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Review on: Shingles, Its Complications & Management

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Shingles is a viral infection that causes a painful rash. Shingles is caused by the varicella-zoster virus – the same virus that causes chickenpox. After had chickenpox, the virus lies inactive in nerve tissue near to spinal cord and brain. Years later, the virus may reactive as shingles. The first sign of shingles is usually pain in the area of the affected nerve. A rash of fluid-filled blisters then appears in the affected area, typically only on one side of the body. This rash is usually present for about seven days but the pain may persist for longer. Anyone with shingles whose immune system is depressed needs prompt treatment with an antiviral drug. The drug that is most commonly used is aciclovir. Other drugs that are sometimes prescribed include valaciclovir and famciclovir. They are all most effective if taken within 3 days of the rash appearing.

Keyword: Herpes zoster, Varicella zoster virus, Neuralgic pain, Antivirals.

1. Introduction

Shingles, sometimes called 'herpes zoster' (HZ), is a painful skin rash and is caused by an infection of a nerve and the area of skin supplied by that nerve. Although shingles can occur

anywhere on the body, it most often appears as a single stripe of blisters that wraps around either the left or the right side of torso. The virus causing this infection is called the varicella-zoster virus (VZV)-the same virus that causes

chickenpox. After had chickenpox, the virus lies inactive in nerve tissue near to spinal cord and brain. Years later, the virus may reactivate as shingles^[1]. It is not possible to develop shingles from exposure to a person with chickenpox. It is possible however, to develop chickenpox as a result of exposure to a person with shingles^[2].

1.1 Epidemiology

Herpes zoster is a viral disease that occurs infrequently in young, healthy patients. However, its incidence rises sharply with age from an estimated 0.5 cases/1000 in children to five to 10 cases/1000 in individuals older than 80 years; this phenomenon has been attributed to an age-related decline in cellular immunity. Association with race, sex, ethnic background, or seasonal variations has not been reported for this disease. In addition to the elderly, immunocompromised patients, particularly those suffering from hematologic or reticulo-endothelial malignancies, have a greater risk of developing HZ. Furthermore, HZ might be the first clinical manifestation of HIV infection. In a study among 48 HZ patients, 35 (73%) were seropositive for HIV on the initial day of diagnosis of HZ. Of these, 34 (97%) were known to be at high risk for AIDS. Therefore, among patients at risk for AIDS, the occurrence of HZ might precede the marked depression of cellular immunity associated with AIDS or AIDS-related complex. Similarly, a greater incidence of HZ has been reported in patients with rheumatoid arthritis receiving weekly, low-dose methotrexate therapy compared with the general population. These observations show that HZ outbreaks are clearly dependent on the breakdown of normal immune surveillance^[3].

1.2 Aetiology

1.2.1 Varicella Zoster Virus(Vzv)

VZV is a DNA virus whose genome codes for about 60 proteins. In 1986, the complete genome of the virus was worked out. The genome is actually the smallest of any of the human herpesviruses. The official name of this virus is human (alpha) herpesvirus. Their genome contains double-stranded DNA and their unique

viral DNA polymerase provides a target for antiviral drugs. An important property of all herpes viruses is their ability to cause lifelong latent infection within the dorsal root and trigeminal sensory ganglia^[4,5].

The most important factor leading to the development of shingles is a decline of the body's immunity. This decline can be as a result of:

- Natural ageing – the incidence of shingles increases with age
- having Hodgkin lymphoma or non-Hodgkin lymphoma
- having chemotherapy or steroid drugs
- lowering of the number of white blood cells after a bone marrow transplant or a stem cell transplant. Overall, the incidence of shingles is approximately equal, whether you are having an autologous stem cell transplant or an allogeneic stem cell transplant.
- immuno-suppressive therapy – such as the treatment given to people after organ transplantation.
- having the human immunodeficiency virus (HIV) or the acquired immune deficiency syndrome (AIDS)^[7].

1.2.2 Transmission

Herpes zoster is contagious and will spread via direct contact with an infected person. The transmission can also occur through inhalation of airborne respiratory secretions. The virus infects the cells of the respiratory tract or conjunctival epithelium and is carried through the body via the blood stream and lymphatic system. It is then spread from the capillary epithelium to the epidermis where viral replication destroys the basal cells. The virus then remains in a latent stage in perineural satellite cells of the dorsal nerve root ganglia. The person with herpes zoster remains in a contagious state from 2 days before the appearance of a rash, and remains contagious until all lesions are crusted with no detectable drainage from the sites^[8].

1.3 Signs and Symptoms

The first symptoms people notice are a feeling of being generally unwell and a band of pain in an area of skin on one side of the body. The pain of shingles can range from mild to severe, it can be a constant dull ache or a burning sensation, and it can also come and go as sharp, stabbing pains. These symptoms can develop before the rash appears^[7].

A rash of fluid-filled blisters then appears in the affected area, typically only on one side of the body. This rash is usually present for about seven days but the pain may persist for longer. Persistent pain is more common in elderly people and is termed 'post herpetic neuralgia'. On average this lasts for 3 to 6 months although it can continue for years^[2].

The symptoms and signs of shingles may include:

- Pain, burning, tingling, itching numbness or extreme sensitivity in a certain
- part of the body.
- Fever
- Headache
- Fatigue
- Chills
- Upset stomach
- Depression^[9]

1.4 Complications

Complications of shingles include:

- post-shingles pain that is still there more than a month after the rash starts (post-herpetic Neuralgia) scarring of the skin.
- superimposed or 'secondary' bacterial infection of the rash.
- spreading of shingles, causing progression of the skin rash.
- Eye problems (if the shingles is on the face, around the eye area), including inflammation of the front of the eye, sometimes of the whole eye, with pain and vision problems.
- Involvement of internal organs.
- This last complication is a relatively rare complication but it is more common in people

- who have received an allogeneic stem cell transplant^[7].

1.5 Diagnosis

1.5.1 Clinical presentation

Clinical presentation before the rash appears, shingles can be confusing. However, there are some clues that should alert providers and thus enable them to begin early treatment^[10].

Three diagnostic stages of herpes zoster are

1. Prodromal stage
2. Active stage (acute stage)
3. Chronic stage

The prodromal syndrome stage presents as sensations described as burning, tingling, itching, boring, prickly or knife-like occurring in the skin over the affected nerve distribution. The patient may present with an odontalgia that may be the only prodromal symptom.

The active stage is characterized by the emergence of the rash that may be accompanied by generalized malaise, headache, low grade fever and sometimes nausea. The rash progresses from erythematous papules and oedema to vesicles in 12 to 24h and finally progresses to pustules within 1 to 7 days. The pustules begin to dry with crust formations that fall off in 14 to 21 days, leaving erythematous macular lesions that result in hyperpigmented or hypopigmented scarring. In severe cases, areas of epidermis and variable amounts of dermis may be lost due to haemorrhagic necrosis. Intraoral lesions usually appear after the cutaneous rash. Pain and dysaesthesia during the active stage are reported to be minimal when the rash is most active. However, there is a return of pain during the crusting and scale phase of the active stage but this pain subsides as the rash and scales clear.

The chronic pain syndrome stage is termed post herpetic neuralgia (PHN). PHN is defined as pain lasting beyond the period of healing of the active skin lesions. This has been described as pain lasting 1 to 3 months after the skin lesions have cleared. PHN pain has been described as pain consisting of three distinct components: (i) a constant, usually deep pain (ii) a brief recurrent shooting or shocking tic-like pain and (iii) a sharp

radiating dysaesthetic sensation evoked by very light touching of the skin, termed allodynia^[8].

1.5.2 Laboratory Diagnosis

The differentiation of the VZV infection from herpes simplex and bullous dermatoses is an important indication for virological diagnosis. Also, VZV infections of pregnant women and of newborn infants, atypical infections of immunodeficient patients and suspected VZV infection of the central nervous system must be confirmed by laboratory diagnosis. The enzyme-linked immuno-sorbent assay and the immuno-fluorescence technique are especially suited for the detection of VZV-specific immunoglobulins of classes IgG, IgM and IgA. VZV/IgG rises may occur spontaneously and in recurrent HSV-infections due to cross reactivity of epitopes. However, additional detection of IgM and high titered IgA anti-VZV antibodies usually indicates of chronic pain. Rapid and specific laboratory diagnosis of VZV infections, whether primary or recurrent, is important to determine the need for antiviral treatment in high-risk patients. The preferred method for rapid diagnosis of skin lesions is immune-peroxidase staining for VZV-infected cells in a scraping of cells from the base of the lesion. Detection of multinucleated giant cells in lesion specimens or tissue sections by Tzanck or Papanicolaou stain was used in the past, but these methods lack sensitivity and do not differentiate VZV from herpes simplex virus (HSV). VZV antigens also can be detected rapidly by using an enzyme immunoassay to test fluid from VZV skin lesions. The gold standard for VZV diagnosis is the isolation of infectious virus in tissue culture, but this virus is less readily isolated than are HSV and other herpes viruses, and it grows slowly, often requiring 3 to 7 days for isolation; therefore, a positive direct antigen detection test is presumed to be diagnostic, even if the culture is negative, and is an indication for antiviral therapy. Polymerase chain reaction (PCR) performed in a reliable laboratory also can be used for rapid diagnosis of VZV; however, the problem of false-positive results must be considered, and reliance on PCR as the only

diagnostic criterion is not recommended. Although it is not a useful guide for antiviral therapy, the serologic diagnosis of varicella can be made retrospectively if an initial serum specimen is obtained within 24 to 72 hours after the appearance of the rash and a convalescent specimen is taken when the illness has resolved. Because antibodies usually are not made during the incubation period, paired sera allow the documentation of sero conversion, indicating primary VZV infection. Although commercial laboratories may offer the test, assays for VZV IgM antibodies are not recommended for the diagnosis of acute VZV infection because of unacceptably high rates of both false-positive and false-negative results. VZV IgG antibodies persist for life after primary infection, although the commercial laboratory methods have substantial false negative rates. When these limitations are recognized, serologic tests for VZV IgG antibodies, when positive, provide useful information that the child has had VZV infection. If the high risk child is sero negative, susceptibility must be assumed, despite the possibility that some children may be immune. Electron microscopy allows the morphological detection of herpes viruses in vesicular fluids or smears. However, this again does not allow differentiation of the herpes viruses VZV, HSV-1 and HSV-2. Furthermore electron microscopy cannot be used routinely^[11,12].

1.5.3 Treatment

The objectives of treating herpes zoster are to control acute pain, accelerate rash healing, minimize complications and reduce the risk of post-herpetic neuralgia (PHN) and other late appearing sequelae. An additional objective, particularly important for immuno-suppressed patients, is to reduce the risk of cutaneous and visceral dissemination of VZV^[6].

1.5.4 Antiviral Therapy

The primary antiviral medications used against shingles are acyclovir, famciclovir, and valacyclovir, and early initiation of antiviral treatment is key to a good outcome. Randomized controlled trials and meta-analyses have shown

that treatment with acyclovir decreases the likelihood of long-term pain. Acyclovir also decreases viral shedding, hastens rash resolution, and decreases all pain end points. The two prodrugs, famciclovir and valacyclovir, may be more effective than acyclovir because of their bioavailability profiles and more convenient dosing. Both are taken 3 times rather than 5 times daily. In one study, valacyclovir significantly shortened the median time to the resolution of zoster related pain compared to acyclovir. Acyclovir, famciclovir and valacyclovir, all of which are nucleoside analogues, are approved for the treatment of HZ in healthy individuals. Oral acyclovir, valacyclovir, and famciclovir are all considered effective in less severely immunocompromised patients, such as those with solid tumor malignancy or patients receiving corticosteroid therapy. In severely immunocompromised patients, such as those with leukemia or receiving bone marrow transplants, intravenous acyclovir is an effective therapy for herpes zoster (HZ). All these medications should be started within 72 hours of the onset of rash, and all should be continued for at least 7 days. Beginning antiviral therapy at the prodrome stage, rather than waiting for the rash to develop, may be reasonable. Furthermore, these drugs are well-tolerated in patients with adequate renal function, and they have few side effects (headache and nausea primarily). The agents also reduce the incidence of PHN (postherpetic neuralgia). The specific indications for treatment with antiviral agents are especially important in the following groups:

- Patients over 50 years of age;
- Immuno-compromised patients;
- Patients with an ophthalmic or cervical localisation of HZ; and
- Patients with moderate to severe pain before or at the start of the rash.

Treatment of pain should be started early and decisively with paracetamol, corticosteroids, non-steroidal anti-inflammatory drugs, opiates, codeine or morphine. The standard dosage of prednisone is 60mg/day for seven days, reducing

the dosage by half each week for two weeks until discontinuation. Corticosteroids are principally indicated in patients over 50 years of age. Topical analgesics are commonly used for the relief of PHN, despite very limited evidence of efficacy. Topical agents for the treatment of PHN include: acetylsalicylic acid (500mg in 95% alcohol 5 mL), lidocaine 5% patch or gel, geranium oil, and capsaicin. Capsaicin cream 0.025% applied three or four times daily, is commonly prescribed. On occasion it is necessary to add to the pain treatment with antidepressant and anticonvulsant drugs. Tricyclic antidepressants (especially nortriptyline, at 25mg daily with a gradual increase by 25mg/daily every two to three days, as tolerated, and up to a maximum of 150mg daily) have been used extensively in this setting. Of the anticonvulsant drugs, the gabapentinoids (gabapentin and pregabalin) are prescribed most often^[6,10,13].

The following list includes some basic hygiene and dietary recommendations and herbal remedies that can be useful in treating elderly patients with herpes zoster in the long-term care setting, especially when attempting to limit the use of pharmacologic agents

1. The skin should be kept clean and contaminated items—towels, combs, clothing and anything that comes in contact with the rash—should not be reused.
2. Non disposable items such as towels, combs and clothing should be washed in boiling water or otherwise disinfected before reuse.
3. Avoid foods rich in arginine, which is required for VZV to replicate. Such foods include almonds, cashews, cereal grains, chocolate, coconut, dairy products, oats, peanuts and soybeans.
4. Consume foods rich in the amino acid lysine. Studies indicate that the process of VZV replication extracts lysine from the blood stream. The virus attempts to use lysine as it would use arginine—to make protein VII, an arginine-rich protein component of the viral core. However, this attempt fails. Thus, lysine acts like an

arginine substitute, “fooling” the virus and preventing it from replicating and causing outbreaks. Foods that contain high levels of lysine include most vegetables, including legumes, as well as fish, chicken and turkey.

5. Use supplements containing the vitamin B12/B6 complex, which aids the body in recovery and reduces the pain associated with shingles.
6. Apply capsaicin cream, which aids in relieving pain associated with shingles.
7. Use olive leaf extract supplements, which have antiviral properties.
8. Avoid foods that encourage an overly acidic body system, such as chocolate, fried foods and red meat, and do not drink caffeine- containing or carbonated beverages.
9. Because sugar suppresses the activity of white blood cells, refined sugar products—including cakes, cookies, sweet baked goods and sodas—should be avoided. Naturally occurring sugars, such as those in fruit, should be eaten in moderation^[14].

1.6 Aromatherapy Approach

Shingles can be treated easily and effectively with aromatherapy by topical application of a 50/50 mix of *Calophyllum inophyllum* and *Ravensara aromatica*. It is extremely effective in the case of shingles and herpes wherever they occur. Dr. Jane Buckle proposed the use of *Ravensara* in Foraha (*Calophyllum inophyllum*) to treat shingles and any sort of herpes outbreak. The most successful essential oil is *Ravensara* aromatic. Len Price says a combination of *Tamanu* (*Callophyllum inophyllum*) vegetable oil and *Ravensara* aromatic essential oil has been used successfully for the treatment of shingles^[11].

1.7 Prevention

An attractive option for the prevention of VZV infection in later life is to use a vaccine to provide immunity. A ‘live’ virus vaccine, sometimes known more accurately as a ‘live attenuated vaccine’, has been in use around the world for

more than 20 years and was approved for use in 1995 in the USA for administration to children with normally functioning immune systems. (7) A vaccine called Zostavax is available to help prevent shingles in adults over 60 years and older, and has dramatically reduced the risk of developing this condition in susceptible individuals^[9].

Zostavax is supplied in vials of lyophilised powder containing a minimum of 19,400 PFU (plaque forming units) of the Oka/Merck strain of varicella zoster virus (VZV) when reconstituted with the accompanying vial of diluent. It is administered by subcutaneous injection as a single dose. A single 0.65 ml dose is sufficient for adults aged 50 years and older. Zostavax is a higher titre formulation of the varicella vaccine and has been tested as a vaccine to protect against herpes zoster^[15].

The varicella virus vaccine is a childhood immunization administered between 12 and 18 months. It is also recommended for older children and adults who have never had chickenpox. If you still contract chickenpox after receiving the vaccination it is generally less severe^[9].

2. Conclusion

Early recognition and aggressive treatment of herpes zoster can minimize the severity and long-term effects of the illness. Predictors of PHN are older age, female sex, and presence of a prodrome, greater rash severity, and greater pain with acute herpetic neuralgia. Antiviral therapy combined with analgesics is the cornerstone of treatment of this prevalent, debilitating illness. The current availability of the VZV vaccine could significantly lower the burden of disease associated with herpes zoster..

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