006). Recurrent benign lymphocytic meningitis. *Clinical infectious diseases, 43*(9), 1194-1197.
43. Shapiro, M., Kvern, B., Watson, P., Guenther, L., McElhaney, J., & McGeer, A. (2011). Update on herpes zoster vaccination A family practitioner's guide. *Canadian Family Physician, 57*(10), 1127-1131.
44. Singh, B. S., & Scholand, S. J. (2011). Herpes zoster: a clinical review. *J Infect Dis Antimicrob Agents, 28*(3), 211-221.
45. Suzuki, K., Yoshikawa, T., Tomitaka, A., Matsunaga, K., & Asano, Y. (2004). Detection of aerosolized varicella-zoster virus DNA in patients with localized herpes zoster. *Journal of Infectious Diseases, 189*(6), 1009-1012.
46. Tischer, B. K., Kaufer, B. B., Sommer, M., Wussow, F., Arvin, A. M., & Osterrieder, N. (2007). A self-excisable infectious bacterial artificial chromosome clone of varicella-zoster virus allows analysis of the essential tegument protein encoded by ORF9. *Journal of virology, 81*(23), 13200-13208.
47. Tortora, G. J., Funke, B. R., & Case, C. L. (2007). *Introducción a la microbiología*: Ed. Médica Panamericana.
48. Tyring, S. K. (2007). Management of herpes zoster and postherpetic neuralgia. *Journal of the American Academy of Dermatology, 57*(6), S136-S142.
49. Tyring, S. K., Beutner, K. R., Tucker, B. A., Anderson, W. C., & Crooks, R. J. (2000). Antiviral therapy for herpes zoster: randomized, controlled clinical trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. *Archives of family medicine, 9*(9), 863.
50. Walther, B. A., & Ewald, P. W. (2004). Pathogen survival in the external environment and the evolution of virulence. *Biological Reviews, 79*(4), 849-869.
51. Willison, C. B., Morrison, L. K., Mendoza, N., & Tyring, S. K. (2010). Shingles vaccine. *Expert opinion on biological therapy, 10*(4), 631-638.
52. Yang, M., Hay, J., & Ruyechan, W. T. (2004). The DNA element controlling expression of the varicella-zoster virus open reading frame 28 and 29 genes consists of two divergent unidirectional promoters which have a common USF site. *Journal of virology, 78*(20), 10939-10952.
53. Yu, X., Zhu, G., Chen, Y., Fang, M., & Chen, Y. (2007). Systematic assessment of acupuncture for treatment of herpes zoster in domestic clinical studies.
54. Zerboni, L., & Arvin, A. M. (2016). The pathogenesis of varicella-zoster virus neurotropism and infection *Neurotropic viral infections* (pp. 135-173): Springer.
55. Zerboni, L., Sen, N., Oliver, S. L., & Arvin, A. M. (2014). Molecular mechanisms of varicella zoster virus pathogenesis. *Nature Reviews Microbiology, 12*(3), 197-210.
56. Zhang, Z., Selariu, A., Warden, C., Huang, G., Huang, Y., Zaccheus, O.,... Zhu, H. (2010). Genome-wide mutagenesis reveals that ORF7 is a novel VZV skin-tropic factor. *PLoS Pathog, 6*(7), e1000971.

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